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Whipple’s operation with a modified centralization concept: A model in low-volume Caribbean centers

Shamir O Cawich, Neil W Pearce, Vijay Naraynsingh, Parul Shukla, Rahul R Deshpande

Abstract

Conventional data suggest that complex operations, such as a pancreaticoduodenectomy (PD), should be limited to high volume centers. However, this is not practical in small, resource-poor countries in the Caribbean. In these settings, patients have no option but to have their PDs performed locally at low volumes, occasionally by general surgeons. In this paper, we review the evolution of the concept of the high-volume center and discuss the feasibility of applying this concept to low and middle-income nations. Specifically, we discuss a modification of this concept that may be considered when incorporating PD into low-volume and resource-poor countries, such as those in the Caribbean. This paper has two parts. First, we performed a literature review evaluating studies published on outcomes after PD in high volume centers. The data in the Caribbean is then examined and we discuss the incorporation of this operation into resource-poor hospitals with modifications of the centralization concept. In the authors’ opinions, most patients who require PD in the Caribbean do not have realistic opportunities to have surgery in high-volume centers in developed countries. In these settings, their only options are to have their operations in the resource-poor, low-volume settings in the Caribbean. However, post-operative outcomes may be improved, despite low-volumes, if a modified centralization concept is encouraged.

Key Words: Pancreas; Surgery; Pancreatectomy; Whipple’s; Pancreaticoduodenectomy
Core Tip: The published data generally support pancreaticoduodenectomies (PD) being reserved for high volume hospitals. However, this is not practical in resource-poor, low volume countries in the Caribbean. Nevertheless, we have documented good short-term outcomes after PD in this setting. In this paper we discuss a modified centralization concept used to incorporate PD into these low volume centers.

INTRODUCTION

Pancreaticoduodenectomy (PD) is a technically complex operation that is accompanied by high complication rates. Although post-operative morbidity has declined over the past 2-3 decades with better supportive care, 30%-50% of patients still experience post-operative complications[1]. Due to PD’s high-morbidity profile, specialized hospitals began to appear at the turn of the 21st century where hepatopancreatobiliary (HPB) services were concentrated. This drove the “high-volume center” concept in developed countries with large populations, and it was fueled by good outcome data emerging from these centers. A change in referral patterns followed, where patients with peri-ampullary lesions were sent to these experienced centers for multidisciplinary teams to perform PDs at high volumes. This was the birth of the era of service centralization and terminology evolved from “experienced centers”[2] to “high-volume centers”[3].

In this paper, we discuss our experience incorporating PD into this low-volume, resource-poor region.

DATA FROM HIGH-VOLUME CENTRES

At the turn of the 21st century, published data emerged to show that high volume centers performed PDs with significantly reduced overall morbidity[1-8], thirty-day mortality[1,8] readmission rates[3], cost[3,9], duration of hospital stay[3,9] and 5-year survival rates[1,8,10]. These data supported the principle of centralization - a concept that seemed predictable and intuitive on first glance. However, a closer look at the existing data revealed that there was no standardized definition of “high volumes”, with researchers applying ad-hoc definitions that ranged from as low as 2 PDs annually[6,8] to as high as 125 PDs annually[11]. We conducted a systematic literature search across the PubMed, Medline and Google Scholar platforms seeking publications that defined “high-volume” hospitals, using the search terms: “high-volume”, “experienced”, “centers of excellence”, “referral centers” and “specialty centers”. The literature search was performed by two researchers and spanned the 27-year period from January 1, 1995 to December 31, 2021. All studies identified were retrieved and reviewed in detail by both researchers who extracted the following data: definition of high-volume center, mortality in low and high-volume centers and study population. We excluded studies that did not document these data, studies with missing data and duplicated studies. The results are outlined in Table 1[1-30]. Most studies demonstrated significant differences in 30-d mortality, but the definitions of “high volume” varied widely. Most papers in the literature quoted numbers ≥ 20 PDs per annum[1,3,4,9,16,17,25].

ARGUMENTS AGAINST REGIONALIZATION

Although data accumulated to support service centralization in developed countries, the concept faced several challenges.

Unclear definitions of “high volume”

With the presumption that medical literature will soon adopt a standardized definition of “high volume” equating to ≥ 20 PDs per annum (Table 1), there are few hospitals across the globe that would qualify as high-volume centers. This creates a logistic problem because it would be impractical for patients to be routed to few centers across the globe for PD. This is especially unrealistic in the
### Table 1 Summary of studies comparing peri-operative mortality according to hospital volumes

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<th>Study population</th>
<th>Definition of high volume (cases per annum)</th>
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<td>Lieberman et al.[1], 1995</td>
<td>Low volume: 18.9%; High volume: 5.5%</td>
<td>2233 PDs over 8 years in New York, USA from 1984-1991</td>
<td>Minimal: &lt; 10; Low: 10-50; High: &gt; 50</td>
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<td>Glasgow et al [9], 1996</td>
<td>Low volume: 14.1%; High volume: 3.5%</td>
<td>1424 PDs using data from the California Office of Health wide State Planning and Development from 1990-1994</td>
<td>I (Low): 1-5; II: 6-10; III: 11-20; IV: 21-30; V: 31-50; VI (High): 50</td>
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<td>Sosa et al,[3], 1998</td>
<td>Low volume: 18.8%; High volume: 0.9%</td>
<td>449 PDs + 47 total pancreatectomies from 48 non-federal hospitals in Maryland, USA from 1990-1995</td>
<td>Low: &lt; 5; Medium: 5-19; High: &gt; 20</td>
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<td>Birkmeyer et al,[1], 1999</td>
<td>Low volume: 16%; High volume: 4%</td>
<td>7229 PDs from the US-based Medicare database from 1992-1995</td>
<td>Very Low: &lt; 1; Low: 1-2; Medium: 2-5; High: &gt; 5</td>
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<td>Gouma et al [12], 2000</td>
<td>Low volume: 13.2%; High volume: 8.1%</td>
<td>1126 patients from 1994-1998 from the National Medical Registry in the Netherlands</td>
<td>I: &lt; 5; II: 5-10; III: 10-25; IV: &gt; 25</td>
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<td>Kottwall et al [6], 2002</td>
<td>Low volume: 12.6%; High volume: 9%</td>
<td>24926 PDs from the US-based National Inpatient Database from 1988-1995</td>
<td>Low: ≤ 1; High: &gt; 1</td>
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<td>Nordback et al [13], 2002</td>
<td>Low volume: 13%; High volume: 4%</td>
<td>350 PDs from the National Hospital Discharge Database in Finland from 1990-1994</td>
<td>Low: &lt; 5; Medium: 5-10; High: &gt; 10</td>
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<td>Finlayson et al [14], 2003</td>
<td>Low volume: 11%; High volume: 3%</td>
<td>3414 pancreatic resections (unspecified) from the US based Nationwide Medicare Database from 1994-1999</td>
<td>Very Low: &lt; 1; Low: 1-2; Medium: 3-4; High: 5-13; Very High: &gt; 13</td>
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<td>Ho et al[7], 2003</td>
<td>Low volume: 14.6%; High volume: 4.7%</td>
<td>6709 PDs in California and Florida (from insurance claims) between 1988-1998</td>
<td>Very Low: 1; Low: 2-3; Medium: 4-9; High: &gt; 10</td>
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<td>Van Heek et al [15], 2005</td>
<td>Low volume: 11.8%; High volume: 3.8%</td>
<td>Systematic review of studies reporting mortality in 1988 unspecified pancreatic resections in the Dutch Nationwide Registry from 1994-2004</td>
<td>Very Low: &lt; 5; Low: 5-9; Medium: 10-24; High: &gt; 24</td>
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<td>Fong et al[41], 2005</td>
<td>Low volume: 8%; High volume: 2%</td>
<td>2592 PDs across 1101 hospitals using data from national Medicare database between 1995-1996</td>
<td>Low Volume: ≤ 5; High Volume: &gt; 25</td>
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<td>McPhee et al [16], 2007</td>
<td>Low volume: 11.1%; High volume: 2.7%</td>
<td>39463 pancreatic resections from the US-based National Inpatient Sample Database from 1998-2003 (27289 PDs analyzed separately)</td>
<td>Low: &lt; 5; Medium: 5-18; High: &gt; 18</td>
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<td>Riall et al[17], 2007</td>
<td>Low volume: 7.4%; High volume: 3.0%</td>
<td>3189 pancreatic resections in Texas using the Texas Hospital Inpatient Discharge Public Use Data File from 1999-2004</td>
<td>Low: &lt; 10; High: &gt; 10</td>
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<td>Mepaid et al [18], 2008</td>
<td>Low volume: 11.1%; High volume: 5.22%</td>
<td>7558 pancreatic resections from the Nationwide Inpatient Sample from 1998-2003</td>
<td>Low: 1-18; High: &gt; 18</td>
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<td>Billimora et al [8], 2008</td>
<td>Low volume: 15.4%; High volume: 4.99%</td>
<td>13107 unspecified pancreatectomies in 1454 hospitals via ACS National Cancer Database from 1994-1999</td>
<td>Low: &lt; 2; Medium: 2-9; High: ≥ 10</td>
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<td>Balzano et al [19], 2008</td>
<td>Low volume: 12.4%; High volume: 2.6%</td>
<td>1576 patients (1044 PDs) from 221 hospitals in Italy using data from Ministry of Health in the year 2003</td>
<td>Low Volume: &lt; 5; Medium: 6-13; High: 14-51; Very High: &gt; 52</td>
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<td>Gasper et al [20], 2009</td>
<td>Pooled estimated effects in favour of high-volume hospitals OR 0.25 (95%CI 0.15-0.41)</td>
<td>5294 patients undergoing pancreatic resections (unspecified) between 1994-2004 from the US-based California Discharge Database</td>
<td>Low: &lt; 5; Medium: 5-49; High: &gt; 50</td>
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<td>Teh et al[21], 2009</td>
<td>OR hospital mortality (95%CI) 4.0 (3.1-5.1) OR hospital mortality (95%CI) 1.7 (1.3-2.4)</td>
<td>103222 patients (76273 PDs) from the Nationwide Inpatient Sample in USA between 1988-2003</td>
<td>Very Low: 3; Low: 3-5; Medium: 6-11; High: 12-23; Very High: 24-35; Extra: &gt; 36</td>
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<td>Nathan et al[11], 2009</td>
<td>Low volume: 33.7%; High volume: 33.5%</td>
<td>8251 PDs from the State Inpatient Databases for Florida, Maryland, and New York from 1998-2005</td>
<td>Low: &lt; 25; Mid: 25-124; High: &gt; 125</td>
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<td>Gooiker et al [22], 2011</td>
<td>Pooled estimated effects in favour of 0.25 (95%CI 0.16-0.57)</td>
<td>Pooled volume groups as defined in individual studies; Lowest: 1-5; Highest: 7-36</td>
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<td>La Torre et al [10], 2012</td>
<td>Low volume: 2.5%; High volume: 2.1%</td>
<td>Pooled volume groups as defined in individual studies; Lowest: 1-5; Highest: 7-36</td>
<td>Low: 9-4; Medium: 9-12; High: 13-18; Very High: &gt; 19</td>
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Caribbean where many patients are not able to afford care in developed countries. The region has some of the poorest countries in the Western Hemisphere and many patients in these territories do not have health insurance.

**Data generalization**

Healthcare personnel should exercise good judgement when interpreting the available data. Pawlik et al [31] made the point that volume-outcome relationships are one way to judge hospitals, but are non-informative about any specific hospital - apart from those from which the data was collected. In other words, it cannot be used to generalize outcomes in every low or high-volume hospital. Thus, if a low-volume hospital published data to show good outcomes, it should trump simple volume data. Additionally, there are many factors that may skew outcomes data: Firstly, within high volume centers, surgeons do not have equivalent experiences, case volumes or clinical outcomes[1,31-34]. Secondly, some high-volume centers may end up treating higher-risk cases while some community or teaching hospitals may treat more indigent patients, potentially skewing outcome data. Thirdly, volume-related data only provides information on patients who underwent PDs, but excludes any useful information on clinician judgement, expertise and decision making when choosing patients for surgery[31]. This critical aspect of care for patients with peri-ampullary carcinomas does not appear in any volume-based data.

**Surgeon volumes**

To be able to complete a PD, surgeons must accrue experience through repetition of the operative steps. Some have argued that PD outcomes are less dependent on hospital volume and more dependent on the technical competence of the operating surgeon[1,2,5,7,13,35]. Numerous authors have demonstrated the association between increasing individual surgeon volume and improved PD outcomes[1,2,5,13,35]. Published data show that high-volume surgeons complete PD with significantly lower mean blood loss [1,2], shorter operating time[1] and greater nodal harvest[1] when compared to low-volume surgeons. Nordback et al[13] also demonstrated that 86% of post-PD deaths were due to surgical or technical complications.

However, it is difficult to meaningfully interpret these data because there is no standardized definition of a “high-volume surgeon”, with researchers applying ad-hoc definitions that range from as low as 3 PDs annually[13] to as high as 50 PDs annually[2,20,30]. We conducted a systematic literature search across the PubMed, Medline and Google Scholar platforms seeking publications that defined: “high-volume” surgeons, using the search terms: “high-volume”, “experienced”, “subspecialty trained” and “specialized”. The literature search was performed by two researchers and spanned the 27-year period from January 1, 1995 to December 31, 2021. Table 2 outlines the results[1,2,3,13,35] and shows a large variation in the definition of “high volume surgeons”.

Schmidt et al[1] introduced the “experienced surgeon” concept being distinct from a high-volume surgeon. They defined an experienced surgeon as one who had performed > 50 PDs in their career. In other words, they suggested that the cumulative experience was important unlike a high-volume

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Year</th>
<th>Volume (%)</th>
<th>Mortality (%)</th>
<th>p-value</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alfsasser et al [23], 2012</td>
<td>32.2% (1-yr mortality)</td>
<td>26.2% (1-yr mortality)</td>
<td>&lt; 0.001</td>
<td>9566 patients who underwent PD or total pancreatoduodenectomy in Germany from 2006-2009</td>
<td>Low: &lt; 32; High: &gt; 32</td>
</tr>
<tr>
<td>Bliss et al[24], 2014</td>
<td>8.1%</td>
<td>3.1%</td>
<td>&lt; 0.001</td>
<td>129609 pancreatectomies from the US based Nationwide Inpatient Sample 2004-2011</td>
<td>Low: &lt; 5; Medium: 5-18; High: &gt; 18; Very High: &gt; 50</td>
</tr>
<tr>
<td>Derogar et al [25], 2015</td>
<td>60% greater mortality risk</td>
<td>NR</td>
<td>HR 1.60, 1.04 to 2.48</td>
<td>3298 pancreatic resections from the Swedish National Register (2818 PDs not separately reported) from 1990-2010</td>
<td>2.4 (not clearly defined)</td>
</tr>
<tr>
<td>Hata et al[26], 2016</td>
<td>Overall pooled OR for mortality in favour of high-volume hospitals: OR 2.37 (95% CI 1.95-2.88)</td>
<td>0.09</td>
<td>Metanalysis of 58023 patients undergoing PD across 13 studies based on nationwide databases from 11 countries</td>
<td>Low: 1-19; Medium: 20-29; High: ≥ 30</td>
<td></td>
</tr>
<tr>
<td>Brizerno et al [27], 2017</td>
<td>5.5%</td>
<td>2.6%</td>
<td>&lt; 0.001</td>
<td>19024 PDs using the US based National Cancer Database from 2010-2015</td>
<td>Low: &lt; 10; Medium: 10-20; High: &gt; 20 per year</td>
</tr>
<tr>
<td>El Amrani et al[28], 2018</td>
<td>4.4%</td>
<td>3.4%</td>
<td>0.047</td>
<td>10632 patients undergoing distal pancreatectomy from 2009-2018 from a French National database</td>
<td>Low Volume: ≤ 10; High Volume: &gt; 10</td>
</tr>
<tr>
<td>Krautz et al [29], 2018</td>
<td>10.4%</td>
<td>8.1%</td>
<td>NS</td>
<td>Analysis of 60858 patients undergoing major pancreatic surgery (unspecified) from a German National Database from 2009-2014</td>
<td>Very Low: &lt; 8; Low: 8-18; Medium: 19-31; High: 32-58; Very High: &gt; 59</td>
</tr>
<tr>
<td>Balzano et al [30], 2020</td>
<td>8.1%</td>
<td>4.4%</td>
<td>&lt; 0.001</td>
<td>Multicenter study of 7631 PDs (12662 pancreatic resections) in 395 Italian hospitals from 2014-2016</td>
<td>Very Low: 0-10; Low: 10-25; Medium: 25-60; High: 60-166; Very High &gt; 167</td>
</tr>
</tbody>
</table>

NR: Not reported; PD: Pancreatico-duodenectomy; US: United States; ACS: American College of Surgeons; HR: Hazard ratio; OR: Odds ratio; CI: Confidence intervals.
surgeon which was time dependent. Schmidt et al[1] were able to demonstrate that, compared to their less-experienced colleagues, experienced surgeons performed more PDs with vein resections (96% vs 4%) and had significantly lower overall morbidity, pancreatic leak rates, operative blood loss and mean operating time. Importantly, they showed that experienced surgeons who currently performed PDs at low volumes had equivalent outcomes to high-volume surgeons.

Schmidt et al[1] suggested that a pancreatic surgeon needs to accrue 50 PDs before the improvement in technical operative skills begins to plateau. Tseng et al[36] suggested that in their experience, surgeons continued to acquire skills and technical expertise even when approaching 200 PDs. Although there is no consensus, and regardless of a time or case-load dependent definition, we believe that pancreatic surgeons continue to gain experience by developing operative maneuvers, recognizing avoidable pitfalls and learning how to get out of trouble when PDs don’t go smoothly. They also develop mature judgement that is important for appropriate patient selection. We cannot downplay the importance of developing inter-personal relationships over time that facilitate better working relationships with colleagues in other specialties to enhance supportive post-operative care. These are lessons that can only be learned with proper surgical mentorship and accrued experience[1,37].

**Combined team expertise**

Taking it a step further, PDs are quite unforgiving when complications arise. When they do, expert multidisciplinary care is required to prevent bad outcomes[7,37]. This includes input from intensivists, gastroenterologists, interventional radiologists, infectious disease specialists, nutritionists, among others. We agree with Sosa et al[3] that it is the “combined experience of the entire team of pancreatic care providers”, and not necessarily the hospital volume, surgeon volume or surgeon experience that make the difference in peri-operative outcomes. We also believe that is feasible to foster the growth of a multidisciplinary support team in low-volume institutions.

**Implementation of centralization**

Although data accumulated to support centralization, there was reluctance to route patients to high-volume centers, even in the developed countries where data proved better outcomes[7,37]. This includes input from intensivists, gastroenterologists, interventional radiologists, infectious disease specialists, nutritionists, among others. We agree with Sosa et al[3] that it is the “combined experience of the entire team of pancreatic care providers”, and not necessarily the hospital volume, surgeon volume or surgeon experience that make the difference in peri-operative outcomes. We also believe that is feasible to foster the growth of a multidisciplinary support team in low-volume institutions.

**Negative effects of centralization**

Finally, there is existing data to show that healthcare inequity has developed in hospitals that adopted the centralization principle. There is clear data to show that patients are significantly less likely to have

---

**Table 2 Summary of studies comparing peri-operative mortality according to surgeon volumes**

<table>
<thead>
<tr>
<th>Author</th>
<th>Low volume surgeon, %</th>
<th>High volume surgeon, %</th>
<th>P</th>
<th>Study population</th>
<th>Definition of low-volume surgeon</th>
<th>Definition of high-volume surgeon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lieberman et al[2], 1995</td>
<td>15.5</td>
<td>4.7</td>
<td>&lt; 0.001</td>
<td>2233 PDs over 8 years in New York State</td>
<td>&lt; 9 cases experience</td>
<td>&gt; 41 cases experience</td>
</tr>
<tr>
<td>Sosa et al[3], 1998</td>
<td>12</td>
<td>1.8</td>
<td>&lt; 0.001</td>
<td>449 PDs + 47 total pancreatectomies from non-federal facilities in Maryland, USA</td>
<td>&lt; 5 PD annually</td>
<td>&gt; 50 PD annually</td>
</tr>
<tr>
<td>Nordback et al[13], 2002</td>
<td>14</td>
<td>3</td>
<td>&lt; 0.05</td>
<td>350 PDs in 33 hospitals by 98 surgeons</td>
<td>&lt; 1 annually</td>
<td>&gt; 3 annually</td>
</tr>
<tr>
<td>Schmidt et al[1], 2010</td>
<td>4</td>
<td>2</td>
<td>0.09</td>
<td>1003 PDs at Indiana University across 2 periods</td>
<td>&lt; 20 annually</td>
<td>&gt; 20 PD annually</td>
</tr>
<tr>
<td>Eppsteiner et al[35], 2009</td>
<td>6.4</td>
<td>2.4</td>
<td>&lt; 0.0001</td>
<td>3581 pancreatic resections from the National Inpatient Sample Database</td>
<td>&lt; 5 annually</td>
<td>≥ 5 annually</td>
</tr>
</tbody>
</table>

**PD:** Pancreatico-duodenectomy.
Table 3 Proportion of pancreatico-duodenectomies performed outside of high-volume centers

<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>PDs performed by low volume hospital, %</th>
<th>Average surgeon volume</th>
<th>Average hospital volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sosa et al[13], 1998</td>
<td>Maryland, United States</td>
<td>47.3</td>
<td>1 per year</td>
<td>1 per year</td>
</tr>
<tr>
<td>Riall et al[17], 2007</td>
<td>Texas, United States</td>
<td>36.7</td>
<td>NR</td>
<td>&lt; 5 PD per year</td>
</tr>
<tr>
<td>Birkmeyer et al[5], 1999</td>
<td>Medicare database, United States</td>
<td>&gt; 50</td>
<td>NR</td>
<td>&lt; 2 PD per year</td>
</tr>
<tr>
<td>Ho et al[7], 2003</td>
<td>Florida and California, United States</td>
<td>77</td>
<td>NR</td>
<td>10% in hospitals doing 1 PD per year</td>
</tr>
<tr>
<td>Bliss et al[24], 2014, For period &lt; 2004</td>
<td>Nationwide inpatient sample database, United States</td>
<td>40.8</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Bliss et al[24], 2014, For period &gt; 2011</td>
<td>Nationwide inpatient sample database, United States</td>
<td>26.9</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Glasgow et al[9], 1996</td>
<td>California, United States</td>
<td>88</td>
<td>NR</td>
<td>&lt; 2 PD per year</td>
</tr>
<tr>
<td>Fong et al[1], 2005</td>
<td>National Medicare Database, United States</td>
<td>89</td>
<td>1 per year</td>
<td>1 PD per year</td>
</tr>
</tbody>
</table>

PD: Pancreatico-duodenectomy; NR: Not reported.

PD in a high-volume center if they are non-white (Table 4)[3,16,17,24,39], female[17] or did not have private insurers (Table 5)[24]. Eppsteiner et al[35] also documented that across the United States, patients were significantly more likely to have their pancreatic resections by high-volume surgeons if they were male, white raced, and a resident of a high-income zip code.

CARIBBEAN EXPERIENCE

The age standardized incidence of pancreatic adenocarcinoma in the Caribbean is 4.4 per 100000 population[40]. However, only 3 of 17 Caribbean countries have populations > 200000 persons. Therefore, few patients develop peri-ampullary lesions and qualify for PD annually. Peri-ampullary malignancies remain the most common indication for PD in the Caribbean, but most patients are not able to access high-volume centers in developed countries because of travel restrictions, lack of social support, financial limitations and/or lack of health insurance. Therefore, local hospitals are often their only options for PD.

After three specialized HPB centers were established in the Caribbean in 2011, general surgeons readily gave up performing major hepatectomies but they have been reluctant to give up PDs. We previously reported that 98% of hepatectomies are now performed by subspeciality trained HPB surgeons[41], but a review of unpublished data from the same database between 2013 and 2020 showed that 80% of attempted PDs were performed by HPB teams (Table 6).

As a surrogate marker of technical expertise, we used the same database to tally the number patients who had PD attempted and those who had PDs completed. The HPB surgeons completed 94% of attempted PDs, but general surgeons performed palliative bypasses in all 18 cases. Schmidt et al[1] suggested that vein reconstruction was a surrogate marker for surgeon experience. In this database, HPB surgeons were more likely to perform vein reconstruction during PD compared to general surgeons (26% vs 0). This suggests that the specialty surgeons were experienced, although none were high-volume surgeons using conventional criteria in Table 1. Published data documented that only 12.8 PDs were performed annually at the busiest specialized HPB center in the Caribbean[42]. Nevertheless, we believe that outcomes can be improved using a modified centralization concept, with attention to the following five points.

Leadership

Surgical leaders must recognize that the concept of centralization is a significant deviation from “cultural norms” in the Caribbean and general surgeons are bound to resist this change. We must also recognize that it is not feasible to send all patients across the region to referral centers. Even if this was feasible, it would be undesirable because it would develop services in a handful of institutions but it would not be beneficial to the entire population at large.

Therefore, an astute leader could instead offer to operate at lower-volume centers assisted by general surgeons. In this way, they could identify and change hospital-based practices and processes. This has several potential advantages: better trained staff, diligence in care administration, development of critical care pathways and improved proficiency of the less experienced facility and their staff to care for...
Table 4 Patients undergoing pancreatico-duodenectomy at high-volume centers (%)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Data source</th>
<th>Whites, %</th>
<th>Non-whites, %</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sosa et al[3], 1998</td>
<td>Non-federal facilities in Maryland, United States</td>
<td>25.2</td>
<td>9.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>McPhee et al[16], 2007</td>
<td>National Inpatient Sample Database, United States</td>
<td>80</td>
<td>20</td>
<td>NS</td>
</tr>
<tr>
<td>Bliss et al[24], 2014</td>
<td>National Inpatient Sample Database, United States</td>
<td>65.6</td>
<td>34.4</td>
<td>0.018</td>
</tr>
<tr>
<td>Eppsteiner et al[35], 2009</td>
<td>National Inpatient Sample Database, United States</td>
<td>79.3</td>
<td>20.7</td>
<td>NS</td>
</tr>
</tbody>
</table>

PD: Pancreatico-duodenectomy; NS: Not specified.

Table 5 Patients undergoing pancreatico-duodenectomy with private insurance coverage (%)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Data source</th>
<th>High-volume center, %</th>
<th>Low-volume center, %</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bliss et al[24], 2014</td>
<td>6144 patients undergoing PD</td>
<td>43.7</td>
<td>36.9</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

PD: Pancreatico-duodenectomy.

Table 6 A comparison of outcomes in 90 patients undergoing pancreatico-duodenectomy in a Caribbean centre

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sub-specialty surgeon, (%)</th>
<th>General surgeon, (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attempted PD</td>
<td>72/90 (80)</td>
<td>18 (20)</td>
<td>&lt; 0.0001$^2$</td>
</tr>
<tr>
<td>Completed PD</td>
<td>68/72 (94)</td>
<td>0</td>
<td>&lt; 0.0001$^6$</td>
</tr>
<tr>
<td>Portal vein resection/reconstruction</td>
<td>19/72 (26)</td>
<td>0</td>
<td>0.0103$^7$</td>
</tr>
</tbody>
</table>

$^5$Statistical analysis using Fishers Exact Test.
$^2$Statistical analysis using Z-test for Proportions.
PD: Pancreatico-duodenectomy.

critical patients. We agree with Pawlik et al[31], Billimora et al[8], Gasper et al[20], Hashimoto et al[43] and Ravaioli et al[55] that we should strive to identify specific elements of patient care in specialized hospitals that lead to better outcomes and introduce them in less-experienced facilities.

**Fostering team spirit**

We have already made the point that PDs are technically complex and unforgiving operations. Complications will occur once sufficient cases are attempted - and, regardless of surgeon skill and experience, it is the multidisciplinary team effort that will save patients. Therefore, it is important to pay attention to the pre- and post-operative care pathways.

Before selecting a patient for PD, there should be rigorous pre-operative evaluation[8,44,45], medical optimization[8], anaesthetic assessment[8,44] and tumour board discussion[46]. Mature surgeon judgment also has a large impact on the patient that makes it to the operating table. All of these factors affect peri-operative outcomes.

When complications develop in the post-operative phase, it is often not the surgeon who comes to the rescue. They rely on multidisciplinary support from a variety of specialties for around-the-clock emergency care[8,47-51]. It goes without saying that these services should be developed concurrently and we should strive for good interpersonal relationships across disciplines.

**Critical assessment of the healthcare environment**

It is clear that the healthcare environment in the Caribbean differs significantly from those in developed countries. We have provided data showing that local subspecialty surgeons are experienced, but they have repatriated to resource-poor settings with many challenges: scarce blood products, lack of readily available specialized equipment, high competition for ICU/HDU beds, an undersupply of consumables and infrequent operating lists.

One is forced to realize that the environment is not always conducive to observing best practice recommendations[41]. In order to maintain quality service delivery, surgeons must perform a critical appraisal of their local facility and understand the pitfalls in their environment. Tailored processes of care would then have to be devised that suit the local healthcare environment. We agree with Sosa et al
[3] who suggested that, instead of focusing on transforming a facility to a high-volume hospital, effort would be better spent on developing a systematic approach to handle these patients by developing critical pathways to enhance the performance of the entire health care delivery team.

Developing partnerships
While the traditional concept of centralization according to hospital volume or surgeon experience may not be practical in the Anglophone Caribbean, we have seen improved outcomes after introducing a partnership concept. In this concept, patients need not be channeled solely to referral centers. Instead, most Caribbean countries are sufficiently small for staff to move from referral centers to less experienced facilities, bringing with them experience, knowledge and select equipment for safe operations to be performed. Similarly, Ravaioli et al.[52] published data to show that their institutions benefited from partnerships between high and low-volume facilities.

With this approach, we found that general surgeons still felt useful and were willing to cooperate with sub-specialists. They benefited because they received oversight from subspecialty surgeons, felt empowered to communicate about complications and increased their skillsets. Other authors have made similar suggestions to transfer mechanisms to improve outcomes into lower-volume hospitals where most patients receive their care[8,31,52].

Regular audit
Over the years that the HPB units have been implemented in the Caribbean setting, we have prioritized data collection because we recognize that this is the way to objectively evaluate our clinical practices. The value of this exercise ultimately lies in improvement in outcomes after PD for the population as a whole, but changes in outcomes will not be fully evident until regular audits are carried out. This is the only way to create tangible benefits for the healthcare system. Regular review of the data also allows us to better understand the challenges in the local healthcare system, ultimately facilitating the development of clinical care pathways and effective use of limited resources.

Knowledge of population based data
It is important for surgeons to be knowledgeable about the characteristics of the population they work with. For example, it has been shown that persons of Caribbean descent harbor greater-than expected HPB anatomic variations[53]. If a surgeon has not anticipated and/or identified these variants, they can be easily injured and create significant complications. An example is a replaced right hepatic artery coursing behind the pancreatic head. This is prone to injury during PD and can lead to hepatic ischemia and mortality. In Caribbean populations, a replaced right hepatic artery coursing behind the pancreatic head is present in 18% of unselected individuals - significantly greater than published reports in medical literature[53].

Ultimately, there seems to be emerging consensus in the recent medical literature that hospital volume, surgeon volume and hospital teaching status are only proxies for not-yet-fully understood processes of care delivery[52,54,55]. These vary between facilities, but include staffing level, tumour board meetings, surgeon skill, care pathways, available technology and support services. Instead of focusing on these proxies, physicians should focus on specific hospital-based outcomes data and find directed ways to improve the quality of care in your hospital despite volume, surgeon, teaching or financial status of the facility.

CONCLUSION
Despite low case volumes, cultural resistance to subspecialty care, financial barriers and resource-poor environments, we have been able to maintain acceptable short-term outcomes after PDs. We advocate developing an intimate knowledge of your health care system to identify processes that will facilitate good outcomes. In our setting we used a modified centralization concept, with attention to creating partnerships with experienced staff, fostering teamwork, appropriate staff training, development of care pathways, regular audits and knowledge of population-based data.

FOOTNOTES
Author contributions: Cawich SO, Naraynsingh V, Deshpande R and Shukla P designed and coordinated the study; Pearce NW, Deshpande R, Shukla and Naraynsingh V acquired and analyzed data; Cawich SO, Naraynsingh V, Deshpande R and Shukla P and Pearce NW interpreted the data; Cawich SO, Naraynsingh V, Deshpande R and Shukla P and Pearce NW wrote the manuscript; all authors approved the final version of the article.

Conflict-of-interest statement: All authors report no relevant conflict of interest for this article.

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S-Editor: Wu YYJ

L-Editor: A

P-Editor: Wu YYJ

**REFERENCES**


Cawich SO et al. Whipple's operation


Role of micronutrients in Alzheimer's disease: Review of available evidence

Hong-Xin Fei, Chao-Fan Qian, Xiang-Mei Wu, Yu-Hua Wei, Jin-Yu Huang, Li-Hua Wei

**Abstract**

Alzheimer’s disease (AD) is one of the most common age-related neurodegenerative disorders that have been studied for more than 100 years. Although an increased level of amyloid precursor protein is considered a key contributor to the development of AD, the exact pathogenic mechanism remains known. Multiple factors are related to AD, such as genetic factors, aging, lifestyle, and nutrients. Both epidemiological and clinical evidence has shown that the levels of micronutrients, such as copper, zinc, and iron, are closely related to the development of AD. In this review, we summarize the roles of eight micronutrients, including copper, zinc, iron, selenium, silicon, manganese, arsenic, and vitamin D in AD based on recently published studies.

**Key Words:** Alzheimer’s disease; Iron; Micronutrient; Zinc

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INTRODUCTION

Alzheimer’s disease (AD) is a common age-related neurodegenerative disease[1,2]. Owing to progressive population aging, the incidence of AD will continue to increase[3,4]. In China, an estimated 14% of the general population over the age of 65 years and approximately 30% general population over the age of 85 years were affected by AD. In China, the estimated annual cost of medical care for AD approaches one hundred billion RMB, as the conventional diagnosis of AD is based on expensive investigations such as magnetic resonance imaging, positron emission tomography, and analysis of cerebrospinal fluid[5].

Individuals with AD typically suffer from loss of learning ability and memory, impaired judgment and reasoning[6,7], and loss of analytical ability[8], which can seriously affect their quality of life. This imposes a heavy economic and psychosocial burden on the affected families and the society. Clinical treatment of AD is typically challenging[9]. Currently, clinical research on AD in China and overseas is only at the stage of exploration, while the basic research on AD is still at the stage of hypotheses or theories. Studies have shown that AD is closely related to the dynamic changes in body micronutrients, such as decrease in iron and zinc content, and increase in copper content[10-12]. This article reviews the evidence from contemporary research conducted across the world on the link between AD and micronutrients.

This article is primarily based on a literature search conducted in the NCBI database for studies investigating the link between AD and micronutrients published in the last five years.

AD AND MICRONUTRIENTS

AD and copper

Copper is a ubiquitous element. Red meat, nuts, and vegetables are rich sources of copper. Copper is one of the most abundant transition metals in the human body. It is involved in collagen synthesis, antioxidant defense, skin pigmentation, neurotransmitter synthesis, and iron homeostasis[13]. Thus, it plays an important role in human physiology.

Copper is closely related to AD[14,15]. The most common neuropathic lesions in AD are plaques of neurofibrillary tangle, amyloid, and soluble oligomers with large amounts of copper at their core. Patients with AD were shown to have significantly higher levels of copper in their brain tissue than the general population, which promotes the formation of neurofibrillary tangle, amyloid, and other proteins[16-18].

Copper promotes the neurofibrillary tangle of hyperphosphorylation Tau, which aggravates homeostatic disorders; in addition, copper promotes oxidative stress, which has been observed in the brain tissue of many patients with AD[19]. Rosmarinic acid is a commonly used anti-AD drug. Rosmarinic acid has been shown to reduce copper-induced neurotoxicity due to its antioxidant effect in vitro and in vivo, by preventing the binding of amyloid protein with copper[20]. The properties of copper-bound amyloid proteins have been employed for auxiliary positron emission tomography in the diagnosis of AD in mouse models[21].

Detection of copper is useful in the diagnosis and prevention of AD[22,23]. In addition, long-term exposure to copper is associated with cognitive decline and microglia degeneration[24]. TDMQ20 was shown to reduce the copper content in the cerebral cortex of mice[25], and ameliorate oxidative stress in the cerebral cortex of mice, further attenuating the neurotoxicity of amyloid[26]. High affinity metal ion chelating agents such as chitosan can be an effective treatment for AD. The therapeutic effect of chitosan is related to its ability to absorb copper ions[27].

AD and zinc

Zinc is one of the essential micronutrients in the body and the second most abundant micronutrient in the central nervous system[28,29]. Zinc is involved in growth and development, wound healing, immune regulation, catalytic reactions, and substance synthesis. Zinc also regulates excitatory and inhibitory neurotransmitters in brain tissue[30,31]. As the zinc content in the body decreases with age, abnormal zinc metabolism may serve as a therapeutic target for AD. In particular, zinc and selenium or iron and zinc have been concomitantly used to treat AD[32,33].

Studies have shown that zinc release increases with age, especially in female rats, and that zinc deficiency leads to neuronal death; this phenomenon is related to the involvement of zinc in the...
recognition of neuronal receptors and ligands, which is one of the main risk factors for AD and its associated brain neuropathology[34]. On the contrary, zinc supplementation was shown to improve cognitive deficit and rescue the decline in key molecular targets of synaptic plasticity and insulin signaling in the hippocampus of rats with sporadic AD[35]. Oxidative stress plays a key role in neurodegeneration and impaired cognitive function. Diet rich in antioxidants is a novel strategy for prevention of AD. Compared with healthy individuals, patients with AD showed significantly lower serum levels of Se, Cu, and Zn[36].

Studies have shown that the disorder of zinc dynamic equilibrium can cause abnormal synthesis and increased deposition of amyloid protein in brain tissue, and increase the degree of neuronal damage. The underlying mechanism involves binding of zinc to histidine residues of brain tissue-amyloid protein leading to the formation of amorphous aggregates of amyloid protein, which then leads to the formation of age spots[37]. The combination of zinc and copper was shown to accelerate the formation of amorphous aggregates of amyloid protein[38], and the high saturation magnetization of zinc ferrite was found to improve the formation of amorphous aggregates of amyloid protein[39].

An increasing body of evidence has shown that the basal level of extracellular zinc in hippocampus is typically in the low nanomolar range, and that the increase in zinc content aggravates the neurotoxicity of amyloid protein[40]. Zinc was shown to increase the expression of amyloid precursor protein in a mouse model of AD, which in turn increased amyloid synthesis.

Pathological dynamic equilibrium of copper, iron, and zinc promotes the deposition of amyloid proteins in brain tissue and affects structural changes in Tau Proteins. S100B is one of the most abundant proteins in the brain[41], which is involved in the regulation of amyloid deposition and zinc homeostasis. Use of zinc chelating agents can improve amyloid deposition levels by interfering with S100B[42]. Klotho protein is a zinc-rich protein which has neuroprotective, anti-inflammatory, antioxidant, and promyelination effects. Increasing serum Klotho protein can play a role in neuroprotection, anti-inflammation, and anti-oxidation[43]. Evidence suggests that AD is associated with increased levels of Tau, which is related to the presence of multiple zinc binding sites in the Tau protein. Low zinc levels stimulate Tau, leading to increased neurofibrillar tangle in the neurons[44]. The antioxidant zinc carboxylate inhibits the activity of acetylcholine esterase (ACHE) and butyrylcholinesterase and plays an anticholinesterase role, which indicates the benefit of zinc carboxylate in the treatment of AD[45]. Zinc homeostasis is involved in the pathogenesis of AD. Zinc can significantly increase the activity of carnosine, which is beneficial in the treatment of AD[46].

Zinc deficiency can lead to a decrease in learning ability and memory in AD. Zinc supplementation (3 mg/kg) was shown to improve learning and memory in a mouse model of AD, which may be related to the decrease in inflammatory activity in NLRP3[47]. Zinc can promote the aggregation of SFPQ in cultured neurons by regulating the nuclear SFPQ protein, which is an important marker of AD[48].

**AD and iron**

Iron is one of the essential trace metal elements which is widely distributed in the human body. Iron is involved in material transportation, growth and development, cell differentiation, gene expression, and lipid peroxidation. Abnormal heme content and deranged iron homeostasis are more common in AD[49].

Accumulation of iron in the brain is a common phenomenon in many neurodegenerative disorders. Postmortem studies have documented markedly increased concentration of ferritin and hemosiderin aggregates in the brain tissues of patients with severe AD[50]. Inadequate iron intake during pregnancy may cause iron deficiency in fetal brain tissue, increasing the risk of neurological defects. With the increase in age, accumulation of iron in brain tissue can also occur because of brain tissue-amyloid protein deposition and plaque, which in turn promotes further iron deposition[51].

A growing body of evidence suggests that iron dysregulation in brain neurons plays a key role in AD[52]. Studies have documented high iron concentrations in deep gray matter structures of brain tissue in patients with AD[53]. Iron deposition promotes increased Tau levels in brain tissue and neurofibrillary Tangle Tau formation[10,54]. Iron also accelerates the deposition of amyloid proteins in brain tissue[55]. Increased concentration of iron-rich pollutants in the air predisposes people to AD[56].

Studies have shown that amyloid precursor protein can be hydrolyzed to amyloid, which is dependent on iron transporter transmembrane transport[57]. CI5D2 gene encodes CDGSH FT-DOMAIN Protein 2, and up-regulation of CDGSH FT-DOMAIN PROTEIN 2 can improve mitochondrial structure and synaptic function, which plays a neuroprotective role[58].

Research has shown that oxidative stress promotes iron deposition in brain tissue, which plays an important role in the development of AD. In a study, scanning electron microscope and transmission electron microscope were used to examine specific iron-rich areas in the hippocampus of anatomical specimens of brain tissue from patients with AD. The authors found a significant increase in both Tau and amyloid proteins in brain tissue, which suggests that the effect of oxidative stress on AD is related to the oxidation of iron[59].

Endothelial cells in brain tissue can promote the formation of new blood vessels in the environment of embryonic development, and they rely on specific metabolic pathways to achieve different cellular functions. Pilin-1, a transmembrane protein of endothelial cells, regulates mitochondrial function and iron homeostasis, thus affecting the development of AD[60]. Use of iron chelating agents such as desfer-
Fei HX et al. Role of micronutrients in AD

Selenium is one of the most common micronutrients in the body. It is involved in biological oxidation, cell differentiation, protein synthesis, and gene transcription. In particular, selenium inhibits ACHE and butyrylcholinesterase, which has a positive effect on the treatment of AD[65]. Selenium is a central component of many antioxidant enzymes (glutathione peroxidase) that regulate redox levels in the body and have a positive effect on the immune system[68].

Selenium deficiency is believed to be involved in the causation of AD. Selenium deficiency impairs immunity and leads to overproduction of oxidized products and amyloid-beta protein. Selenium can interact with metals by using selenomethionine and improve the body’s antioxidant capacity[69]. Chondroitin sulfate selenium has been shown to improve spatial learning and memory impairment in mice with AD, reduce the degree of synaptic edema of hippocampal neurons, and protect the integrity of mitochondria. The underlying mechanism involved activation of the P38 mitogen activated protein kinase signaling pathway by chondroitin sulfate selenium[70].

Glutathione peroxidase 1 is a major antioxidant enzyme that has a protective effect against memory impairment induced by-amyloid in mice with AD; this phenomenon is related to the activation of Erk signal pathway by glutathione peroxidase-1[71]. Memory impairment is the most well-known symptom of AD. The combination of nano-selenium (0.4 mg/kg) and stem cells increased the levels of brain-derived neurotrophic factor and reduced amyloid deposition in an Alzheimer mouse model; these results suggest that the combination of selenium and stem cells can reduce neurotoxicity in mice with AD[72].

Clinical studies have shown that AD is associated with cognitive decline. Higher blood selenium levels in older people were shown to be associated with higher cognitive scores; a general linear model was observed between blood selenium concentrations and cognitive function. It is suggested that selenium ameliorates the decrease of cognitive ability[73,74]. Selenium is essential for brain health. In a study of 984 men and 1032 women conducted between 2011 and 2014, selenium was found to be associated with cognitive function. The study involved assessment of whole blood selenium concentrations; there was no correlation between blood selenium concentration and sex. The results indicated that adequate selenium was positively associated with cognitive ability in the elderly[75].

Alzheimer’s and silicon

Silicon is one of the most common micronutrients in the body. It is divided into amorphous silicon and crystalline silicon, which exists in the form of silicate or silicon dioxide. Silicon is involved in collagen synthesis, immune system regulation, bone mineralization, and Tau phosphorylation[76]. Silicon was shown to lower the risk of AD[77].

Recent studies have shown the health benefits of silicon in humans. Soluble silicic acid is a useful form of silicon in the human body. The absorption, distribution, and metabolic characteristics of soluble silicic acid in human body are closely related to human health. The unique cross-linking ability of soluble silicic acid and its antagonism to toxic aluminum may protect against AD[78].

Studies have shown an increase in the incidence of degenerative diseases in Western countries. Diet has a positive effect on AD. Beer, which is rich in silicon and hops, plays an important role in preventing brain disorders. This is primarily related to the ability of beer to regulate inflammation, oxidation, and cholinesterase activity[79]. Nerve growth factor (NGF) plays an important role in reducing the number of cholinergic neurons in AD. Studies have demonstrated the neuroprotective effect of NGF on rat pheochromocytoma PCL2 cells by using biodegradable porous silicon oxide carriers[80].
**AD and manganese**

Manganese is one of the essential micronutrients in the body. It is involved in oxidation-reduction, lipid synthesis and, protein degradation, which are mostly related to the alkylation of manganese. Various aromatic, heterocyclic aromatic, and aliphatic secondary amines, such as indole and resveratrol-derived amines, can be obtained by alkylation reaction\[81]. Most studies have found that AD can occur with decreased or normal levels of manganese\[82].

With rapid industrialization and the increasing environmental pollution, excessive intake of heavy metal manganese will have a neurotoxic effect and promote neurodegeneration. Astrocyte is the main stable cell type in the central nervous system. Excessive intake of manganese can affect the structure and function of astrocytes, as well as the synthesis and degradation of glutamate. Effective control of manganese neurotoxicity may be a potential strategy for preventing or slowing AD\[83]. Abnormal conformation of prion proteins in normal cells can lead to their transformation into pathogenic prion proteins, which can bind to manganese, copper, zinc, and other micronutrients, and thus induce AD\[84].

Studies have shown the role of manganese in the diagnosis of AD. Manganese enhanced magnetic resonance imaging can be used to assess the level of pathological Tau accumulation\[85]. Treatment with Manganese chelating agents may play a role in neurodegenerative diseases such as AD, providing a new strategy for the clinical treatment of AD\[86].

AD is associated with a decline in learning and memory. Use of naringin reduces amyloid accumulation, a manganese-induced form of AD in rats. It is suggested that naringin has a neuroprotective effect, which is closely related to the anti-oxidant, anti-inflammatory and anti-amyloid degeneration effect of naringin\[87]. Manganese-rich nanocapsules were shown to improve cognitive ability in animal models with AD, which is related to the decrease of Tau protein in animal brain tissue\[88].

**AD and arsenic**

Arsenic is an essential micronutrient of the body. It is widely found in nature in the form of Ash, black, and yellow arsenic. Arsenic is highly toxic, but in small amounts it is beneficial. Arsenic participates in biotransformation, protein synthesis, and material metabolism.

Sodium arsenite (1–10 mol/L) was shown to increase Tau phosphorylation and promote the formation of neurofibrils in human neuroblastoma SH-SYSY cells, which are used to study AD. This effect was related to the activation of Erk Pathway by sodium arsenite\[89].

Animal studies have shown that arsenic in drinking water can cause abnormal circadian rhythm and movement behavior in mice with AD, as well as accumulation of amyloid proteins in the frontal cortex and hippocampus. This was found to be related to arsenic-induced lipid peroxidation in mice\[90]. Sodium arsenite was shown to cause behavioral disorders and memory change in male rats with AD, which was alleviated by gallic acid (100 mg/kg); this indicated the neuroprotective effect of gallic acid\[91].

In a clinical study, arsenic levels were measured in the nails and hair of 40 individuals with AD using inductively coupled plasma mass spectrometry. Arsenic levels in AD were higher than those in controls. This implies that individuals with AD often have elevated levels of arsenic\[92].

**Alzheimer’s and vitamin D**

Vitamin D is an antioxidant hormone. There is a close linkage between vitamin D, human microbiome, and the immune system. Vitamin D can regulate innate and adaptive immune responses\[93].

Vitamin D enhances the immune function and may delay aging; thus, it may play a role in the treatment of AD\[94].

The key findings of the aforementioned micronutrients related to AD are summarized in Table 1.

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**CONCLUSION**

AD is the most common type of dementia with an elusive etiology. An increasing number of studies have explored the effects of micronutrients on the pathogenesis and development of AD\[95]. Abnormal copper homeostasis plays an essential role in the development of many neurodegenerative diseases, including AD\[14]. Zinc status affects the progression of AD, as evidenced by cognitive decline observed under conditions of zinc deficiency\[32]. Excessive iron contributes to the deposition of β-amyloid and the formation of neurofibrillary tangles in AD, as well as other neurodegenerative diseases\[96]. Selenium may have a protective role against the development of AD\[97]. Silicon may lower the risk of AD by protecting against accumulation of toxic substances in the brain\[98]. Manganese is critical for neurodevelopment but has also been implicated in the pathophysiology of several neurological diseases, including AD\[99]. Chronic manganese exposure increases the risk of amyloid plaques and the development of AD\[100]. Increased level of arsenic was shown to be associated with brain damage and neurobehavioral changes, which may exacerbate AD symptoms\[90]. Vitamin D and its receptors are fundamentally involved in neurodegenerative mechanisms and vitamin D deficiency is recognized as a risk factor for AD\[101]. Collectively, these findings suggest that aberrant homeostasis of these micronutrients is a key contributor to AD progression.
## Table 1 Roles of different micronutrients in Alzheimer's disease

<table>
<thead>
<tr>
<th>Micronutrient</th>
<th>Key findings related to AD</th>
</tr>
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| Copper        | Plaques of neurofibrillary tangle, amyloid, and soluble oligomers have large amounts of copper at their core[^18^]  
AD patients have significantly higher levels of copper in brain tissues[^19^-^21^]  
Copper promotes neurofibrillary tangle of hyperphosphorylation Tau and oxidative stress[^22^]  
Copper is useful marker for the diagnostic and prevention of AD[^27^] |
| Zinc          | Zinc and selenium or iron and zinc have been concomitantly used to treat AD[^35^-^36^]  
Combination of zinc and copper accelerates the formation of amorphous aggregates of amyloid protein[^40^]  
High saturation magnetization of zinc ferrite improves the formation of amorphous aggregates of amyloid protein[^41^]  
Zinc increases the expression of amyloid precursor protein in a mouse model of AD[^43^]  
Zinc deficiency leads to a decrease in the learning ability and memory of AD mice[^51^] |
| Iron          | Markedly increased concentration of ferritin and hemosiderin aggregates in the brain tissues of patients with severe AD[^55^]  
Iron dysregulation in brain neurons plays a key role in AD[^57^]  
Iron deposition increases Tau levels in brain tissue and promotes neurofibrillary Tangle Tau formation[^10^-^59^]  
Iron accelerates the deposition of amyloid proteins in brain tissues[^60^]  
Iron oxide nanoparticles have been used in clinical studies to improve AD[^68^] |
| Selenium      | Chondroitin sulfate selenium improves spatial learning and memory impairment in mice with AD[^75^]  
The combination of nano-selenium and stem cells increases the levels of brain-derived neurotrophic factor and reduces amyloid deposition in AD mice[^77^]  
Selenium ameliorates the decrease of cognitive ability[^78^-^79^] |
| Silicon       | Silicon may lower the risk of AD[^82^]  
The unique cross-linking ability of soluble silicic acid and its antagonism to toxic aluminum may protect against AD[^83^] |
| Manganese     | Excessive intake of manganese can affect the structure and function of astrocytes, as well as the synthesis and degradation of glutamate. Effective control of manganese neurotoxicity may be a potential strategy for preventing or slowing AD[^88^]  
Abnormal conformation of prion proteins in normal cells can lead to their transformation into pathogenic prion proteins, which can bind to manganese, copper, and zinc, and thus induce AD[^89^]  
Manganese-rich nanocapsules improve cognitive ability in animal models with AD[^93^] |
| Arsenic       | Sodium arsenite increases Tau phosphorylation and promotes the formation of neurofibrils in human neuroblastoma cells[^94^]  
Presence of arsenic in drinking water induces accumulation of amyloid proteins in the frontal cortex and hippocampus of AD mice[^95^]  
Sodium arsenite causes behavioral disorders and memory change in male AD rats[^96^]  
The levels of arsenic in the nails and hair of AD patients were higher than that in healthy controls[^97^] |
| Vitamin D     | Vitamin D regulates innate and adaptive immune responses, which may play a role in the development of AD[^98^]  
Vitamin D enhances the immune function and may delay aging; thus, it may be used in AD treatment[^99^] |

AD: Alzheimer’s disease.

Some limitations of this review warrant mention. First, this is a narrative review, which lacks predetermined research question or specific search strategy. Future studies with a systemic design and a specified protocol are required for a more in-depth characterization of the roles of these micronutrients in AD. Secondly, the animals studies included in this review only used rodent AD models. The results from other animal AD models should be taken into account in future analysis.

In conclusion, this review summarizes the recent findings on the relationships between AD and micronutrients, which may provide a new perspective and direction for future scientific research, development of new drugs, and preventive measures against AD. Although significant advances have been made in characterizing the relationships between AD and these micronutrients, further studies are required to provide more robust evidence.
FOOTNOTES

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Fei HX et al. Role of micronutrients in AD


Application of imaging techniques in pancreaticobiliary maljunction

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Abstract

Imaging techniques are useful tools in the diagnosis and treatment of pancreaticobiliary maljunction (PBM). PBM is a precancerous lesion often relative to the disease of the pancreas and biliary tract, for example, cholecystolithiasis, protein plugs, and pancreatitis. For patients with PBM, early diagnosis and timely treatment are highly important, which is largely dependent on imaging techniques. The continuous development of imaging techniques, including endoscopic retrograde cholangiopancreatography, magnetic resonance cholangiopancreatography, computed tomography, ultrasound, and intraoperative cholangiography, has provided appropriate diagnostic and therapeutic tools for PBM. Imaging techniques, including non-invasive and invasive, have distinct advantages and disadvantages. The purpose of this paper is to review the application of various imaging techniques in the diagnosis and treatment of PBM.

Key Words: Pancreaticobiliary maljunction; Endoscopic retrograde cholangiopancreatography; Magnetic resonance cholangiopancreatography; Ultrasound; Computed tomography; Intraoperative cholangiography

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Core Tip: Pancreaticobiliary maljunction (PBM) is a congenital structural abnormality, which is one of the risk factors for many pancreaticobiliary diseases such as cholangitis, pancreatitis, cholangiocarcinoma, and gallbladder cancer. Early diagnosis of PBM is a procedure to improve the prognosis of PBM, which is closely related to the development of various imaging techniques. Imaging techniques can achieve the purpose of early diagnosis and timely treatment, which highlights the significance of imaging techniques.

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INTRODUCTION
Pancreaticobiliary maljunction (PBM) was first recorded in the early 20th century, and officially named in 1969, which is referred to as congenital malfunctional[1]. The main anatomical feature of PBM is that the bile duct and pancreatic duct join out of the duodenal wall, forming a lengthy common duct (Figure 1)[2,3], often combined with sphincter of Oddi dysplasia. As a result, the pancreatic duct and bile duct lose control, causing reflux[4]. Due to this anatomical abnormality, PBM is often associated with certain diseases, such as cholelithiasis, cholangitis, pancreatitis, and increased risk of cholangiocarcinoma[5]. PBM is often reported in Asian countries and is one of the main reasons for biliary tract cancer. In PBM patients, the pressure in the pancreatic duct is usually higher than that in the bile duct. Pancreatic juice often flows back to the bile duct[6] and mixes with bile to produce cytotoxic substances, such as lysophosphatidic acids. Due to the persistent pancreatic juice reflux to the bile duct, the mucosa of the bile duct and gallbladder is continuously damaged. The repeated repair and damage process of the biliary tract and gallbladder mucosa is related to DNA mutation, thus contributing to various gene mutations. This results in histological variety, for instance, hyperplasia, metaplasia, and dysplasia, and finally leads to biliary and gallbladder carcinogenesis. Kamisawa et al[7] reported that prevalence of biliary tract cancer is 21.6%–42.4% among adult PBM patients[8]. The theory of the hyperplasia-dysplasia-carcinoma sequence seems to explain the carcinogenesis of PBM[9]. This is different from the general principle of carcinogenesis that arises from the adenoma-carcinoma sequence. Rungsupakulkitj et al[10] set forth that there is evidence that gene mutations are accompanied with carcinogenesis, such as in the K-ras and p53 genes, which are involved in the carcinogenesis of gallbladder cancer in this condition. Thus, patients with PBM have higher rates of stones and tumors within the biliary tract and gallbladder [11]. The characteristic of pathological change seen in PBM patients is epithelial hyperplasia of the gallbladder and biliary tract due to long-standing continuous stasis of the bile intermixed with refluxed pancreatic juice. In summary, PBM is greatly associated with pancreatic biliary disease[12]. The early diagnosis of PBM is very important. The treatment of choice for PBM is prophylactic surgery before malignant changes can take place, which is heavily dependent on imaging techniques. Endoscopic retrograde cholangiopancreatography (ERCP) is the most effective way to detect PBM, which could show the connection structure clearly. On ERCP, there is communication between the pancreas and the bile duct despite the contraction of the sphincter, and therefore PBM is diagnosed. Magnetic resonance cholangiopancreatography (MRCP) and computed tomography (CT) can diagnose PBM, based on findings of an abnormal combination between the common bile duct (CBD) and the pancreatic duct, in addition to a long common channel. Thickening of the gallbladder wall and expansion of the bile duct on conventional ultrasound (US) are clues to the diagnosis of PBM. Intraoperative cholangiography (IOC) is used during surgery to observe the anatomy of the pancreaticobiliary system and the function of Oddi sphincter, which therefore has great value in both diagnosis and treatment. For patients with PBM, early diagnosis and timely treatment are highly important, which are largely dependent on imaging techniques. The following imaging features can be used for the diagnosis of PBM: Abnormal long pancreatic bile duct confluence common channel and a morphological anomaly of the confluence [13]. In this paper, we review the current literature about imaging techniques for PBM, in order to help clinicians make early diagnosis and timely treatment of the disease.

DIAGNOSTIC IMAGING TECHNIQUES

ERCP
ERCP is the most effective way to detect PBM, which could show the connection structure clearly. ERCP has been widely applied for the diagnosis of biliary and pancreatic diseases. On ERCP, there is communication between the pancreas and the bile duct despite the contraction of the sphincter, by
MRCP is a noninvasive and low-risk cholangiopancreatography technique, which is widely used in the diagnosis of pancreatic and biliary abnormalities. It was rapidly applied in clinical trials in the 1990s. MRCP can reliably measure the length of the pancreaticobiliary channel\cite{15, 14}. For MRCP, half Fourier acquisition single shot turbo spin echo was used with multilayer thin coronal and axial T2-weighted imaging [repetition time (TR): 1200 ms; echo time (TE): 80 ms; slice thickness: 4 mm]. Oblique thick slabs were acquired in the planes of the CBD and pancreatic duct. For multi-angle imaging, TR was 4500 ms, TE 950 ms, and slice thickness 60 mm. It provides high-resolution three-dimensional images of the CBD and pancreatic duct at multiple locations and angles. MRCP can clearly show the pancreaticobiliary junction. Compared with other imaging techniques (such as US and CT), MRCP can better display the unexpanded pancreatic duct in PBM with common channel protein plug in the case of unclear body and tail of the pancreas. MRCP should be performed on individuals who show gallbladder wall thickening in patients with PBM. Before ERCP, all patients underwent initial tests, including trypsin test, liver function test, US, and MRCP to preliminarily evaluate the basic condition of the patients\cite{16}. If MRCP or US indicates some diseases, such as biliary pancreatitis, obstructive jaundice, cholangitis, CBD dilatation, bile duct stones, or pancreatic obstruction, these diseases will increase the risk of surgery. Therefore, doctors and patients can consider ERCP\cite{16}. Before surgery, ERCP can improve drainage, solve complications, and allow subsequent safe surgery. Post-ERCP pancreatitis was the main complication that was considered\cite{17-19}. Zeng et al\cite{16} reported that it was diagnosed according to the following criteria: Presence of pancreatic pain persisting for at least 24 h and serum amylase level at least 3 times higher than the normal level after ERCP. Weng et al\cite{20} set forth that it is worrisome that ERCP could yield false positive findings (5.35%), with a specificity of 94.65%, when the contrast does not fill the CBD. During ERCP operation, bile can be extracted by fine needle to detect the amylase level in bile. If the bile amylase level is higher than the upper limit of serum amylase, PBR can be suspected after excluding some cases, such as enterobiliary reflux. Enterobiliary reflux (flow of pancreatic juice into the biliary tract) usually occurs in patients with PBM. For these patients, further examination and verification are needed. ERCP is often used as the golden standard for the diagnosis of PBM, but requires anesthesia. For some patients, the procedure is difficult. In addition, Paris et al\cite{21} reported that the incidence of complications after ERCP in children was as high as 13.5%, thus demonstrating a certain risk of complications, for example, pancreatitis and bleeding\cite{22}. The characteristics of invasive examination and postoperative complications mean that we should carefully consider ERCP as a diagnostic examination.

**MRCP**

MRCP is a noninvasive and low-risk cholangiopancreatography technique, which is widely used in the diagnosis of pancreatic and biliary abnormalities. It was rapidly applied in clinical trials in the 1990s. MRCP can reliably measure the length of the pancreaticobiliary channel\cite{23}. For MRCP, half Fourier acquisition single shot turbo spin echo was used with multilayer thin coronal and axial T2-weighted imaging [repetition time (TR): 1200 ms; echo time (TE): 80 ms; slice thickness: 4 mm]. Oblique thick slabs were acquired in the planes of the CBD and pancreatic duct. For multi-angle imaging, TR was 4500 ms, TE 950 ms, and slice thickness 60 mm. It provides high-resolution three-dimensional images of the CBD and pancreatic duct at multiple locations and angles. MRCP can clearly show the pancreaticobiliary junction. Compared with other imaging techniques (such as US and CT), MRCP can better display the unexpanded pancreatic duct in PBM with common channel protein plug in the case of unclear body and tail of the pancreas. MRCP should be performed on individuals who show gallbladder wall thickening on US for further examination, in order to detect PBM without bile duct dilatation early before the onset of gallbladder cancer. Sometimes, measuring the common channel is difficult to achieve, either because it is too narrow or because the CBD prevents the connection with the pancreatic duct from being evaluated. In addition, in patients with cholangitis, motion artifacts will reduce the imaging quality. Some researchers found that lemon/orange juice can improve the view of the pancreatic duct. When secretin stimulates pancreatic exocrine secretion, dynamic MRCP can observe the backflow of pancreatic juice into the bile duct. Diagnostic accuracy can be upgraded with tridimensional MRCP or dynamic MRCP with secretin stimulation. For common short channels, such as infant PBM imaging, the effect of
ordinary MRCP is not as good as that of ERCP, and there are image quality defects such as motion artifacts. The disadvantages of MRCP are the potentially poor definition of the pancreatic duct branch and peripheral biliary tree and the inherent poor spatial resolution compared with ERCP. In some cases, the display of the pancreatic body and tail is not satisfactory[24]. The accuracy of diagnostic MRCP can be increased through using 3D or dynamic MRCP with secretin stimulation. An overwhelming amount of evidence shows that the information provided by MRCP is almost equivalent to that by ERCP. To some extent, MRCP can be used as an image alternative to ERCP. Compared with invasive ERCP, this is a non-invasive imaging technique. When the pancreatic duct and bile duct merge in the duodenal wall to form an abnormally long common channel, the diagnosis of PBM can be made (Figure 3). In a way, this imaging technique allows ducts to be visualized, although the ducts are as narrow as 1 mm in diameter. It also proved to provide other findings not found on ERCP, and the consistency with ERCP was 81%. MRCP allows for a detailed visualization of the CBD and PBM, with detection rates of PBM between 82% and 100%[25]. MRCP plays key role in the early relative accuracy diagnosis and preventive treatment of pancreaticobiliary diseases. Overall, MRCP, as a non-invasive method, has become the first choice for the diagnosis of pancreaticobiliary diseases. This technique has certain limitations, high price, and limited availability, and is related to the subjectivity of long-time exploration and imaging interpretation due to its dependence on operators. Compared with ERCP, MRCP has limitations in the diagnosis of PBM, even if pancreatin is used. However, for diagnosing patients with anatomical maljunction, ERCP remains the gold standard. When ERCP is used as the reference standard, the detectability rate of MRCP for this anomaly has been reported to be 82%[26].

**US**

As a safe, rapid, accurate, and economical routine examination tool, US can be used to detect gallbladder wall thickening and intrahepatic extrahepatic bile duct dilatation (Figure 4A and B). In addition, it also can show pancreatic duct dilatation and other features for the diagnosis of pancreatitis. Although US can observe common pancreaticobiliary channels, this method is limited because it cannot provide accurate measurement of common channels because the coronal plane is not visible. PBM patients without biliary dilatation rarely have some symptoms such as acute abdominal pain and vomiting hyperamylasemia, hyperbilirubinemia, and abnormal liver function (ASD), so most patients are not diagnosed before advanced gallbladder cancer. Kamisawa et al[27] reported that gallbladder wall thickening is a diagnostic clue for PBM patients without bile duct dilatation. US can detect gallbladder wall thickening and bile duct dilatation, so US plays a key role in the pre-diagnosis of PBM. Although gallbladder wall thickening has its own limitations, it is a key factor of PBM. Patients need further examinations, such as MRCP, CT, ERCP, and IOC, to further clarify. In most cases, US is often used as a screening modality. We did not find the literature describing the detection rate of PBM by ultrasound. Endoscopic ultrasound (EUS) is useful for obtaining high-resolution images of pancreaticobiliary diseases. In the normal gallbladder wall, EUS shows a two layered structure consisting of an inner hypoechoic layer composed of the mucosa and the muscular layer, and an outer hyperechoic layer
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Figure 3 Magnetic resonance cholangiopancreatography. Coronal 4 mm-thick half fourier acquisition single shot turbo spin echo image shows the pancreatic duct joining the common bile duct outside the duodenal wall[24]. Citation: Guo WL, Huang SG, Wang J, Sheng M, Fang L. Imaging findings in 75 pediatric patients with pancreaticobiliary maljunction: a retrospective case study. Pediatr Surg Int 2012; 28: 983-988. Copyright © The Authors 2022. Published by Springer Nature Switzerland AG.

Figure 4 Ultrasound imaging and endoscopic ultrasound. A: Ultrasound showing a thick-walled gallbladder and intraluminal mass (arrow); B: Ultrasound showing intrahepatic bile duct dilation[10]. Citation: Rungsakulkij N, Boonsakan P. Synchronous gallbladder and pancreatic cancer associated with pancreaticobiliary maljunction. World J Gastroenterol 2014; 20: 14500-14504. Copyright © The Authors 2022. Published by Baishideng Publishing Group Inc; C: The confluence of pancreatic duct and bile duct in the proximal portion of the duodenal wall[19]. Citation: Kamisawa T, Takuma K, Itokawa F, Itoi T. Endoscopic diagnosis of pancreaticobiliary maljunction. World J Gastrointest Endosc 2011; 3: 1-5. Copyright © The Authors 2022. Published by Baishideng Publishing Group Inc.

composed of the subserosal layer and the serosa. On EUS, the gallbladder wall of PBM patients showed two layers of thickening, showing epithelial hyperplasia and subserosal fibrosis, or three layers of thickening, one of which was medium and low echo layer, showing hypertrophic muscle layer. In PBM, EUS can detect the confluence of the pancreatic duct and bile duct in the proximal portion of the duodenal wall, the so-called common channel (Figure 4C)[28]. However, it is not a routine test, because it requires dedicated endoscopes (e.g., endoscopes for radial and linear EUS). The imaging capability of EUS is generally good, but the technique of EUS imaging is sometimes difficult, and the diagnostic performance of EUS is operator-dependent. In fact, several investigators have reported that EUS could confirm the PBM in 4 (2.9%) of 137 patients who underwent screening US[28]. When ERCP is used as the reference standard, the detectability rate of EUS for this anomaly has been reported to be 88%. Intraductal ultrasonography (IDUS) during ERCP is highly helpful to describe pancreaticobiliary confluence. However, IDUS also has its own limitations, such as weak penetration and poor operability in exploring narrow biliary tract[29]. Increasing the number of ultrasonic examinations is also necessary to facilitate the early diagnosis of pancreaticobiliary diseases. Because most PBM patients without biliary dilatation are not easy to find in the early stage and are in a bad situation once found, a new method for early diagnosis and treatment of PBM should be developed to improve the prognosis. Despite its own limitations, US can raise questions as soon as possible and suggests us to make further
diagnosis. Compared with other imaging methods, US has its unique advantages: Noninvasiveness, no radiation, and moderate price. Compared with other imaging techniques, it uses a more comprehensive method to screen all patients with recognized PBM risk factors because it is fast, flexible, and easy to operate[30].

CT
CT has a higher resolution even than MRCP. CT is widely used in pancreaticobiliary diseases. Traditional examination can observe the relationship between the size of lesion area and surrounding tissues, and further formulate the operation plan. The thickening of the gallbladder wall on US can be used as an indication for further examination of CT. Wall thickening at the stricture site may suggest malignancy because primary ductal stricture lacks wall thickening. Enhanced CT has been strengthened in the diagnosis and treatment of irregular biliary nodules. Postoperative follow-up screening and canceration monitoring have certain value. Because of its own characteristics, CT is more used for the differentiation of pancreaticobiliary diseases than used for PBM. Conventional CT scan is axial scanning, which cannot show the overall shape and cavity of the biliary tract, so it is not satisfied with the observation of the biliary system[31]. Some researchers reported that it is difficult to accurately measure the length of the common channel on CT due to the following reasons: First, the whole process of the common channel is not visible on CT, because in many cases, the common channel part is involved by the area showing less contrast enhancement between the pancreatic head and duodenum. Second, in some cases, the whole process of common channel is not described on the single-layer multiplane reconstructed (MPR) image. Third, public channels are tortuous in some cases. Recent advances in spiral CT techniques, such as multi-detector and sub-second rotation, make it possible to scan the pancreas and pancreas biliary system with a collimation of 1.25 mm and less. This will lead to further improvements, in the mass of multi-plane reformatting (multiplanar reconstruction) due to the high-resolution and MPR images on the z-axis enable us to select the best section to evaluate the pancreas and bile duct and their function confluence. By using high-resolution MPR images, Modified Discrete Cosine Transform (MDCT) allows us to diagnose abnormal pancreaticobiliary connections according to the relationship between catheter confluence and pancreatic parenchyma (Figure 5). The sensitivity of MPR images of MDCT in the diagnosis of abnormal pancreaticobiliary confluence was 78% [32]. It has been reported that perfusion cholangiography spiral CT (spiral CT during drip cholangiography; DIC-CT) is used in the diagnosis of PBM[33]. High resolution images were obtained by intravenous hepatobiliary drugs (lipperamide meglumine) and three-dimensional CT. Pancreaticobiliary cholangiome. Flux of pancreatic and bidirectional reflux of bile and common channel. Due clearly to the necessity to exposure to ionizing radiation, this technique has not been widely used in patients. Another major drawback of DIC-CT is that injection of contrast agents (meglumine iodoacetate) may produce adverse reactions, which occur in 0.8%-3.4% of patients, although the main symptom is rash and usually does not need treatment[34]. At present, it is only used as a second-line diagnostic tool for PBM.

IOC
IOC has become an indispensable technique in hepatobiliary surgery, which provides an intuitive understanding of the anatomy of the biliary system, especially suitable for judging bile duct stenosis, stones and protein embolism, and can safely guide the operation in real time[34]. During the operation, IOC was used to observe the anatomical structure of the pancreaticobiliary system and the function of Oddi sphincter. The diagnosis of PBM can be determined according to the cholangiography results (Figure 6). It can also be used to evaluate the patency of the distal bile duct. IOC is usually divided into intraoperative total cholangiography (ITCP) and intraoperative selective pancreatography (ISCP). The method of IOC is chosen according to the patient’s condition and the degree of disease development. If the total bile duct cist is huge, the duodenum is displaced forward. Using ITCP contrast is not easy to show the distal end of the bile duct and bile and pancreatic duct confluence[35]. ITCP can display the intrahepatic and external bile duct and the pancreatic duct, to understand the pathological morphology of all the biliary ducts and pancreatic ducts. ISCP is suitable to focus on the distal intrahepatic or extrahepatic biliary tract and the pancreatic duct. Intraoperative biliary structure shadow combined with preoperative MRCP can reduce the image occlusion of large cyst and is conducive to the imaging of PBM patients with proximal total bile duct stenosis. IOC is a diagnostic and therapeutic method with surgical and anesthetic risks. During IOC, due to the increased pressure in the bile duct, this technique can lead to slight dilatation of the bile duct, which is similar to ERCP[36]. The clinical application of IOC faces several challenges. These challenges include the need for detailed anatomical understanding before IOC, which may be technically difficult (in acute or chronic inflammatory diseases), the need to insert short, thin, or curved cystic duct, and the risk of avulsion when inserting inflammatory cystic duct. In addition, intraoperative cholangiography has some disadvantages, such as being time-consuming, the need for additional equipment and technicians, the risk of radiation exposure to staff and patients, and the need to inject contrast agent into the bile duct, which may increase the risk of bile duct injury[37,38]. Compared with traditional ERCP, MRCP, US, CT, and other imaging techniques, IOC has the advantages of intraoperative navigation, high sensitivity, simple operation, and low price[39]. We firmly believe that this imaging technique provides a new source of real-time anatomical information for hepatobiliary surgery[40]. Intravenous injection of indocyanine
**Figure 5 Computed tomography.** Coronal images generated from pancreatic phase scanning show that the pancreatic and biliary ducts join within pancreatic parenchyma. Furthermore, these images make it possible to visualize common channel (arrowhead) and ventral pancreatic duct (thin arrows), which is narrow and tortuous. Thick arrows indicate dorsal pancreatic duct.[51]. Citation: Itoh S, Fukushima H, Takada A, Suzuki K, Satake H, Ishigaki T. Assessment of anomalous pancreaticobiliary ductal junction with high-resolution multiplanar reformatted images in MDCT. *AJR Am J Roentgenol* 2006; 187: 668-675. Copyright © The Authors 2022. Published by American Roentgen Ray Society.

**Figure 6 Intraoperative cholangiography.** Intraoperative cholangiography shows the junction of the bile and pancreatic ducts located outside the duodenal wall. The common bile duct joins the pancreatic duct.[24]. Citation: Guo WL, Huang SG, Wang J, Sheng M, Fang L. Imaging findings in 75 pediatric patients with pancreaticobiliary maljunction: a retrospective case study. *Pediatr Surg Int* 2012; 28: 983-988. Copyright © The Authors 2022. Published by Springer Nature Switzerland AG.

green (ICG) has potential advantages over conventional radiographic cholangiography in saving time and avoiding bile duct injury associated with the catheterization required for injection of contrast materials.[41,42]. ICG fluorescence imaging has been gradually applied to hepatobiliary surgery, and there are no relevant reports on the application of ICG fluorescence imaging to PBM-related diseases. We can boldly imagine that fluorescence imaging technique will also be suitable for pancreatic bile system anatomy in the near future. We searched the literature for intraoperative cholangiography. Most of the literature was related to endoscopic cholecystectomy, and few were related to PBM. Therefore, the accuracy of intraoperative cholangiography in the diagnosis of PBM could not be retrieved.

**TREATMENT OF PBM**

PBM can be divided into PBM with biliary dilatation and PBM without.[43]. It is agreed that preventive surgery should be performed on PBM patients as soon as possible after diagnosis.[44]. For bile duct
dilatory PBM, current cholecystectomy, extrahepatic cholecystectomy, and hepatic tube-jejunal Roux-en-Y reconstruction is the standard surgical modality. New complications may also occur later, such as narrow anastomosis, reflux cholangitis, intra-hepatic duct stones, and bile duct tumors. There are some PBM patients with obstructive jaundice or acute pancreatitis or other diseases.[45,46]. The operation of these patients is considered to increase the postoperative risk. With the continuous progress of imaging techniques, ERCP is not only the standard technique for diagnosing PBM, but also used to improve drainage and solve complications[47,48]. ERCP is also an effective therapeutic option for patients with PBM. ERCP can improve drainage, solve complications, and allow subsequent safe surgery. The indications for ERCP (one case may involve one or more indications) are pancreatitis, pancreaticobiliary calculli, biliary obstruction, and stent displacement. Endoscopic treatments for PBM primarily include endoscopic sphincteropapillotomy (EST), stent insertion, and endoscopic nasobiliary drainage (ENBD)/endoscopic nasal and pancreatic duct drainage (ENPD). If pancreaticobiliary stones or protein plugs are detected, stone removal treatment is required. ERCP needs to be performed under general anesthesia. Two experienced endoscopists intubate the trachea in the prone position and use duodenoscopy. After successful intubation of the CBD, 10 mL of bile samples are taken to measure bile amylase (PBM is indicated when bile amylase level is higher than the upper limit of serum amylase level). EST can help bile and pancreatic juice flow into the duodenum regularly. Endoscopic hemostatic clip is also used to treat high-risk patients with bleeding after EST. Endoscopic papillary balloon dilatation is used if there are large CBD stones. Finally, ENBD/ENPD or endoscopic retrograde cholangiopancreatic drainage is performed when necessary to prevent complications. Jin et al[46] reported that the total effective rate of ERCP in the treatment of PBM was 60.7% (34/56). It is useful to plan the timing and choice of the appropriate surgical procedure.

For PBM patients without biliary dilatation, prophylactic cholecystectomy is recommended to prevent gallbladder cancer. Nevertheless, the risk of developing cancer in the remnant biliary tract is still high, so careful follow-up is needed for such patients in the future. During laparoscopic cholecystectomy, in order to perform accurate resection and prevent bile duct and vascular injury, it is necessary to understand the anatomy of the bile duct and vessels[49]. Laparoscopic ultrasound (LUS) during cholecystectomy allows minimal invasive study of the biliary tract and has excellent ability to identify anatomical structures. LUS, which is cheap, fast and non-irradiated, can be repeated as needed during laparoscopic surgery. Adjacent organs can also be explored[49]. LUS can be a valuable adjunct and can be performed before dissection, and repeated as needed to guide the surgeon. LUS can be performed before Calot’s triangle dissection, which facilitates the mapping of biliary and hilar structures during difficult scenarios such as severe inflammation and fibrosis. Conventional abdominal ultrasound and CT examination are usually performed before operation to provide a reference for operation. To some extent, imaging techniques is also of great value in the treatment of PBM. With the continuous progress of imaging techniques, the relationship between diagnosis and treatment of the disease is becoming closer and more inseparable. In the diagnosis and treatment of PBM, imaging techniques run through the whole process and play an important role in clinical practice.

CONCLUSION

In summary, the clinical features of PBM are atypical and usually characterized by pancreaticobiliary diseases. PBM is one of the pathogenic factors of pancreaticobiliary diseases such as cholangitis, pancreatitis, cholangiocarcinoma, and gallbladder cancer. Early diagnosis and timely treatment are very important. Early diagnosis of PBM can improve the prognosis of PBM, which is closely related to the development of various imaging techniques such as ERCP, MRCP, CT, US, and IOC. If imaging shows that the bile duct and pancreatic duct outside the duodenal wall are connected through a long common tube, a diagnosis of PBM can be made[50]. The imaging techniques mentioned in this paper (ERCP, MRCP, US, CT, and IOC) are valuable for the diagnosis and treatment of PBM patients. ERCP can be used as the gold standard for the diagnosis of PBM and can also be used to alleviate PBM related complications, but this technique is invasive and its application needs careful consideration. As a noninvasive imaging technique, MRCP can clearly show the junction of the pancreaticobiliary duct. It is the first choice for the diagnosis of PBM in most patients. US can be used to detect gallbladder wall thickening and congenital biliary dilatation, which can play a warning role and need further examination. CT has high resolution in the diagnosis of PBM. IOC provides an intuitive understanding of the anatomy of the biliary system and guides the operation in real time. Each imaging technique has its unique advantages and disadvantages. No paper has been found to report the official golden standard. So, further research is needed on golden diagnosing imaging techniques for PBM. Appropriate techniques should be chosen according to the actual situation to achieve the desired effect. The imaging techniques mentioned in this paper guide various diagnostic and treatment procedures, help surgeons accurately perform some surgical operation, and reduce the risk of intraoperative and postoperative complications. They can achieve complete and correct diagnosis and real staging, and help to establish an appropriate treatment attitude. We believe that the imaging technique with all the above characteristics is of great value in the diagnosis and treatment of PBM.
In conclusion, imaging techniques allow us to diagnose an anomalous pancreaticobiliary ductal junction on the basis of findings regarding the relationship between the duct confluence and the pancreatic parenchyma. The detection rates of ERCP, MRCP, EUS, and MDCT for PBM are 90%-100%, 82%-100%, 88%, and 78% [,], respectively. Various imaging techniques also play a great role in the treatment of PBM. In order to achieve the purpose of early diagnosis and timely treatment, imaging techniques for PBM should be used more and more clinically.

FOOTNOTES

Author contributions: Wang JY and Mu PY as the co-first authors contributed equally to this work; Wang JY reviewed and searched the literature, analyzed and interpreted the imaging findings, drafted the manuscript, and gave critical comments; Xu YK, Bai YY, and Shen DH gave critical comments and contributed equally to this work.

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Update on gut microbiota in gastrointestinal diseases

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Abstract

The human gut is a complex microbial ecosystem comprising approximately 100 trillion microbes collectively known as the “gut microbiota”. At a rough estimate, the human gut microbiome contains almost 3.3 million genes, which are about 150 times more than the total human genes present in the human genome. The vast amount of genetic information produces various enzymes and physiologically active substances. Thus, the gut microbiota contributes to the maintenance of host health; however, when healthy microbial composition is perturbed, a condition termed “dysbiosis”, the altered gut microbiota can trigger the development of various gastrointestinal diseases. The gut microbiota has consequently become an extremely important research area in gastroenterology. It is also expected that the results of research into the gut microbiota will be applied to the prevention and treatment of human gastrointestinal diseases. A randomized controlled trial conducted by a Dutch research group in 2013 showed the positive effect of fecal microbiota transplantation (FMT) on recurrent Clostridioides difficile infection (CDI). These findings have led to the development of treatments targeting the gut microbiota, such as probiotics and FMT for inflammatory bowel diseases (IBD) and other diseases. This review focuses on the association of the gut microbiota with human gastrointestinal diseases, including CDI, IBD, and irritable bowel syndrome. We also summarize the therapeutic options for targeting the altered gut microbiota, such as probiotics and FMT.

Key Words: Inflammatory bowel disease; Clostridioides difficile (Clostridium) infection; Irritable bowel syndrome; Probiotics; Fecal microbiota transplantation

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Core Tip: In this review, we discuss the gut microbiota in human gastrointestinal diseases, including *Clostridioides difficile* infection, inflammatory bowel disease, and irritable bowel syndrome. We review the role of the gut microbiota in human gastrointestinal diseases and the therapeutic options for manipulating it.


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INTRODUCTION

The human gastrointestinal system harbors approximately 100 trillion microorganisms, also known as the gut microbiota, whose collective genetic material comprises at least 100-fold more genetic diversity than the entire human genome[1]. The gut microbiota includes not only bacteria but also archaea, bacteriophages, fungi, and protozoa species. Recent advances in genomic techniques, including next generation sequencing, mediated metagenomics that rely on 16s rRNA gene amplification, and whole-genome sequencing, have helped us to more clearly understand important interactions, such as host-microbiota and microbe-microbe interactions[2]. The recent additions of artificial intelligence and deep learning to the field of research into the gut microbiota have enabled the rapid identification of thousands of microbes[3].

Recent studies have revealed that the gut microbiota is metabolically active and performs various functions, including those associated with nutrition, immune development, and host defense[4]. Therefore, the gut microbiota plays important roles in the maintenance of human health. A perturbation in the composition and function of the gut microbiota is known as dysbiosis[1,4] and accumulated evidence suggests that this condition is involved in the loss of beneficial microbial input or signaling and a colonization of pathogenic microbes. Dysbiosis is thought to trigger inflammatory effects and immune dysregulation associated with human disorders[5-9].

Fecal microbiota transplantation (FMT) is an emerging treatment intended to rebalance the disturbance by introducing feces from healthy donors to diseased individuals. After obtaining intestinal microbiota from an appropriate donor, the samples can be transplanted in a number of ways, including via colonoscopy, oro gastric tube, enema, or orally in the form of a capsule that contains the freeze-dried substance. FMT has been described in ancient medical literature, and in 4th century China, Ge Hong described the use of human fecal suspension by mouth for patients with severe diarrhea. In modern medicine, FMT was reported in 1958 for pseudomembranous colitis by Eiseman et al[10]. In 2013, the first randomized controlled clinical trial of FMT for recurrent *Clostridioides difficile* (C. difficile) infection (CDI) was reported[11]. FMT has entered the era of evidence-based medicine, attracting growing interest as a potential treatment for various gastrointestinal diseases, as well as metabolic and cardiovascular diseases.

Probiotics have been defined by an expert group as “live microorganisms, which when administered in adequate amounts, confer a health benefit on the host”[12]. There is an increasing body of evidence indicating that probiotics can be used in the treatment and prevention of infections and chronic inflammatory disorders of the gastrointestinal tract. However, the mechanisms of action of probiotics, which are diverse, heterogeneous, and strain specific, have received little attention. Most studies have mainly reported clinical effects, tolerance, and safety data but have not discussed potential mechanisms of action. Major probiotic mechanisms of action include enhancement of the epithelial barrier, increased adhesion to intestinal mucosa with concomitant inhibition of pathogen adhesion, competitive exclusion of pathogenic microorganisms, production of anti-microbial substances, and modulation of the immune system[12-14].

In addition to probiotics, other therapeutic interventions for modulating the gut microbiota include prebiotics and symbiotics. Prebiotics have been defined as a substrate that is selectively utilized by host microorganisms conferring a health benefit[15]. Prebiotics compounds stimulate growth, activate metabolism, and promote protection of bacteria that are beneficial to the host organisms. In the intestine, prebiotics selectively enhance the fermentation activity of certain groups of beneficial microbes, such as *Bifidobacterium* and *Lactobacillus* spp.[16]. Prebiotics exert beneficial effects via mucin production by providing fermentable compounds that contribute to a prevention of bacterial translocation. The production of metabolites, including folate, vitamins, and short chain fatty acids during their fermentation by gut microbiota shows antimicrobial activity and maintains a healthy gut barrier[12].

Symbiotics are a combination of prebiotics and probiotics that are believed to have a synergistic effect by inhibiting the growth of pathogenic bacteria and enhancing the growth of beneficial organisms[12]. Symbiotics are those products in which the prebiotic compound selectively favors the growth of...
probiotics and their metabolite production\[15,17\]. Symbiotic effects can occur in two ways: by improvement in the host’s health after ingestion of a mixture of prebiotics and probiotics strains or by the promotion of indigenous beneficial microbiota, such as \textit{Bifidobacteria} after ingestion of prebiotics alone\[15,17\]. Multiple mechanisms of prebiotics and synbiotics in controlling growth and infection of enteric bacterial pathogens have been proposed, but systematic studies are still needed to understand how predesign prebiotics and synbiotics can improve the human gut health and prevent diseases (Figure 1).

In this review, we summarize the recent findings regarding the role of the gut microbiota in gastrointestinal diseases, and therapeutic options for targeting it.

**CLOSTRIDIODES DIFFICILE INFECTION**

\textit{C. difficile} is a gram-positive, spore-forming anaerobic bacillus that has attracted attention as a cause of antibiotic-associated enteritis. \textit{C. difficile} was first reported to have been found in the feces of healthy newborns in 1935 and was subsequently reported in 1978 as the causative agent of antibiotic-associated pseudomembranous colitis\[18,19\]. Toxins A and B are important for the onset of CDI. In the United States, around 50,000 cases of CDI occur annually, of which about 20% relapse, with approximately 29,000 deaths\[20\]. The increased incidence, severity, and mortality of CDI have been largely attributed to the epidemic strain ribotype 027 (formerly referred to as NAP1/BI/027), which emerged in the early 2000s and has resulted in out-breaks\[20\]. This strain has high-level fluoroquinolone resistance and can produce substantially higher amounts of toxins A and B than other strains\[21,22\]. Moreover, it dramatically increases the severity with more incidence of septic shock, toxic megacolon, gut perforation, and death.

Recurrent CDI (rCDI) is usually defined as an episode of CDI occurring within 8 wk of a previous episode. The recurrence rate of CDI also continues to increase, thereby raising important clinical concerns. About 25% of patients who initially respond to antimicrobial therapy experience rCDI. A second recurrence rate of 40% has been reported among patients with resolved first recurrence\[20,23\]. Advanced age, use of antibiotics, severe underlying disease, chronic kidney disease, proton pump inhibitor exposure, prolonged hospital stays, and previous CDI have been recognized as risk factors\[23,24\].

There are two prerequisites for developing \textit{C. difficile} associated diarrhea: disruption of the normal gastrointestinal microbiota, causing diminished colonization resistance favoring \textit{C. difficile}, and acquisition of the organism from an exogenous source\[25\]. Prolonged antibiotic use is the main risk factor for the development of CDI. Antibiotic therapy causes alterations of the intestinal microbial composition, enabling \textit{C. difficile} colonization and consecutive toxin production leading to disruption of the colonic epithelial cells.

While antibiotics are still the treatment of choice for CDI, a new therapy targeting the gut microbiota called FMT has emerged in recent years\[26-28\]. FMT is the most direct and effective way of changing the patient’s intestinal bacterial composition. FMT is a procedure in which fecal matter, or stool, is collected from a tested donor, mixed with saline or another solution, strained and either placed in a bank or directly into a patient, by colonoscopy, endoscopy, nasogastric tube, or enema\[26\]. In 2013, a Dutch research group conducted a randomized controlled trial against rCDI and found that FMT was much more effective than antibiotics\[11\]. Because of these findings, FMT for gastrointestinal diseases has attracted worldwide attention\[27,29-33\] and several large randomized controlled trials (RCTs) and cohort studies have since been performed, all of which have shown the effectiveness of FMT for rCDI. Moreover, systematic reviews and meta-analyses targeting these studies have been reported\[29,34-39\].

All reports show the effectiveness of FMT for rCDI, but the methods of FMT vary from study to study. Differences in methodology include those involving donor selection, preparation of fecal material, clinical management, and fecal delivery. Systematic reviews and meta-analyses showed that lower gastrointestinal FMT delivery was more effective than the upper gastrointestinal FMT delivery\[34,35\]. Moreover, a systematic review showed that encapsulated FMT is as effective as FMT performed through the nonoral route\[38,40\]. Some systematic reviews and meta-analysis found that there was no difference between frozen FMT and fresh FMT\[34,40\]. Furthermore, FMT by multiple infusions could effectively and significantly improve the clinical diarrhea remission rate\[40\]. Collectively, these systematic reviews and meta-analyses indicated the use of FMT via colonoscopy or encapsulated FMT, and the use of fresh or frozen feces as being the best strategy for treatment of rCDI.

The American College of Gastroenterology guidelines recommend FMT for severe antibiotic-resistant CDI\[41\]. The guidelines published by the Infectious Disease Society of America and Society for Healthcare Epidemiology of America consider FMT to be an appropriate treatment for rCDI after standard antibiotic treatment\[42\].
Figure 1  Mechanism underlying the efficacy of probiotics, prebiotics, synbiotics, and fecal microbiota transplantation. Probiotics promote mucin production, production of bacteriocins, and short chain fatty acids (SCFAs), which are responsible for the inhibition of pathogens, inhibition of bacterial translocation, and inhibition of pathogens due to competition for receptors and nutrients. Prebiotics act as nourishment for beneficial bacteria in the commensal microbiota, including the production of SCFAs and antimicrobial peptide. Another mechanism by which prebiotics can inhibit pathogens is by interaction with an adhesion receptor, such as the lectin receptor, demonstrating an antiadhesive action. Synbiotics have mechanisms of action of both probiotics and prebiotics. Moreover, synbiotics have the advantage of generating a synergic effect, which promotes balance in the gut microbiota, increased immunomodulation, reduced bacterial translocation, and reduction of infections due to strong competition by probiotics against pathogens. Fecal microbiota transplantation (FMT) provides normalization or modification of intestinal microbiota composition and function. Improvement of diseases after FMT has been associated with changes in microbial community structure as well as restoration of microbial diversity, increase in secondary bile acid production, and niche exclusion by other bacteria.

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FEATURES OF THE GUT MICROBIOTA IN INFLAMMATORY BOWEL DISEASES

Inflammatory bowel diseases (IBD) are chronic inflammatory disorders of the gastrointestinal tract encompassing two main clinical entities: Crohn’s disease (CD) and ulcerative colitis (UC). Although the etiology of IBD remains unknown, it occurs in genetically susceptible individuals after an exaggerated immune response to a normal stimulus, such as food and the gut microbiota[43,44]. Recent studies have suggested that the gut microbiota plays an important role in the pathogenesis of IBD[4].

Many studies have compared the gut microbiota of patients with IBD and healthy individuals. In 2020, Pittayanon et al[45] systematically reviewed 48 studies comparing the gut microbiota of IBD patients and healthy individuals. In CD, Christensenellaceae (Firmicutes phylum), Coriobacteriaceae (Actinobacteria phylum), and Faecalibacterium prausnitzii (F. prausnitzii) were decreased, while Actinoyces, Veillonella and Escherichia coli (E. coli) were increased compared to healthy subjects. It was also reported that Eubacterium rectale and Akkermansia were decreased, and E. coli was increased in UC patients compared with healthy subjects. The diversity of gut microbiota was found to be reduced or not significantly different in IBD patients compared to healthy individuals.

Each study analyzed in the review reported that the gut microbiota of IBD patients and healthy individuals was different. However, it was pointed out that the results of the reviewed studies were inconsistent. One of the most common findings in each of the studies was a decrease in α-diversity compared to healthy individuals and a decrease in F. prausnitzii in CD patients and UC patients. F. prausnitzii is known as a butyrate-producing bacteria and is thought to contribute to anti-inflammatory properties in CD by inhibiting the NF-κB pathway in the intestinal epithelium[46]. In addition, Christensenellaceae, which has been reported to be reduced in CD patients compared to healthy subjects, belongs to the Firmicutes phylum and is a butyrate-producing bacteria like F. prausnitzii[46]. In the Pittayanon et al[45] review, it was reported that Akkermansia was decreased in UC patients, but it is unclear whether it is the cause or a secondary change due to the pathology of UC patients. Previous studies have reported that Akkermansia acts as an anti-inflammatory in colitis, while the energy source of Akkermansia is reduced in UC patients, indicating that Akkermansia accompanies a decrease in mucus. It is noted that the decrease of Akkermansia is a secondary result consequent to the decrease of mucus in UC patients[47]. E. rectale, which is also a major butyrate-producing bacterium, is reduced in UC
patients compared to healthy individuals[48]. Collectively, the gut microbiota of IBD patients is characterized by a decrease in butyrate-producing bacteria compared to healthy subjects.

*Coriobacteriaceae* (Actinobacteria phylum) belong to the same family as *Collinsella*, *Eggerthella*, *Sloackia*, and *Atopobium*. Bile acids have been reported to play an important role in the pathology of IBD, but these bacteria are said to have the ability to convert bile acids, and *Coriobacteriaceae* also have the same function[49]. It is suggested that they may contribute to the pathogenesis of IBD. One of the most common results is an increase in *Escherichia*, especially *E. coli* belonging to the family *Enterobacteriaceae*, which has been suggested to be harmful in IBD. Among *E. coli*, adherent-invasive *E. coli* is known to increase in the ileal mucosa of CD, and inflammation is caused by adhering to and invading the intestinal epithelium[50]. This suggests that an increase in *Escherichia* may be involved in the chronic inflammation of IBD.

As mentioned above, various alterations of the gut microbiota have been reported in patients with IBD. Most studies have demonstrated the reduced diversity of the gut microbiota in IBD patients. However, results related to some bacterial species, such as *Bacteroides*, *Bifidobacteria*, and *E. coli*, vary among studies. These inconsistencies in results may be caused by various factors: (1) The ratio of the number of patients with CD and UC; (2) Disease activity (active or quiescent); (3) Disease activity of sampling location (inflammatory or noninflammatory site); (4) The analysis method of gut microbiota; (5) Medication.

For future studies of the gut microbiota with IBD patients, it is necessary to define which research method is the most appropriate, and to use the same method (including sample storage, DNA extraction, sequencing, and analysis methods) among studies to produce consistent results.

**EFFECTS OF PROBIOTICS ON IBD**

Probiotics are defined as living microorganisms which, when administrated in adequate amounts, confer a health benefit on the host[12]. The concept of probiotics was initially suggested in 1908 by Elie Metchinkoff, a Russian Nobel Laureate who observed that consumption of fermented foods containing lactic acid bacteria had a beneficial effect on human health. Since then, the efficacy of probiotics has been investigated in various diseases and is currently suggested as a possible therapeutic or preventive option in several gastrointestinal diseases[51]. The precise mechanisms of probiotics in human health remain unknown. They have been suggested to act through inhibition of the overgrowth of pathogenic bacteria and the prevention of pathogenic bacterial invasion of the host, and the improvement of gut barrier function by production of substances, such as short chain fatty acids[16].

Some RCTs have been conducted and systematic reviews have analyzed their findings to investigate the efficacy of probiotics on induction of remission and maintenance of remission in IBD patients. The efficacy of probiotics has been examined more extensively in UC than CD but, due to poor study design or the small number of subjects, their efficacy on IBD currently remains unknown.

A systematic review of 14 RCTs examined the efficacy of probiotics on induction of remission in active UC patients. The review showed that the induction of remission rate was higher in the probiotic group than the placebo group (RR: 1.73, 95%CI: 1.19-2.54). In contrast, the induction of remission rates were similar in the placebo group and the 5-aminosalicylic acid (ASA) group (RR: 0.92, 95%CI: 0.42-2.59) [52]. Moreover, another systematic review of 12 RCTs investigated the efficacy of probiotics on maintenance of remission in UC patients. It showed that no clear superiority was observed in the maintenance of remission rate in the probiotic group compared to the placebo group (RR: 0.87, 95%CI: 0.63-1.18) or the 5-ASA group (RR: 1.01, 95%CI: 0.84-1.22)[53].

A systematic review of two RCTs reported on the efficacy of induction of remission in CD patients. The review showed that the induction of remission rate in the probiotic group was higher than the placebo group at 6 mo after administration (RR: 1.06, 95%CI: 0.65-1.71)[54]. However, another systematic review did not point out the efficacy of probiotics on the maintenance of remission in CD patients[55]. Regarding adverse events associated with probiotics, no significant difference was shown between the probiotic group and the placebo group.

It will be necessary to conduct large-scale RCTs with many subjects in the future to establish high-quality evidence on the efficacy of probiotics on the induction and maintenance of remission in IBD patients. Moreover, further research is warranted to elucidate the underlying biological mechanisms.

**THE EFFICACY OF FECAL MICROBIOTA TRANSPLANTATION ON IBD**

The effect of FMT has been investigated as a therapeutic option targeting the gut microbiota of IBD.

A 2018 Cochrane’s systematic review analyzed the efficacy of FMT on UC[56]. The remission rates at week 8 were 37% (52/140) and 18% (24/137) in the FMT group and the control group, respectively (RR 2.03, 95%CI: 1.07-3.86). Forty-nine per cent (68/140) of FMT participants had a clinical response compared to 28% (38/137) of control participants (RR 1.70, 95%CI: 0.98-2.95). Thirty percent (35/117) of FMT participants achieved endoscopic remission compared to 10% (11/112) of control participants (RR 3.87, 95%CI: 2.19-6.92).
In addition, approximately 10% of IBS patients believe that their symptoms began around 11.2% of the world’s population.[66] The clinical features of IBS include bloating, flatulence, abdominal pain, or discomfort associated with a change in bowel habits, such as diarrhea, constipation, or a mix of the two. The pathophysiology of IBS remains unknown, but it is suggested that the condition is multifactorial, affected by genomes, cerebrointestinal peptides, gastrointestinal motility abnormalities, visceral hypersensitivity, gastrointestinal immunity, mucosal permeability, the gut microbiota, and psychosocial factors. This relationship between the brain and gastrointestinal function is called the gut-brain axis, which is an important concept when considering the pathophysiology of IBS. Although in recent years, accumulating evidence has suggested that the alternation in the gut microbiota plays an important role in the pathophysiology of IBS, a concept has arisen from clinical observations of symptoms developing after an infection, also known as post-infectious IBS.[67]

There have been numerous comparative studies of the gut microbiota of IBS patients and healthy individuals. In 2019, Pittayanon et al.[68] systematically reviewed 24 studies comparing the gut microbiota of IBS patients with healthy individuals. Four studies showed that the Proteobacteria is increased in IBS patients compared to healthy individuals at the phylum level, while another two reports showed that there was no significant difference of the gut microbiota between IBS patients and healthy individuals. Consistent results were not obtained for Bacteroidetes, Actinobacteria, or Firmicutes. In addition, an analysis at a lower-level than the phylum reported a significant increase in Enterobacteriaceae (Proteobacteria) and Bacteroides (Bacteroidetes) in IBS patients compared to healthy individuals. However, another two studies showed that there was no significant difference in these bacteria between the two groups.

Pathogenic bacteria, such as Escherichia, Shigella, Campylobacter and Salmonella belong to the family Enterobacteriaceae. In addition, approximately 10% of IBS patients believe that their symptoms began following a bout of infectious dysentery, leading to the coinage of the term post-infectious-IBS, and it is presumed that dysbiosis occurring as a result of infection causes IBS-like pathology. Post-infectious IBS may be associated with these pathogenic bacteria. The genus Bacteroides also contains bacteria that produce intestinal toxins, such as Bacteroides fragilis, which breaks down glycoproteins in mucus[69] and affects the wall movement (motility), which induces symptoms of IBS, including abdominal pain and diarrhea[70].

Three studies from Europe reported a reduction of Clostridiales I, difficult-to-culture bacteria, in IBS patients, which is the most consistent result. In addition, four other studies showed a significant reduction in Faecalibacterium (Clostridiales) in 119 patients with diarrhea-predominant IBS. Furthermore, two studies showed a significant reduction of F. prausnitzii in the IBS group compared to healthy individuals, while two other studies showed a non-significant reduction of F. prausnitzii in the IBS group compared to the control group. It has been suggested that these bacteria, including Clostridiales I and F. prausnitzii, may play a protective role in IBS. F. prausnitzii, which belongs to the order Clostridiales, is known to contribute to the maintenance of homeostasis of the intestinal tract. F. prausnitzii is known to be a bacterium that exerts an anti-inflammatory effect by having the ability to produce butyrate. It has been reported that in a rat model, F. prausnitzii regulates the production of interleukin-17, leading to the improvement of IBS symptoms[71]. The genus Bifidobacterium (Bifidobacteriaceae) was examined in seven studies, five of which reported a
significant decrease in the genus *Bifidobacterium* in IBS patients, but another of which reported a tendency to decrease but no significant difference in *Bifidobacterium* in IBS patients. The genus *Tannerella* (Phylum Bacteroidetes) was reported to be significantly reduced in two studies, while no significant difference was noted in the other two studies. The genus *Bifidobacterium* is reduced regardless of the subtype of IBS, suggesting that *Bifidobacterium* may improve IBS symptoms. A placebo-controlled trial of *Bifidobacterium longum* for IBS found that the *Bifidobacterium longum* group had improved depression scores and QOL of IBS patients compared to a placebo group. It has been suggested that p-cresol sulfate is decreased in the *Bifidobacterium longum* group, which may contribute to IBS symptoms.[72] p-Cresol sulfate has been shown to reduce the oxygen consumption of colonocytes and to be cytotoxic.[73] The production of p-cresol sulfate is dependent upon intestinal environmental factors, such as the composition of the microbiota, food intake, and pH of the intestinal tract.[74] p-Cresol sulfate is synthesized from tyrosine and phenylalanine via 4-hydroxyphenylacetate by the gut microbiota. *Clostridiodes difficile* and certain *Lactobacillus* strains are known to produce p-cresol by decarboxylation of 4-hydroxyphenylacetate.[75,76] Furthermore, bacterial production of bioactive substances from dietary protein has been implicated in inflammation and tissue permeability in the gut.[77] Moreover, p-cresol sulfate has been shown to act on the dopamine / norepinephrine pathway in depressive symptoms.[72]

In addition, a systematic review of probiotics for IBS reported that the IBS symptoms were improved in the group containing *Bifidobacterium* compared to the control group.

The diversity of the gut microbiota of IBS patients has been investigated. Nine studies examined α-diversity in IBS patients and, of these, five reported that α-diversity in the gut microbiota was significantly reduced in IBS patients compared to healthy individuals while the other four reported no significant difference.

In subgroup analysis, gut microbiota has been analyzed according to IBS subtype, including diarrhea-predominant IBS (IBS-D), constipation-dominant IBS (IBS-C), and mixed bowel habit IBS subtype (IBS-M).[88] Six studies described the gut microbiota in 130 subjects with IBS-M and all found no differences between this subtype and IBS-C or IBS-D. In all cases, any differences between IBS and healthy control were the same in the IBS-M group compared with the IBS-C or IBS-D subgroups. In terms of IBS-D, 3 of 5 articles assessing genus *Bacteroides* demonstrated a significant increase of this genus in IBS-D patients, whereas another 2 showed insignificant results compared to controls. In contrast, the majority of studies evaluating the genus *Bifidobacterium* showed a significant decrease in IBS-D patients. Only one study evaluated IBS-C alone. This study found differences between IBS-C and healthy controls, but it is difficult to draw conclusions from one study.

As in the studies of the gut microbiota of IBD, the conclusions of the studies of the gut microbiota in IBS also lacked consistency. It is considered that the inconsistency of results was mainly caused by the variety of research methods.

**THE TREATMENT FOR IBS TARGETING THE GUT MICROBIOTA**

Several therapeutic options aimed at improving dysbiosis in IBS patients, including probiotics and FMT, have been studied. Probiotics supplements with beneficial effects on IBS symptoms may lead to more effective therapeutic options. The proposed theory is that the supplementation of probiotics improves IBS symptoms by modulating or restoring the gut microbiota or its metabolic pathways.[78] A meta-analysis published in 2018 comprehensively analyzed thirty-seven studies (21 combinations of probiotics, total of 4430 subjects), which examined the efficacy of probiotics on IBS.[79] It was shown that probiotics were effective in improving IBS symptoms. This meta-analysis has demonstrated that amongst combination probiotics, LacClean Gold, which consists of *Bifidobacterium longum* (B. longum), *Bifidobacterium bifidum*, *Bifidobacterium lactis*, *Lactobacillus acidophilus* (L. acidophilus), *Lactobacillus rhamnosus*, and *Streptococcus thermophiles* and the seven-strain combination of three *Bifidobacterium*, three *Lactobacillus* and one *Streptococcus* were associated with significant improvement in IBS global scores, and there was a trend towards an improvement in global symptom scores or abdominal pain scores with LSL#3, a probiotic mixed with 4 *Lactobacilli* (L. casei, L. acidophilus, L. delbrueckii subsp., *Bulgarius*), 3 *Bifidobacteria* (B.) (B. longum, B. breve, B. infantis), and a *Streptococcus* (Streptococcus-salivarius subsp. thermophilus). However, this study has shown a limitation that for probiotics, it remains whether a particular combination of probiotics, or a specific species or strain, is more likely to be effective, or there is a particular IBS subtype that is more likely to benefit. A therapeutic option for IBS using probiotics is expected to become more important in the future.

A systematic review published in 2019 comprehensively analyzed four RCTs that examined the effects of FMT on IBS patients.[80] One study included IBS-D only, 2 studies included IBS without constipation, and 1 study included all 3 subtypes of IBS. It showed that the response rates were 49.3% and 51% in the FMT group and the placebo group, respectively, suggesting FMT is not effective for IBS symptoms. This study did not show the subgroup analysis according to IBS subtypes. However, FMT for IBS is not recommended in clinical practice guidelines of IBS. The clinical guidelines of IBS provided by the Japanese Society of Gastroenterology, AGC[81], AGA[82], and the British Society of Gastroenterology[83] do not recommend the use of FMT due to insufficient evidence of its efficacy for IBS in...
clinical studies, and point out the need for large-scale and high-quality RCTs in the future.

**ADVERSE EVENTS OF FMT**

A systematic review analyzing FMT-related adverse events has been reported[84]. It analyzed 129 studies, including 4241 subjects and a total of 5688 FMTs. The incidence rate of adverse events was 19.0%. Most reported adverse events were self-limiting gastrointestinal symptoms comprising abdominal discomfort/abdominal pain/abdominal bloating (7.0%) and diarrhea (10%). Serious adverse effects such as infection and death were reported in 1.4% of patients. Although current evidence deems FMT to be a generally safe therapeutic method with few adverse events, the long-term outcomes of its use have not been completely elucidated. Therefore, establishing periodicity and length of regular follow-up after FMT to monitor the clinical efficacy and long-term adverse events are other essential issues. Aside from standardization of donor screening and clear protocols for adverse events monitoring, an FMT registry should be established to collect long-term data and follow-up outcomes and complications.

**CONCLUSION**

In the present review, we provided an overview of the role of the gut microbiota in the pathogenesis of CDI, IBD, and IBS and of promising treatments aimed at the modulation of the gut microbiota, including FMT and probiotics.

Microbiome research has been able to reap the benefits of technological advancements in systems and synthetic biology, biomaterials engineering, and traditional microbiology. Recently, gut microbiome research has been revolutionized by high-throughput sequencing technology, permitting composition and functional analyses. The accumulating evidence by using sequencing technology enables us to understand the role of the gut microbiota in human diseases.

FMT is considered effective in restoring imbalances of the gut microbiota. Consequently, it can be performed in a variety of human diseases associated with dysbiosis, including not only gastrointestinal diseases, but other systemic disorders such as metabolic syndrome, diabetes mellitus, autoimmune diseases, and cardiovascular diseases. Many unanswered questions remain however, including identification of a standardized FMT methodology for factors, such as the optimal route of administration and donor selection, as well as those concerning the long-term benefits of FMT and adverse effects.

Probiotics have considerable potential for preventive and therapeutic applications in various gastrointestinal disorders. Although, from the ongoing research more promising potential health effects of probiotics are being observed, more standardized and verifiable clinical studies are needed to demonstrate the safety, efficacy, and limitations of a putative probiotic, to determine whether it is superior to existing therapies, and to determine both the short- and long-term effects on the immune system in healthy and diseased individuals.

**FOOTNOTES**

Author contributions: Nishida A wrote the paper; Nishino K, Masashi O, Sakai K, Owaki Y, Noda Y, and Imaeda H contributed critical revision of the manuscript.

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Vascular complications of pancreatitis

M Ammar Kalas, Monica Leon, Luis Omar Chavez, Eduardo Canalizo, Salim Surani

Abstract

More than 200000 hospital admissions happen per year for acute pancreatitis and more than 50000 for chronic pancreatitis in the United States of America. Necrotizing pancreatitis accounts for 20%-30% of the cases. One-quarter of the patients with pancreatitis develop vascular complications, which carries a high mortality. This mini-review will address these complications that can help primary care physicians and hospitalists in managing their patients effectively.

Key Words: Acute pancreatitis; Vascular complications; Gastrointestinal bleeding; Pseudoaneurysm; Hemosuccus pancreaticus; Pancreas

Core Tip: Vascular complications of acute pancreatitis carry high morbidity and mortality. Physicians must be aware of the possible complications, proper diagnosis, and treatment options. Herein, we review the vascular complications and up-to-date management.

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INTRODUCTION

Acute pancreatitis is a disorder characterized by inflammation of the pancreas secondary to variable etiologies, with the most common being gallstones and alcohol abuse. This disorder is the leading cause of gastrointestinal disease hospital admissions in the United States, with an incidence of 13-45 per 100000. Since 2000, the incidence of pancreatitis has risen by approximately 30%[1]. Smoking was found to be associated with an increased risk of developing pancreatitis, specifically among alcohol users. Moreover, the most reported complication of endoscopic retrograde cholangiopancreatography (ERCP) was found to be pancreatitis, with an incidence of approximately 3.5%[1].

Acute pancreatitis can be classified into mild, moderate, and severe based on organ failure and its duration (greater than 48 h or less than 48 h), presence or absence of local complications such as pseudocysts, acute peripancreatic fluid collections, acute necrotic collections, or walled-off necrosis[1]. The diagnosis is made on the basis of clinical, laboratory, and radiological evidence of pancreatitis. Management of acute pancreatitis is primarily supportive with volume resuscitation, analgesia, and bowel rest with or without nutritional support. Management should be started step-wise, and surgical options should be considered at the later stages if needed. Vascular complications of pancreatitis carry high morbidity and mortality. It is estimated that one-quarter of patients with pancreatitis may develop vascular complications[2-4]. Hence this review aims to address the common vascular complications associated with pancreatitis.

PSEUDOANEURYSM

Pseudoaneurysm (PSA) associated with pancreatitis is rare but potentially a serious complication with the risk of rupture and lethal hemorrhage. It is caused by reactive local arteritis induced by pancreatic proteolytic enzymes. The exposure of visceral arteries to the enzymes may cause autodigestion of the wall leading to necrotizing arteritis, resulting in the weakening of the vessel lumen, causing a PSA formation. They are usually associated with a preexisting pseudocyst but can also occur without a pseudocyst[5,6].

This complication can present in both acute and chronic pancreatitis. Pseudoaneurysm usually develops 3 wk after the onset of acute pancreatitis[7]. The true incidence is unknown, but it ranges from 4% to 17% in single-center reports, with a higher incidence in males[7-9]. PSA is reported mostly in alcohol-induced pancreatitis, but the etiologic factor is not exclusive, and pediatric/hereditary pancreatitis cases have also been reported[5,8]. Patients present with abdominal pain or gastrointestinal bleeding secondary to rupture. Intra-abdominal bleeding, retroperitoneal bleeding, bleeding into the pancreatic duct, or common bile duct is another less common presentation[9]. The size at diagnosis may vary from a few mm to 5.6 cm[7].

The affected arteries are in proximity to the pancreas. The splenic artery (30%-50%) is most affected, followed by the left gastric, gastroduodenal artery, and pancreaticoduodenal artery. The superior mesenteric, proper hepatic artery, and small intrapancreatic arteries may also be affected[7,9,10]. Early diagnosis of PSA is important to avoid life-threatening hemorrhage. Clinicians should be aware of PSA as a pancreatitis complication. Diagnosis based on clinical presentation encompasses a challenge; abdominal pain can be from pancreatitis per se. Since PSA is more common in chronic alcohol abuse, gastrointestinal bleeding may mislead the diagnosis as a complication of cirrhosis[6].

PSA diagnosis is achieved by ultrasound (US), computed tomography (CT), and angiography. The US is a quick and easy tool for diagnosis that uses the color doppler, which shows a mass with the pulsatile, swirling flow which fills during systole unless filled with thrombus. Clot-filled and small PSA are difficult to diagnose by the US alone. The US operator must recognize sonographic appearance and thrombus age[7]. CT of the abdomen can be suggestive, but CT angiography has a higher sensitivity (95%). Angiography is considered the gold standard for diagnosis and can show smaller PSA, but it is expensive and invasive. Therefore, it is reserved for identifying the bleeding site and guiding the endovascular treatment[11].

Fang et al[9] described a peripancreatic PSA classification system. They included pancreatitis-related PSA but also postoperative PSA[9]. The classification is based on the type of artery involved, communication with the gastrointestinal tract, and exposure to pancreatic juice. Type 1: Minor artery: > 5mm away from the major artery with no communication to GI tract and no exposure to pancreas; Type 2: major artery can be sacrificed. It does communicate with the GI tract and with exposure to pancreas. Type 3: major artery cannot be sacrificed. The proposed classification can assist in treatment strategy. PSA management can be endovascular or surgical. Studies published after 2000 favor embolization as the initial treatment option[9]. Surgery continues to be an important tool for selected patients in whom angiographic intervention with embolization fails or those with hemodynamic compromise. Surgical procedures may vary from direct vessel ligation to pancreas resection, gastrectomy, or small intestine resection, depending on the affected vessel and compromise of blood perfusion to adjacent organs. Patients with concomitant pancreatitis complications may need simultaneous surgical debridement, necrosectomy, or pancreatectomy[12].
Endovascular management allows for embolization if bleeding is the main presentation but also for early treatment with stent deployment. Embolization can be done with metallic coils, transcatheter thrombin injection, covered stents, gel foam, or microparticles. Usually, coils are placed distal to the PSA and then proximal, preventing collateral backfilling. Angioembolization interventions have a reported success rate of 70%-90%[7]. Although the benefits of endovascular management have been proven with an increased success rate over the years, recurrence, stent infection, displacement, migration, and splenic infarction are possible complications. Therefore, management should be tailored to individual patients, and embolization may be used only as a bridge treatment for some[9].

VENOUS THROMBOSIS

Thrombosis is more often associated with severe pancreatitis compared to mild cases[13]. Necrotizing pancreatitis (NP) is a severe systemic inflammatory process that may lead to splanchnic venous system thrombosis (SVT), involving splenic, portal, and superior mesenteric veins, either independently or in combinations[14]. Also, thrombosis of peripheral vasculature has been described in the literature. In most patients, a single venous territory is involved[13].

Numerous risk factors have been described, such as male gender, history of previous Venous Thromboembolism (VTE), infected necrosis, and organ failure[15]. In multivariate analysis, the development of VTE did not increase mortality in patients with NP[16]. VTE risk in NP patients is among the highest of any hospitalized patients[17]. SVT develops in approximately 50% of patients with NP, and the incidence drops significantly in the absence of necrosis (1%-17%)[13,18].

Four main mechanisms of SVT have been proposed: (1) Swelling and necrosis of the pancreas and local inflammatory infiltration leading to vascular endothelial damage; (2) Extrinsic compression of the splanchnic vein (pancreas enlargement or pseudocyst) causing stasis; (3) Increased level of inflammatory mediators triggering coagulation cascade; and (4) Activation of the coagulation system due to release of tissue factors from the damaged pancreas[19].

Clinical manifestations can be divided into secondary to acute thrombosis and complications of portal hypertension[19]. They include abdominal pain due to mesenteric extension, gastrointestinal bleeding secondary to portal hypertension, and splenomegaly.

Color Doppler ultrasound is considered the first-line diagnostic approach for screening for SVT[19]. It has a sensitivity of 83% compared with angiography for the portal vein (PV). It has a less accurate assessment of the splenic vein due to its anatomic location[13]. Contrast-enhanced CT or magnetic resonance imaging is used to confirm SVT diagnosis[19]. It has a sensitivity of 90%. CT scan findings of acute SVT include persistent, well-defined intraluminal filling defects with low central attenuation and surrounding well-defined, rim-enhancing venous walls[13]. Angiography remains the golden standard for diagnosing SVT, but it is an invasive approach.

Approximately one-third of patients present with spontaneously splanchnic vein recanalization. The other two-thirds are at risk of developing severe complications such as bowel ischemia and liver failure. At this time, there is no consensus on whether patients with SVT should receive therapeutic anticoagulation since the theoretical risk of bleeding exists. According to a meta-analysis by Chandan et al[20], therapeutic anticoagulation can recanalize the involved vessels without increasing the risk of bleeding in the setting of SVT due to acute pancreatitis. Also, a retrospective study of 273 patients with AP-induced SVT reported a reduction in SVT incidence and improvement in the clinical outcomes without increasing the risk of bleeding[21]. Consistent with these findings, in a meta-analysis, the use of therapeutic anticoagulation resulted in a statistically significant increase in recanalization rate with no increase in hemorrhagic complications or mortality. However, there was no difference in overall mortality between the treated and control group to justify anticoagulation therapy[22]. High-quality randomized trials with an adequate sample size should be encouraged to elucidate this topic.

ARTERIAL THROMBOSIS

The incidence and prevalence of arterial thrombosis have not been reported due to the rarity of the condition. Several cases of arterial thrombosis associated with pancreatitis have been reported in the literature (Table 1). Arterial thrombosis is the result of atheromatous plaque rupture. In pancreatitis, several theories have been proposed, such as the release of proteolytic and lipolytic enzymes, which results in endothelial injury and the activation of the coagulation cascade with resultant thrombosis. In addition, adjacent inflammation can result in localized vascular inflammation, third spacing, necrosis, and mass effect, which increases the risk of thrombus development[23].

Cases reported thrombus development in the abdominal aorta and its branches, such as the superior mesenteric artery and renal arteries. A case report showed widespread aortic thrombi with sparing of the celiac trunk, splenic artery, common hepatic artery, and superior mesenteric artery[24]. Arterial thrombosis in pancreatitis can be unpredictable, with a case presenting with intracardiac thrombus following pancreatitis. It should be noted that the patient had valvular atrial fibrillation and was on

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**Table 1**

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warfarin, and the clot was adherent to the left atrial appendage. Therefore, the thrombus could be secondary to atrial fibrillation, with pancreatitis as a possible provoking factor[25]. Cases reporting evidence of arterial thrombosis were primarily noted in patients with acute necrotizing pancreatitis. Presentations are variable depending on the vessel involved with general symptoms, including; vague abdominal pain, nausea, and vomiting. Biphasic computed tomography with angiography is sufficient for the diagnosis of arterial thrombi. In cases of small pseudoaneurysms or unclear diagnoses, angiography can be performed. Management of arterial thrombosis in pancreatitis can be complex and is variable depending on the location of the thrombus[26]. In the cases reviewed, intravascular management with thrombectomy followed by intravenous heparin was used in the patient with superior mesenteric artery thrombosis[27]. Intravenous heparin drip followed by warfarin or enoxaparin was utilized in the rest of the cases. The duration of anticoagulation remains unclear. However, in most cases, treatment for 3-6 mo with correction of the underlying pathology is agreed upon. Complications of arterial thrombosis carry high morbidity and mortality, with cases reporting the development of resultant gastric necrosis in a case of splenic artery thrombus and renal dysfunction due to renal artery thrombosis resulting in end-stage renal disease[28].

### PANCREATIC-PORTAL FISTULA FORMATION

Pancreatic fistula is described as the leakage of pancreatic enzymes and secretions due to an abnormal connection with adjacent structures (e.g., organs, blood vessels, or spaces). Fistulas can be classified as internal or external depending on the location of the connection. Pancreatic fistula formation following pancreatitis episodes has not been well studied, and evidence is found only through case series. Internal pancreatic fistula is more likely to occur in cases of pancreatitis, specifically in chronic pancreatitis secondary to alcohol use[29]. Pancreatic fistulas occur due to disruption of the pancreatic ducts in trauma, acute pancreatitis, chronic pancreatitis, and pancreatic resection. Initially, fluid collection can be the only finding; however, when persistent, this can lead to pseudocyst formation with potential erosion of adjacent hollow structures and fistula formation. In a review of the literature by Brown et al [30] in 2014, patients with pancreatic portal fistula had the presence of a pseudocyst, with the majority being located in the head of the pancreas.

Clinical manifestations include; abdominal pain, abdominal distention (pancreatic ascites), nausea, vomiting, shortness of breath (pleural effusion), fever, and life-threatening hemorrhage in a small subset of patients. Disseminated fat necrosis has been reported in the literature with presentations of peripheral subcutaneous fat necrosis, which is thought to be secondary to the introduction of pancreatic enzymes into the systemic circulation. An elevated amylase level (> 6000) was found in all patients with disseminated fat necrosis[30]. Several diagnostic modalities have been performed in the literature ranging from the US to ERCP. Although there have been no studies to accurately assess the sensitivity and specificity of these tests for pancreatic fistula detection, most case series have an ERCP performed for definitive diagnosis and possible therapeutic intervention, and hence is considered the most accurate testing modality by clinicians[31]. The US can show the complex fluid collection in the portal vein with no flow on the doppler. CT with contrast generally demonstrates a fluid-attenuated portal vein with possible collateral periporal vessels and pseudocyst. Magnetic resonance cholangiopancreatography findings on T2 weighted sequences include; hyperintense portal vein and fluid signal; occasionally, visualization of the hyperintense fistulous tract could be seen[32]. In contrast, in cases of portal vein thrombosis only, ultrasonography would show decreased or absent flow on the doppler without
complex fluid collection. Narrowing of the portal vein can be seen in cases of extrinsic compression; on CT with contrast, the portal vein would be hypodense with no contrast enhancement, and on MRCP, T1 weighted sequences would show an isointense portal vein with no fluid signal. Secretin enhanced MRCP can also help further characterize pancreatic ducts in cases of diagnostic uncertainty.

Percutaneous transhepatic portography (PTP) is another diagnostic modality, especially in uncertain diagnosis, and can provide an accurate assessment of the portal circulation anatomy and the extent of portal venous invasion, which has been correlated with surgical procedures findings. In addition, PTP allows for fluid extraction and examination[30].

The management of pancreatic-portal vein fistulas is variable and ranges from conservative management to surgical management involving partial or complete pancreatectomy with fistula repair. Conservative management has been successful, as reported in several cases in the literature. However, it was primarily done among stable patients with minimal clinical manifestations[33-37]. Endoscopic management with endoscopic ultrasound cyst drainage and ERCP with pancreatic stent placement has been successful in hemodynamically stable patients. Surgical management with partial or total pancreatectomy is another mode of management, specifically in patients with disseminated fat necrosis or those who are not candidates for endoscopic management or failed endoscopic management. However, there is no current treatment algorithm for pancreatic-portal fistulas due to the acute nature of the disease[38].

HEMOSUCCUS PANCREATICUS

Hemosuccus pancreaticus (HP) is a rare cause of gastrointestinal bleeding secondary to pancreatic pathology. It is characterized by bleeding through the ampulla of Vater due to the presence of blood in the main pancreatic duct. In some cases, bleeding could be through the accessory pancreatic duct and drain through the minor duodenal papilla[39].

The bleeding source could be from the pancreas, pancreatic duct, or surrounding vessels such as the splenic or gastroduodenal artery. The incidence of HP as the cause of upper gastrointestinal bleed (GI) is estimated at 1 in 1500 cases of upper GI bleed with a strong male predilection (approximately 7:1). Several etiologies have been proposed in the literature, such as pancreatic inflammation, arterial aneurysm or PSA, pancreatic masses, iatrogenic, congenital, or trauma[40].

Pancreatic inflammation (acute, chronic, or hereditary) was found in approximately 80% of cases of HP. It is likely due to ductal inflammation-promoting vascular wall rupture. Local irritation due to gallstones and pseudocyst also contributes to local vascular inflammation and potential hemorrhage. Pseudocysts contain activated lytic enzymes such as elastase which can result in erosion of adjacent vessel walls and hemorrhage. Intrapancreatic or extrapancreatic arterial aneurysm or PSA is another major cause of HP, with the commonly involved vessels being splenic, gastroduodenal, pancreaticoduodenal, or hepatic arteries[41].

A review of the literature and cases between 1977 and 2020 by Cui et al[42] in 2021 reviewed the variable clinical presentations of HP. GI bleed (melena) was the most commonly reported symptom at 52%, followed by abdominal pain at 46%. Other symptoms include; nausea, vomiting, loss of appetite, weight loss, and lower GI bleeding (hematochezia).

GI bleed is generally intermittent, likely secondary to clot formation in the pancreatic duct leading to the cessation of GI bleed but persistent abdominal pain. As time passes, clot resolution occurs, leading to rebleeding and abdominal pain improvement due to decreased intraductal pressure[42].

Diagnosis and evaluation of HP remain a challenge due to the vague and variable presentation of HP. A retrospective single-center study by Yashavanth et al[43] in 2021 evaluated patients with suspected HP over a 10-year period. The study showed that the median duration of bleeding prior to diagnosis was ten days, with 40.2% of patients exhibiting symptoms for > 1 mo. The study showed that 62% of patients with HP had evidence of visceral artery aneurysms. Upper GI endoscopy showed evidence of bleeding in 64.4% of patients, and angiography was successful in localizing the source of bleeding in 94.2% of cases[43].

Serum testing (amylase, lipase, or bilirubin levels) in cases of HP is of limited use with possible hyperbilirubinemia due to pancreaticobiliary reflux and elevations in amylase and lipase in cases of pancreatitis. Therefore, the primary modes of diagnosis are through imaging modalities. Upper GI endoscopy is crucial in patients with HP and can show evidence of bleeding through the ampulla of Vater via the use of side-facing endoscopy in addition to ruling out other causes of GI bleed. Bleeding in the second part of the duodenum should prompt the suspicion of HP. Rates of upper GI endoscopy for detection of HP have been variable and range between 30%-65%. This can be explained due to the intermittent nature of the bleeding[44].

ERCP could be used as it can view filling defects in pancreatic ducts, which can aid in the diagnosis; however, this modality is not commonly utilized by clinicians. Ultrasonography with Doppler can reveal the presence of aneurysms or pseudocyst; however, it is only positive in approximately 38% of cases. Abdominal CT with contrast is commonly used in pancreatic pathology to diagnose and can show intraductal blood clots, aneurysmal opacification, pseudocyst presence, and/or contrast persistence.
Kalas MA et al. Vascular complications of pancreatitis

Figure 1 Proposed algorithm of hemosuccus pancreaticus workup and management.

following the arterial phase. Abdominal CT with contrast often aids in the diagnosis in 90% of cases of HP cases. However, angiography remains the gold standard for diagnosis of HP due to accurate localization of the bleeding or abnormal vessel, visualization of the arterial anatomy, and potential for therapeutic intervention.

The management of HP should focus on maintaining stable hemodynamics, intravenous hydration, blood transfusion as needed, and controlling the source of bleeding (Figure 1). Therefore, supportive management is not recommended and is associated with high mortality (up to 90%). The approach to HP management is dependent on patients’ hemodynamics. Interventional radiology (IR) procedures such as coil embolization, balloon tamponade, and stent-graft placement can be performed in stable patients with immediate positive results in 79%-100% of patients and an overall success rate of 67%. Recurrence rates following interventional radiology procedures are estimated to be 30%. Recurrence etiology remains unclear. However, one theory proposed bleeding from collateral vessels in the adjacent diseased pancreas[45].

In cases with hemodynamic instability, unclear angiography findings, hemorrhagic pseudocyst, or IR procedure failure, a surgical approach should be pursued. Surgical procedures include; pancreatectomy (complete or partial) with or without splenectomy, pseudocyst excision, culprit blood vessel ligation, or bypass graft placement. The surgical approach carries high success rates of 70%-80%; however, this comes with a high mortality rate of 10%-50%. Nonetheless, surgical management has lower bleeding recurrence rates of 0-5%[39,46,47].

INTRAABDOMINAL HEMORRHAGE

Intraabdominal hemorrhage can also occur in cases of pancreatitis. Several case reports have been published in the literature, with few studies done to address this issue. A retrospective study in a single center in Germany by Philipp et al[48] in 2013 evaluated spontaneous bleeding in pancreatitis patients and the treatment by transcatheter arterial embolization. In their study, intraabdominal hemorrhage was reported in < 1% of patients with pancreatitis, and 73% of those with hemorrhage had evidence of necrotizing pancreatitis. The most common source of bleeding was arterial, with one case of splenic vein hemorrhage. The diagnosis was made with contrast-enhanced CT in all patients, and angiography showed evidence of active bleeding in 57% of the cases. Patients were treated with transcatheter coiled embolization, and the in-hospital mortality was 36%; however, only 7% of the mortality was attributed
directly to intraabdominal hemorrhage. Rebleeding following coil embolization was noted to be 14% [48].

A retrospective study by Chen et al [49] in 2017 evaluated the prevalence and characteristics of pancreatitis patients with intraabdominal hemorrhage. The prevalence of intraabdominal bleeding in pancreatitis patients in the study was 3.4%, with the risk factors being a high CT severity index and creatinine elevation with statistical significance. The median time between pancreatitis onset and bleeding was 17.5 d. Management of intraabdominal bleeding depends on the patient’s hemodynamic stability and can be through IR or surgical procedures.

CONCLUSION

Vascular complications of pancreatitis carry high morbidity and mortality if untreated. The prevalence of the vascular complications of pancreatitis has been studied primarily through radiological research and is estimated to be present in up to 25% of the patients. Knowledge of the possible complications can lead to timely diagnosis and management. A multidisciplinary approach tailored for individual patient care is the best approach. Over the years, minimally invasive procedures have shown good results in select patients.

FOOTNOTES

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Clinical and Translational Research

Network pharmacology and molecular docking reveal zedoary turmeric-trisomes in Inflammatory bowel disease with intestinal fibrosis

Lie Zheng, Yong-Yi Ji, Yan-Cheng Dai, Xin-Li Wen, Shi-Cheng Wu

Abstract

BACKGROUND
Inflammatory bowel disease (IBD) is a complex chronic IBD that is closely associated with risk factors such as environment, diet, medications and lifestyle that may influence the host microbiome or immune response to antigens. At present, with the increasing incidence of IBD worldwide, it is of great significance to further study the pathogenesis of IBD and seek new therapeutic targets. Traditional Chinese medicine (TCM) treatment of diseases is characterized by multiple approaches and multiple targets and has a long history of clinical application in China. The mechanism underlying the effect of zedoary turmeric-trisomes on inducing mucosal healing in IBD is not clear.

AIM
To explore the effective components and potential mechanism of zedoary turmeric-trisomes in the treatment of IBD with intestinal fibrosis using network pharmacology and molecular docking.
pharmacology and molecular docking techniques.

**METHODS**

The chemical constituents and targets of *Rhizoma zedoary* and *Rhizoma sanarum* were screened using the TCMSP database. The GeneCards database was searched to identify targets associated with intestinal fibrosis in IBD. The intersection of chemical component targets and disease targets was obtained using the Venny 2.1 online analysis platform, and the common targets were imported into the STRING 11.0 database to construct a protein interaction regulatory network. A “zedoary turmeric-trisomes-chemical composition-target-disease” network diagram was subsequently constructed using Cytoscape 3.7.2 software, and the topological properties of the network were analyzed using the “Network Analysis” plug-in. Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses of the common targets were performed using the DAVID 6.8 database to elucidate the mechanism of zedoary turmeric-trisomes in the treatment of IBD. Subsequently, molecular docking of the compounds and targets with the highest intermediate values in the “zedoary turmeric-trisomes-chemical composition-target-disease” network was performed using Sybyl-x 2.1.1 software.

**RESULTS**

A total of 5 chemical components with 60 targets were identified, as well as 3153 targets related to IBD and 44 common targets. The protein-protein interaction network showed that the core therapeutic targets included JUN, MAPK14, CASP3, AR, and PTGS2. The GO enrichment analysis identified 759 items, and the KEGG enrichment analysis yielded 52 items, including the cancer pathway, neuroactive ligand-receptor interaction, hepatitis B, and the calcium signaling pathway, reflecting the complex biological processes of the multicomponent, multitarget and multipathway treatment of diseases with zedoary turmeric-trisomes. Molecular docking showed that the compound bonded with the target through hydrogen bond interactions and exhibited good docking activity.

**CONCLUSION**

This study identified the potential mechanism of action of zedoary turmeric-trisomes in the treatment of inflammatory bowel fibrosis using network pharmacology and molecular docking technology, providing a scientific basis for further expansion of their clinical use.

**Key Words:** Network pharmacology; Molecular docking; Zedoary turmeric trisomes; Inflammatory bowel disease; Intestinal fibrosis

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**Core Tip:** Intestinal fibrosis is one of the common complications of inflammatory bowel disease (IBD). Finding effective drug treatment is an important issue that needs to be solved at the moment. The mechanism of zedoary turmeric-trisomes in the treatment of IBD with intestinal fibrosis can be predicted through network pharmacology and molecular docking, so as to provide theoretical reference for it to better play its therapeutic role.

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**INTRODUCTION**

Intestinal fibrosis is a common complication of inflammatory bowel disease (IBD)[1]. In severe cases, intestinal obstruction leads to a decrease in the quality of life of patients; most patients require surgical intervention, which poses a major challenge for clinicians[2]. Fibrosis forms after repeated stimulation of intestinal tissue by long-term chronic inflammation. Similar to fibrosis in other organs, the potential mechanism of action is complex and may be related to the interactions between a variety of cells and cytokines[3]. Due to the destruction of the epithelial barrier observed in IBD, intestinal bacterial products penetrate the stroma, and the epithelial gap induced by immune cells and immune cell...
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activation mediates the innate immune response[4]. Changes in environmental factors and chronic inflammation due to repeated stimulation result in obvious changes in intestinal extracellular matrix components and, through their mechanical properties, facilitate the formation of fibrosis[5]. The traditional view that intestinal fibrosis is an inevitable and irreversible process is gradually changing based on studies of its underlying pathological, cellular and molecular mechanisms[6]. In addition, clinical studies have shown that stenosis formation is reversible in patients undergoing septoplasty[7].

Previously prescribed drugs, such as mesalazine and risadomide, cannot prevent or improve intestinal fibrosis, and their side effects are obvious[8]. Therefore, the use of traditional Chinese medicine (TCM) for the treatment of intestinal fibrosis is gradually increasing due to the advantages being safe and having stable efficacy and no obvious side effects.

Zedoary turmeric-trisomes are from the three-rib-pill prescription written by Yao Jun in the Qing dynasty. Studies have shown that zedoary turmeric-trisomes can inhibit or reverse fibrosis changes in multiple organs[9,10], but the specific active components and their interactions remain unclear. In this study, the mechanism of action of zedoary turmeric-trisomes in the treatment of IBD intestinal fibrosis was systematically studied using a network pharmacology approach. The virtual binding of compounds in zedoary turmeric-trisomes to receptor molecules was analyzed by molecular docking to identify the targets and binding sites, and the potential mechanism of action of zedoary turmeric-trisomes in the treatment of IBD intestinal fibrosis was elucidated. This study provides a theoretical and scientific basis for further research.

MATERIALS AND METHODS

Construction and screening of chemical constituents of zedoary turmeric-trisomes

The TCM Systems Pharmacology (TCMSP) database and analysis platform can be used to predict the absorption, distribution, metabolism and excretion of TCM chemical components in vivo and to screen for the targets of chemical components. The TCMSP database (https://tcmspw.com/tcmsp.php) was used to search for the keywords "zegoary turmeric" and "trisomes" to determine the chemical composition; the criteria of an oral bioavailability (OB) of 30% or higher and a medicinal property (drug likeness, DL) of 0.18 or higher were used to select the results. The PubChem database (https://pubchem.ncbi.nlm.nih.gov/) was used to check the name of the chemical components and molecular structure, and the information for the qualified compounds was imported into Excel. Moreover, the TCMSP database was queried to retrieve the action targets of the chemical components in an Excel table, and the targets were imported into the UniProt database (https://www.UniProt.org/) to correct the names of the targets for standardization purposes. The chemical components and action targets of the abovementioned drug pairs were classified, sorted and saved in Excel for future use.

Acquisition of targets of intestinal fibrosis in IBD

The GeneCards database is a comprehensive database of human genes that integrates multiple genetic database resources. Using the keywords “inflammatory bowel diseases-intestinal fibrosis”, we searched the GeneCards (https://www.genecards.org/) database to identify associations between IBD and intestinal fibrosis target information.

Screening of common drug-disease targets and construction of the protein-protein interaction network

The notable drug targets included Rhizoma zedoariae trisomes based on an analysis using the Venny 2.1 online platform (https://bioinfogp.cnb.csic.es/tools/venny/), IBD intestinal fibrosis target mapping, a Venn diagram and common targets. The common targets were identified as potential targets of zedoary turmeric-trisomes in the treatment of IBD intestinal fibrosis. The common targets were imported into the STRING 11.0 database (https://string-db.org/), the species was limited to Homo sapiens, the minimum required interaction score was set to ≥ 0.7, and the option “Hide disconnected nodes in the network” was selected to construct the protein-protein interaction (PPI) network. An analysis of the topological properties of the network was conducted to predict the core regulatory targets in the network.

Network construction and analysis

Data files for the chemical components, corresponding targets and diseases were prepared and imported into Cytoscape 3.7.2 software to construct a network diagram of “zegoary turmeric-trisomes - chemical component - target - disease”. The “Network Analysis” plug-in was used to analyze the topological properties of the network and to measure the importance of the various nodes in the network according to the node degree value. Thus, the mechanism of action of zedoary turmeric trisomes on IBD intestinal fibrosis was predicted.
Gene enrichment analysis
The DAVID database is an online functional annotation system based on a web server for gene function enrichment analysis and pathway enrichment analysis that includes analysis tools and biological knowledge bases and is mainly used for the identification of target function and pathway information, disease analysis and other analyses. To further understand the function of a target and its role in the signaling pathway, DAVID (https://david.ncifcrf.gov/) was used to identify 1.3 and 6.8 common targets for subsequent Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses using “Homo sapiens” as the background. To elucidate the potential mechanism of zedoary turmeric-trisomes in the treatment of IBD intestinal fibrosis, GO and KEGG pathway enrichment analyses based on biological process (BP), cellular component (CC) and molecular function (MF) were performed on the potential targets.

Molecular docking
Molecular docking is a widely used computer virtual screening technology for predicting the interaction mode and affinity between a ligand and a receptor that is based on geometric and energy matching principles. In this study, the Chemical Book database (https://www.chemicalbook.com/Product-Index.aspx)[14] was used to obtain the active ingredient in a .mol format file. The file was then imported into the SYBYL-x 2.1.1 energy optimization software program, and the file was saved in mol2 format for later use. After downloading the PDB format file of the crystal structure of the core target protein from the RSCB PDB database (https://www.rcsb.org/), Sybyl-x 2.1.1 software was used for a series of optimization operations, such as ligand extraction and hydrodehydration of the target protein. The docking mode of the receptor protein and ligand compound was observed using the Surflex-Dock module in the software program.

RESULTS
Screening of the chemical constituents of zedoary turmeric-trisomes
Using “zegoary” and “trisomes” as the keywords, 81 chemical constituents of zedoary and 30 chemical constituents of trisomes were obtained from a search of the TCMSP database. After applying the filters for OB ≥ 30% and DL ≥ 0.18 and removing compounds without targets, 5 active components were obtained, which corresponded to 60 targets, and these included 1 chemical component of zedoary and 5 chemical components of trisomes. These compounds include the components common to zedoary turmeric and trisomes. Table 1 shows the chemical composition of zedoary turmeric trisomes.

Screening of intestinal fibrosis targets in IBD
A total of 3153 targets related to intestinal fibrosis in IBD were retrieved from the GeneCards database using the key words “inflammatory bowel disease-intestinal fibrosis”.

Target screening and PPI network analysis of zedoary turmeric-trisomes in the treatment of IBD intestinal fibrosis
Sixty targets of the active ingredients of zedoary turmeric-trisomes and 3153 targets of enteric fibrosis in IBD were introduced into Venny 2.1 for intersection operation, and 44 common targets were obtained, reflecting the synergistic effect of zedoary turmeric-trisomes on multiple targets in the treatment of diseases (Figure 1). Forty-four common targets were imported into the STRING database, the species was set to Homo sapiens, and the minimum required interaction score was set to ≥ 0.7. After selecting the option “Hide disconnected nodes in the network”, the PPI network was generated (Figure 2A). The network involved 36 nodes with 65 edges, and the average node degree was 3.61. The node degree represents the number of edges connected to a specific node in the network. The larger the degree is, the more critical the node. Figure 2B shows the information for the top 30 targets in the PPI network based on node degree values, and the node degrees of JUN, MAPK14, CASP3, AR, PTGS2, CASP8, ESR1, BCL2, CHRM1, ADRA1B, BAX, CASP9, PGR, PRKCA and RXRA were greater than 3.61 (the average node degree value). These results indicate that these nodes interact more with other proteins in the network, which suggests that these targets play important roles in the treatment of IBD intestinal fibrosis.

Construction and analysis of the “zegoary turmeric-trisomes - chemical component - target - disease” network
Cytoscape 3.7.2 software was used to visualize the “zegoary turmeric-trisomes - chemical composition - target - disease” regulatory network. The “Network Analyzer” plug-in was used to analyze the topological properties of the network, and the node degree was used as an important indicator describing the nodes in the network. As shown in Figure 3, the red arrow represents IBD, the green triangle represents TCM, the yellow square represents chemical components, and the blue oval
Table 1 Chemical composition information of zedoary turmeric and trisomes

<table>
<thead>
<tr>
<th>No.</th>
<th>Compound ID</th>
<th>Compound name</th>
<th>Oral bioavailability (%)</th>
<th>Dibenzodiazepines</th>
<th>Herbs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MOL001297</td>
<td>Trans-gondoic acid</td>
<td>30.7</td>
<td>0.20</td>
<td>Trisomes</td>
</tr>
<tr>
<td>2</td>
<td>MOL000358</td>
<td>Beta-sitosterol</td>
<td>36.91</td>
<td>0.75</td>
<td>Trisomes</td>
</tr>
<tr>
<td>3</td>
<td>MOL000392</td>
<td>Formononetin</td>
<td>69.67</td>
<td>0.21</td>
<td>Trisomes</td>
</tr>
<tr>
<td>4</td>
<td>MOL000449</td>
<td>Stigmasterol</td>
<td>43.83</td>
<td>0.76</td>
<td>Trisomes</td>
</tr>
<tr>
<td>5</td>
<td>MOL000296</td>
<td>Hederagenin</td>
<td>36.91</td>
<td>0.75</td>
<td>Trisomes, zedoary turmeric</td>
</tr>
</tbody>
</table>

Figure 1 Venn diagram of the targets of zedoary turmeric-trisomes and intestinal fibrosis in inflammatory bowel disease.

Figure 2 Protein-protein interaction network construction and analysis. A: Protein-protein interaction (PPI) regulatory network diagram; B: PPI network topology analysis.

represents the targets of the chemical components. The network consisted of 52 nodes, including 1 disease node, 2 TCM nodes, 5 chemical component nodes and 44 chemical component action targets. The average degree of the chemical components in the network was 19.20, and the average degree of the chemical component action targets was 3.05. An analysis of the compounds revealed that the degrees of hederagenin, beta-sitosterol, formononetin and stigmasterol were greater than 19.20. Regarding the targets, 12 had degrees greater than 3.05, and the top 5 targets were identified as PTGS1, CHRM1, PTGS2, GABRA1 and PGR, reflecting the synergistic effect of zedoary turmeric-trisomes on the treatment of IBD based on multiple components and multiple targets. The degree values of the compounds (No. 1-5) and targets (No. 6-49) are shown in Table 2.

GO and KEGG enrichment analyses

GO and KEGG enrichment analyses of the common targets were performed using the DAVID 6.8
database. A total of 759 items were obtained from the GO enrichment analysis, including 629 BP items, 41 CC items and 89 MF items. The results from the GO enrichment analysis were then sorted according to the corrected P-value, and a bar chart of the top 20 items was generated (Figure 4). The length of each bar in the figure represents the number of enriched genes, and the color difference represents the significance of the gene enrichment. The top BP terms included regulation of the membrane potential, response to steroid hormones, regulation of blood pressure, regulation of tube diameter, regulation of blood vessel size, and regulation of blood vessel diameter. The top CC terms included the intrinsic component of the postsynaptic membrane, the integral component of the postsynaptic membrane, the intrinsic component of the presynaptic membrane (membrane), the integral component of the presynaptic membrane (raft), the intrinsic component of the presynaptic membrane, and the membrane microdomain. The top MF terms included steroid hormone receptor activity and G protein-coupled amine receptor activity. Adrenergic receptor activity, nuclear receptor activity, transcription factor activity, and sequence-specific DNA binding activity are directly regulated by ligands, which also regulate sequence-specific DNA binding and catecholamine binding, among other processes.

The KEGG enrichment analysis yielded 52 items, and the top 19 items were selected to create a bubble map for visualization purposes according to the number of enriched genes, as shown in Figure 4. In the figure, the bubble size represents the number of enriched genes, and the color difference represents the significance of the gene enrichment. The KEGG enrichment results mainly involved pathways in cancer, neuroactive ligand-receptor interaction, hepatitis B, the calcium signaling pathway, adrenergic signaling in cardiomyocytes, and tuberculosis.

**Molecular docking results**
The top 4 target proteins (PTGS1, CHRM1, PTGS2 and GABRA1) in the network constructed as
described in Section 2.4 were extracted. Sybyl-x 2.1.1 was used for the molecular docking of hederagenin, beta-sitosterol, formononetin and stigmasterol. In the docking results (Figure 5), the purple color represents the above four compounds, and the red dotted lines represent hydrogen bond interactions. As shown in Figure 5A, ivy saponins interact with GABRA1 through Trp65, Ser130, Ser131, Gln348 and Glu349, and as depicted in Figure 5B, beta-sitosterol interacts with PTGS2 through hydrogen bonds via Thr212 and Gln454. Moreover, as indicated in Figure 5C, formononetin interacts with CHRM1 through hydrogen bond interactions between Thr189 and Thr192, and as illustrated in Figure 5D, stigmasterol interacts with PTGS1 through hydrogen bond interactions between Arg120 and Glu524. In
conclusion, the compounds saponin, β-sitosterol, formononetin and stigmasterol interact with GABRA1, PTGS2, CHRM1 and PTGS1 through hydrogen bonds and thus fully bind to the active site of the target protein, exhibiting good binding activity with the target protein.

**DISCUSSION**

*Application of network pharmacology for the prediction and analysis of the compatibility relationship between zedoary turmeric and trisomes*

Network pharmacology aims to further clarify the interactions and mechanism of a TCM and provide new strategies for drug research and development through the construction of a “drug - target - disease” network[15]. As an auxiliary screening method, molecular docking technology has been widely used to analyze the features of pharmacodynamic substances of TCM, to search for drug targets and to explore the mechanism of action of a TCM[16]. Network pharmacology combined with molecular docking technology has shown significant advantages in basic research on the activity of a TCM[17]. In this study, through the construction of the “drug - component - target - disease” network, the 8 active ingredients with higher degree values were analyzed to provide a reference for identifying the compatibility relationship between zedoary turmeric and trisomes and were found to jointly participate in the regulation of IBD intestinal fibrosis[18]. Studies have proven that ivy saponin has anti-inflammatory, anticoagulant, antidepressant, antitumor, antibacterial and other effects[19]. β-Sitosterol exerts antioxidant, cholesterol-lowering, anti-inflammatory, immunomodulatory and antitumor effects and can also enhance the secretion of IL-2 and interferon-γ, inhibit the secretion of IL-4, and exert anti-inflammatory effects by inhibiting IL-6 and tumor necrosis factor[20]. Formononetin, as an active component of flavonoids extracted naturally, was recently applied in a variety of disease models as a new inflammatory inhibitor and may have potential therapeutic value for IBD by activating Nrf2 expression[21]. Zielińska et al[22] showed that stigmasterol significantly reduced the inflammatory factors IL-1β, IL-6, and MCP-1 and the related cytokine synthase COX-2, inhibited colon shortening, and reduced the severity of IBD. These researchers also found that stigmasterol had greater anti-inflammatory activity than β-sitosterol and inhibited the symptoms of colitis[23]. In this study, the molecular docking results showed that hederagenin, β-sitosterol, formononetin and stigmasterol might be the core components of zedoary turmeric and trisomes involved in the treatment of intestinal fibrosis and might play an antifibrotic role through immune regulation and anti-inflammatory effects[24]. According to the synergistic effects of multiple components, we speculate that trisomes regulate immunity and exhibit anti-inflammatory effects in the treatment of IBD intestinal fibrosis, whereas zedoary aids the treatment of IBD intestinal fibrosis and improves body function[25].
**Association analysis between core target expression and IBD intestinal fibrosis**

Further analysis of the core targets in the “drug - chemical - target - disease” network and PPI network revealed that the top 5 targets were PTGS1, CHRM1, PTGS2, GABRA1 and PGR, suggesting that these genes may be the core targets in the treatment of IBD intestinal fibrosis. Among the top 30 targets in the PPI network based on the node degree value, the cancer-related targets included AR, ESR1, BCL2, CHRM1, ADRA1B, BAX, PGR, RXRA, CCNA2, ADRB1, ADH1C, SLC6A3, NR3C2, MAOB, ADRA2A, PPARG, PRKCA, NOS2, ESR2, CHRM3, ADRB2, and ADRA1A. The targets associated with hepatitis B were CCNA2, ADRB1, MAOB, and ADRB2, and the immunomodulatory targets included IL-4 and MAPK14. The targets associated with inflammation are PTGS2, PPARG and IL-4, and the targets related to the calcium signaling pathway, which include CHRM1, CHRM3, CASP3, CASP8, and CASP9, interact with the neuroactive ligand receptor. Recent studies have found that CASP activation can be observed in tumor cell apoptosis. CASP refers to a family of cysteine aspartate-specific proteases, and these proteases are the main enzymes that perform cell apoptosis and are involved in the occurrence and development of various diseases, particularly tumors and autoimmune diseases[26]. As a key protease, CASP8 participates in the transmission of exogenous apoptosis signals in mammals, and CASP9 plays a crucial role in the mitochondria-mediated endogenous apoptosis pathway[27]. CASP3 plays a central role as a key protease in apoptosis and is also known as the “death protease”, and the cascade reaction of apoptosis continues after the action of this enzyme[28]. Immune factors, including helper T cells, regulatory T cells, cytokines and autoantibodies, play an important role in the pathogenesis and progression of IBD[29]. The cytokine IL-4 plays an important role in regulating intestinal barrier function, is mainly synthesized by activated lymphocytes, and can inhibit the production of other cytokines, including IL-1, IL-6, IL-8 and TNF-α, and the generation of lymphocytes and macrophages[30]. Several studies have reported that in IBD, IL-4 significantly reduced vascular endothelial growth factor (VEGF) and inhibited the formation of blood vessels[31], but the expression of VEGF in the tumor tissues of patients with colorectal tumors was significantly increased[32]. The results of this study indicated that PRKCA was involved in the regulation of the proliferation, differentiation, survival, migration, cell polarity and cell cycle of various cancer cells; in mediating cell proliferation, differentiation, cell cycle progression and apoptosis; in regulating gene expression; and in promoting tumor formation and metastasis and participates in metabolic regulation[33]. The PTGS2 gene is induced by COX2 and is involved in the inflammatory response, cell proliferation, apoptosis and other pathological processes[34]. Further analysis of the core targets in the “drug - components - target - disease” network and PPI network revealed that the mechanism of action of zedoary turmeric-trisomes in the treatment of IBD intestinal fibrosis was primarily related to inflammatory factors and antitumor and immune regulation[35].

**The main mechanism of zedoary turmeric and trisomes in the treatment of IBD intestinal fibrosis reveals the synergistic relationship and compatibility of TCMs**

Compared with other organs where fibrosis occurs, the gut is the only organ where a large number of microorganisms coexist, and gut microbes have a profound impact on mucosal homeostasis between health and disease. Changes in the intestinal barrier can cause bacteria to migrate into the intestinal mucosa or portal vein circulation, which alters the host-microbe interactions that are key to intestinal inflammation[36]. In particular, gut cells can sense microbe-derived, pathogen-associated molecular patterns through pattern recognition receptors[37].

TCMs have achieved good results in the treatment of diseases through dialectical treatment and a holistic approach[38]. TCM or TCM compounds have multiple components and can have a regulatory role through multiple channels, multiple targets and multiple links[39]. The typical characteristic of IBD intestinal fibrosis is intestinal fibrosis formed by stenosis, which seriously affects the quality of life of patients[40]. This study focused on the factors and mechanisms related to fibrosis and found that trisomes and zedoary had therapeutic effects through inflammatory factor regulation, immune regulation, antitumor activity and other pathways[41,42]. Vermeire et al[43] used a San-ling pill prescription combined with Western medicine to reduce the Crohn’s disease activity index score, platelet activity index and D-dimer index of patients with Crohn’s disease and to improve the rate of endoscopic fibrosis. The underlying fibrosis mechanism in IBD is complex, involving a variety of cellular and molecular mechanisms, and the traditional view that intestinal fibrosis is an inevitable and irreversible process is gradually changing[44].

**CONCLUSION**

In summary, zedoary turmeric and trisomes influence each other and act together to treat IBD intestinal fibrosis through multiple pathways with their multiple components and targets, and this finding fully reflects the holistic and comprehensive characteristics of TCMs in the treatment of diseases[45]. The results of the analysis of their mechanism of action in the treatment of IBD intestinal fibrosis via a technical approach consisting of network pharmacology and molecular interconnections lay the foundation for further research and provide a new perspective for multidimensional and multilevel
research on treatments with TCM compounds.

**ARTICLE HIGHLIGHTS**

**Research background**
Intestinal fibrosis is a serious complications of inflammatory bowel disease (IBD), but there is no effective drug treatment. Therefore, it is important to find drug treatments with fewer side effects.

**Research motivation**
To provide an objective basis for zedoary turmeric-trisomes in the treatment of IBD with intestinal fibrosis.

**Research objectives**
To investigate the use of network pharmacology and molecular docking technology in analyzing the effective components and mechanism of zedoary turmeric-trisomes in the treatment of IBD with intestinal fibrosis.

**Research methods**
The Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform were used to extract the active components and action targets of zedoary turmeric-trisomes.

**Research results**
The protein-protein interaction network showed that the core therapeutic targets included JUN, MAPK14, CASP3, AR, and PTGS2. The GO enrichment analysis identified 759 items, and the KEGG enrichment analysis yielded 52 items. Molecular docking showed that the compound bonded with the target through hydrogen bond interactions and exhibited good docking activity.

**Research conclusions**
This study identified the potential mechanism of action of zedoary turmeric-trisomes in the treatment of IBD using network pharmacology and molecular docking technology.

**Research perspectives**
TCM has a potential mechanism in the treatment of IBD with intestinal fibrosis.

**FOOTNOTES**

**Author contributions:** Zheng L, Ji YY, Dai YC and Wu SC reviewed the literature and prepared the manuscript, performed the writing and revising of the manuscript; Zheng L and Wen XL contributed to design this work, and performed overall supervision; Zheng L wrote and revised the paper; all authors approved the final manuscript.

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Case Control Study

Comprehensive proteomic signature and identification of CDKN2A as a promising prognostic biomarker and therapeutic target of colorectal cancer

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Abstract

BACKGROUND
The carcinogenesis of colorectal cancer (CRC) involves many different molecules and multiple pathways, and the specific mechanism has not been elucidated until now. Existing studies on the proteomic signature profiles of CRC are relatively limited. Therefore, we herein aimed to provide a more comprehensive proteomic signature profile and discover new prognostic markers and therapeutic targets by performing proteomic analysis of CRC and paired normal tissues.

AIM
To investigate the proteomic signature and identify novel protein prognostic biomarkers of CRC.

METHODS
Cancer tissues and paired normal tissues were collected from 48 patients who underwent surgical removal at the China-Japan Friendship Hospital from January 2020 to June 2021. Data independent acquisition (DIA) quantitative proteomic analysis was performed using high-performance liquid chromatography-mass spectrometry/mass spectrometry (nano-UHPLC-MS/MS) to identify differen-
tially expressed proteins, among which those with a \( P \) adj value \((t\) test, BH correction) < 0.05 and an absolute fold change \( (|\log_{2}\text{FC}|) > 2 \) were identified as potential markers. Differentially expressed proteins were selected by bioinformatics analysis and validated by immunohistochemical tissue microarrays, and their association with prognosis was further analyzed with the Gene Expression Profiling Interactive Analysis database to identify prognostic protein biomarkers of CRC.

RESULTS

Significantly differential protein expression was observed between cancer tissues and normal tissues. Compared with normal tissues, 1115 proteins were upregulated and 705 proteins were downregulated in CRC based on \( P \) adj < 0.05 and \( |\log_{2}\text{FC}| > 2 \), and bioinformatics analysis revealed that the differentially expressed proteins were involved in multiple biological processes associated with tumorigenesis, including ribosome biogenesis in eukaryotes, focal adhesion, extracellular matrix-receptor interactions and other tumor metabolism processes. Moreover, cyclin-dependent kinase inhibitor 2A (CDKN2A) expression was markedly upregulated in CRC, as validated by immunohistochemistry \((0.228 \text{ vs } 0.364, \ P = 0.0044\)\), and was significantly enriched in tumor proliferation and signal transduction pathways such as the cell cycle and p53 signaling pathways. High CDKN2A expression was significantly correlated with poor prognosis \( (P = 0.021) \). These results demonstrated that CDKN2A functions as a driver of CRC.

CONCLUSION

Our study provides a comprehensive proteomic signature of CRC and highlights CDKN2A as a potential powerful prognostic marker and precision therapeutic target.

Key Words: Colorectal cancer; Proteomic analysis; Cyclin-dependent kinase inhibitor 2A; Prognostic biomarker; Therapeutic target; Precision treatment

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Core Tip: In this study, quantitative proteomic analysis of colorectal cancer (CRC) was comprehensively performed, revealing many differentially expressed proteins that may be useful for mining novel targets. The results revealed the overexpression of thousands of tumor proteins, among which cyclin-dependent kinase inhibitor 2A (CDKN2A) was the highlight of this study, and high CDKN2A expression in CRC was significantly associated with poor prognosis and could serve as a powerful prognostic marker and precision therapeutic target.

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INTRODUCTION

According to the newest global cancer statistics, colorectal cancer (CRC) has become the second leading cause of cancer-related morbidity and mortality worldwide, and these rates continue to increase every year[1]. In the past few decades, the primary CRC treatment methods, including surgical resection, chemo- or chemoradiotherapy, immunotherapy and targeted therapy, have significantly improved[2]. However, the prognosis of CRC patients, especially those diagnosed at an advanced stage, remains poor. Colorectal carcinogenesis encompasses mechanisms of abnormal proliferation, differentiation, resistance to apoptosis and surrounding invasion of colonic epithelial cells[3]. A variety of genes and the interplay of multiple signaling pathways have been proposed to underlie the tumorigenesis of CRC, but the complex mechanism remains incompletely understood.

On the basis of the biological central dogma, gene mutation plays an important role in the occurrence and development of malignant tumors, including CRC. Previous studies have revealed possible gene mutations in patients with CRC; however, their effects are not completely consistent. For example, Pearlman et al[4] proposed that cyclin-dependent kinase inhibitor 2A (CDKN2A) mutation had nothing to do with CRC risk; in contrast, Lee et al[5] found that CDKN2A was a tumor suppressor, and Li et al[6] insisted that CDKN2A was an oncogenic gene that was significantly correlated with poor prognosis.
Therefore, gene mutation alone could not fully explain the occurrence and metastasis of tumors: the perspective of proteins, the executors of function, were also needed.

Proteins play important physiological roles and have an enormous impact on cellular biology and human health, and proteomics has thus become an indispensable tool for mechanistic studies\(^7\),\(^8\). Although rapidly accumulating omics studies, such as genomic, transcriptomic and epigenetic studies, have been conducted, genomic and epigenetic analyses cannot be used to fully elucidate the large variance in cancer mechanisms\(^9\). Proteomics analysis has been gradually applied to a variety of cancer types, such as pancreatic ductal adenocarcinoma and breast cancer, to characterize the tumor stage, predict metastasis, identify candidate cancer biomarkers, and evaluate therapeutic effects\(^10\),\(^11\). Nevertheless, our knowledge of the proteomics mechanisms of CRC is still limited.

Therefore, this study aimed to elucidate the proteomic profiles of CRC by performing proteomics analysis of CRC tissues and adjacent normal mucosal tissues. By performing tissue microarray validation, gene expression profiling interactive analysis (GEPIA) genomics and survival analyses in combination, we aimed to identify potential target proteins among numerous differentially expressed proteins and provide clinicians with more evidence for precision CRC treatment.

### MATERIALS AND METHODS

**Study population**

A total of 48 CRC patients underwent surgical resection of colorectal tumors between January 2020 and June 2021 at the China-Japan Friendship Hospital. The inclusion criteria were as follows: The diagnosis of CRC was confirmed via identification by the pathology department. The exclusion criteria were as follows: (1) Patients with familial adenomatous polyposis, hereditary nonpolyposis colorectal cancer, or synchronous multiple CRCs; (2) Patients with inflammatory bowel disease; (3) Patients who had received prior treatments, including chemoradiotherapy, targeted therapy, and immunosuppressive therapy, during the previous 6 mo before resection; and (4) Patients were lacking informed consent or had missing data. Medical records were reviewed to obtain clinicopathological information, such as the patient’s age, sex, differentiation status, and TNM stage. The study was approved by the Ethics Committee of China-Japan Friendship Hospital (No. 2018-116-K85) and was conducted in accordance with the Declaration of Helsinki.

**Sample collection and preparation**

After resection of fresh colorectal cancer tissues along with the adjacent noncancerous tissues (>5 cm away from the tumor), the collected samples were cleaned with cold normal saline, immediately frozen in liquid nitrogen and stored at -80 °C until use. Sample preparation includes multiple steps: washes, denaturation, reduction and alkylation, digestion by trypsin and extraction and cleanup of mixed peptides. Commercially available iST Sample Preparation kit (PreOmics, Germany) was used following the manufacturer’s recommendation. Briefly, 50 µL of Lyse buffer was added and heated at 95 °C for 10 min at 1000 rpm with agitation. After cooling the sample to room temperature, trypsin digestion buffer was added, and the sample incubated at 37 °C for 2 h at 500 rpm with shaking. The digestion process was stopped with a stop buffer. Sample clean-up and desalting was carried out in the iST cartridge using the recommended wash buffers. Peptides were eluted with elution buffer (2 × 100 µL), and then lyophilized by SpeedVac.

**Nano-UHPLC–MS/MS analysis**

The peptides were redissolved in solvent A (A: 0.1% formic acid in water) and analyzed by an Orbitrap Fusion Lumos Tribrid coupled to an EASY-nanoLC 1200 system (Thermo Fisher Scientific, MA, USA). Next, 4 µL of the peptide sample was loaded onto a 25 cm analytical column (75 μm inner diameter, 1.9 µm resin (Dr Maisch)) and separated by gradient applied over 90 min as follows: 4% buffer B (80% ACN with 0.1% FA) for 3 min; a stepwise increase to 50% buffer B in 82 min; increase to 95% buffer B in 1 min; and a hold for 7 min. The column flow rate was maintained at 250 nL/min, and the column temperature was 55°C. The electrospray voltage was set to 2 kV. The mass spectrometer was run under data independent acquisition (DIA) mode with hybrid data strategy. A survey scan was acquired at 120,000 resolution, normalized AGC target of 250% and a maximum injection time of 100ms. In the DIA MS2 acquisition, variable Isolation window were performed. One full scan followed by 20 windows with resolution of 50,000, normalized AGC target of 200%, a maximum injection time of 86ms and normalized collision energy at 33.

**MS data analysis**

Raw DIA data were processed and analyzed by Spectronaut 15.0 (Biognosys AG, Switzerland) with default settings. Spectronaut was set up to search the UniProt-Homo sapiens database (version 201907, 20428 entries) assuming that trypsin was used as the digestion enzyme. Carbamidomethyl (C) was specified as the fixed modification. Oxidation (M) was specified as the variable modification. The
retention time prediction type was set to dynamic iRT. Data extraction was performed by Spectronaut based on extensive mass calibration. Spectronaut was used to determine the ideal extraction window dynamically depending on the iRT calibration and gradient stability. The Q value (FDR) cutoff on the precursor level was 1%, and the protein level was 1%. Decoy generation was set to mutated, which was similar to scrambled but only applied a random number of AA position swamps (min = 2, max = length/2). The normalization strategy was set to local normalization. The average top 3 filtered peptides that passed the 1% Q value cutoff were used to calculate the major group quantities. After application of the t test, differentially expressed proteins were identified by a P adj value < 0.05 and an absolute fold change > 2. The R package was used to visualize the differential expression for bioinformatics analysis. Gene set enrichment analysis (GSEA) was completed by using GSEA v4.2.3 (https://www.gsea-msigdb.org/gsea/index.jsp).

**Immunohistochemical analysis**

The Human Protein Atlas (HPA, http://www.proteinatlas.org/) contains images of histological sections from normal and cancer tissues obtained by immunohistochemistry and is publicly available at v20.proteinatlas.org. Antibodies were labeled with DAB (3, 3'-diaminobenzidine), and the resulting brown staining indicated where an antibody had bound to its corresponding antigen. The section was further counterstained with hematoxylin to enable visualization of microscopic features. Each sample was represented by 1 mm tissue cores. CRC pathology and normal colon tissue microarrays were downloaded to quantify protein expression. ImageJ software was used to assess the staining area and integrated optical density (IOD) to determine the average optical density (AOD) values. All images were manually evaluated by two independent observers. The Mann–Whitney U test was used for statistical analyses, and the statistical significance level was set to 0.05.

**Gene expression and survival analysis**

GEPIA (http://gepia.cancer-pku.cn/index.html) provides customizable functions such as tumor/normal differential expression analysis and patient survival analysis[12]. A box plot was generated to compare gene expression in CRC. Genes with |log(FC)| values >1 and q values < 0.01 were considered to be differentially expressed. GEPIA was also used to perform overall survival (OS) analysis based on gene expression. We selected the median gene expression as a group cutoff for splitting the high- and low-expression cohorts. Kaplan–Meier plots and the log-rank test were used to analyze differences in survival times between patients with high and low expression.

**RESULTS**

**Proteomic signatures**

We collected a total of 48 pairs of cancer tissues and matched adjacent normal tissues after surgical treatment of CRC for quantitative proteomic detection. We found differences in the protein signatures between the CRC group and the normal group, and PLS-DA could clearly distinguish the two groups (Figure 1A). In total, we identified 7643 proteins as well as 1820 differentially expressed proteins with an FDR < 1% in the CRC group vs the normal group, which were used for subsequent enrichment analysis and tumor target mining. There were 1115 proteins upregulated in the tumor group, including CEAM6/5, IFM1, LAT1, RA13, VISL1, TACC3, HS71L, IMA1, DIXF, and UPAR, while 705 proteins, including SYUG, NOS1, RT26, GEMI4, HAUS5, TET1, NB5R2, PERI, LIPS and PPLA, were downregulated in the tumor group compared with the normal group (Figure 1B, Supplementary Figure 1).

GO analysis of the differentially expressed proteins was performed, and the differentially expressed proteins were significantly enriched in biological processes (BPs; RNA metabolic processing, RNA processing, biological adhesion, and other processes), cellular components (CCs, binding, protein binding, catalytic activity, RNA binding, etc.), and molecular functions (MFs, extracellular exosome, intracellular nonmembrane-bounded organelle, nucleoplasm, etc.) (Figure 1C). The differentially expressed proteins were further subjected to subsequent Kyoto encyclopedia of genes and genomes pathway analysis, which identified the PI3K-Akt signaling, focal adhesion, ribosome biogenesis in eukaryotes, cell cycle, extracellular matrix-receptor interaction and DNA replication pathways as being significantly enriched (Figure 1D). To explore the mechanisms of the differentially expressed proteins in cancer development to the greatest extent possible, we performed further GSEA, which showed that transcription factors, the cell cycle, the p53 signaling pathway, and other processes were significantly enriched in CRC tissues (Figure 1E and F, Supplementary Figures 2 and 3).

Visualizing and displaying the bioinformatics analysis results led to the identification of a special protein, CDKN2A, which was significantly upregulated in tumors compared with the normal tissues. KEGG pathway enrichment analysis showed that CDKN2A was involved in the cell cycle, PI3K-Akt signaling pathway, and p53 signaling pathway. GSEA further confirmed that CDKN2A was involved in regulating the cell cycle and p53 signaling pathway and functioned as a core gene in the gene set. Therefore, we speculated that CDKN2A plays a pivotal role in colorectal carcinogenesis and has potential as a prognostic biomarker.
Wang QQ et al. Proteomic signature and CDKN2A as biomarker

A

PLS-DA plot (CRC_vs_CN)

Group
- CRC
- CN

B

Volcano plot (CRC_vs_CN)

Color
- Down
- Nochange
- Up

C

GO classification plot (CRC_vs_CN)

Biological process

Molecular function

Cellular component
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Figure 1 Quantitative proteomic profiling and bioinformatic analysis of colorectal cancer. A: Partial least squares-discriminant analysis of colorectal cancer and normal tissues; B: The volcano plot shows 1115 upregulated and 705 downregulated proteins in tumors; C: Gene ontology analysis shows that differentially expressed proteins are involved in biological processes, cellular components, and molecular functions; D: Kyoto encyclopedia of genes and genomes analysis shows that differentially expressed proteins are significantly enriched in multiple pathways including ribosome biogenesis in eukaryotes, focal adhesion, cell cycle and extracellular matrix-receptor interaction; E and F: Gene set enrichment analysis shows that differentially expressed proteins are enriched in the cell cycle and p53 signaling pathway. PLS-DA: Partial least squares-discriminant analysis; CRC: Colorectal cancer tissue; CN: Normal colon tissue; GO: Gene ontology; KEGG: Kyoto encyclopedia of genes and genomes; ECM: Extracellular matrix; NES: Normalized enrichment score.

Immunohistochemical validation of CDKN2A
We collected protein microarrays from a total of 3 normal colon tissues and 12 CRC tissues from the HPA database that had been subjected to antigen antibody labeling reactions using CAB00093 antibodies (Supplementary Figure 4). The AOD value of each chip was calculated using ImageJ (Supplementary Table 1). The protein expression of CDKN2A was significantly different between CRC and normal samples \((P < 0.05)\) (Figure 2A and B). Low or no protein expression of CDKN2A was observed in the normal samples, while the staining intensity and area were significantly increased in CRC samples, implying that CDKN2A protein expression was significantly upregulated \((P = 0.0044)\). These results were consistent with those of proteomic analysis and further confirmed that the protein expression of CDKN2A was significantly increased in CRC. The results are presented as a bar graph (Figure 2B).

CDKN2A gene expression and survival analysis
To explore the expression profile of the CDKN2A gene in normal mucosa and CRC tissues as well as its association with patient prognosis, we performed differential gene expression analysis and survival analysis using the GEPIA database. We found that CDKN2A gene expression differed significantly between CRC and normal tissues, with significantly higher expression in colon cancer \((P < 0.05)\), and the same trend was observed in rectal cancer compared with normal tissue \((P < 0.05)\) (Figure 2C). Further overall survival analysis using GEPIA showed that a total of 362 colorectal cancer patients were matched to normal tissues from the TCGA and GTEx databases and that patients with high expression of the CDKN2A gene had a significantly decreased overall survival \((P = 0.021)\), while patients with low
Wang QQ et al. Proteomic signature and CDKN2A as biomarker

Figure 2 Immunohistochemical validation of cyclin-dependent kinase inhibitor 2A and overall survival analysis. A: Immunohistochemical images showing cyclin-dependent kinase inhibitor 2A (CDKN2A) negativity in normal colon tissues and CDKN2A positivity in colorectal cancer (CRC) tissues; B: Comparison of CDKN2A expression in CRC and normal tissues based on the average option density (AOD). AOD calculated using ImageJ software; C: GEPIA shows gene overexpression of CDKN2A in both colon adenocarcinoma and rectum adenocarcinoma patients in comparison with normal people; D: The relationship between CDKN2A expression and overall survival in CRC patients. Patients with high CDKN2A expression have a poor prognosis, and those with low CDKN2A expression have a longer survival time. CRC: Colorectal cancer; AOD: Average option density; COAD: Colon adenocarcinoma; READ: Rectum adenocarcinoma; CDKN2A: Cyclin-dependent kinase inhibitor 2A.

expression of the CDKN2A gene had a relatively good prognosis (Figure 2D).

DISCUSSION

Signaling proteins are very attractive for the precise treatment of cancer. However, research on the proteomic spectrum of CRC is still limited. In this study, 48 pairs of cancer and adjacent normal tissues were collected for proteomics analysis, and 1115 upregulated proteins and 705 downregulated proteins were observed in the CRC group. First, we made an enormous effort to provide more comprehensive proteomic signatures for CRC. Second, we identified many proteins with abnormal expression abundance in CRC and validated their potential as tumor targets. Interestingly, among all the differentially expressed proteins, we highlighted one upregulated protein, cyclin-dependent kinase inhibitor 2A (CDKN2A), which is involved in both the cell cycle and the p53 signaling pathway, and a tissue microarray confirmed that the CDKN2A protein was highly expressed in CRC and was associated with low OS survival and poor prognosis. This suggests that CDKN2A plays a cancer-driving role in CRC and is predictive of poor survival.

CDKN2A, is a well-known tumor suppressor located at chromosome 9p21[13,14]. Two proteins are encoded, p16INK4a and p14ARF, which exert different regulatory effects on the cell cycle: p14ARF interacts with and degrades MDM2, preventing p53 inactivation by ubiquitin-mediated proteolysis or transcriptional silencing, and P16INK4a binds CDK4 and CDK6 to prevent phosphorylation of the Rb protein[13,13]. Loss-of-function mutations or homozygous deletions of CDKN2A resulted in the loss of both proteins, releasing the G1–S and G2–M cell cycle checkpoints and resulting in uninhibited cell proliferation and tumor formation[16]. A literature database search revealed that CDKN2A has been extensively researched in the context of melanoma, pancreatic cancer and other tumor types, but the findings are controversial[15,17].
CDKN2A plays a role in CRC initiation and progression via multiple mechanisms. Ferroptosis, a newly defined form of cell death that differs from apoptosis and autophagy and is characterized by iron overload, lipid reactive oxygen species and lipid peroxidation, is involved in the carcinogenesis, progression, and treatment of CRC\[^{15}\]. A study showed that CDKN2A is a ferroptosis-associated gene that is involved in the iron metabolism and tumorigenesis of CRC by enhancing p53-dependent transactivation and ferroptosis. The upregulation of this gene in CRC correlated with poor prognosis and could be considered part of a predictive model\[^{19}\]. However, our differential protein enrichment analysis did not reveal the involvement of CDKN2A in this process. In addition, CDKN2A is a prominent hallmark of cellular senescence, whereas reactive oxygen species, DNA damage, and chronic inflammation all induce cellular senescence\[^{20-22}\]. In mice, p53 genes in senescent cells might transform these cells into highly aggressive, cancer-initiating cells with long-term accumulation progressing to a cancerous state\[^{23}\]. Another recent study on the inflammatory microenvironment in CRC found significant differences in CDKN2A expression between the epithelium and stroma, with a 10-fold decrease in the epithelium and a 17-fold increase in the stroma\[^{24,25}\]. This study speculated that the activation of CDKN2A expression in the stroma was influenced by cellular senescence and oncogene activation, and senescent fibroblasts prematurely accumulated in the stroma as a result of chronic inflammation and oxidative stress\[^{24}\]. Moreover, CDKN2A participates in the development of CRC through the Wnt/β-catenin signaling pathway\[^{15,26}\].

The role of CDKN2A in CRC is also controversial. In 2017, a comprehensive cancer center conducted exploratory research on CRC cancer susceptibility genes and found that CDKN2A had high- or moderate-level gene mutations. This study pointed out that CDKN2A gene mutation was not traditionally associated with CRC risk\[^{4,27}\]. Some studies have shown that CDKN2A usually acts as a tumor suppressor. On the one hand, CRC patients have a poor prognosis due to the occurrence of promoter region hypermethylation, CDKN2A gene silencing or dysfunction, which causes uncontrolled cell proliferation and carcinogenesis\[^{5,28}\]. On the other hand, CDKN2A participates in the ILF3-AS1/EZH2/CDKN2A/H3K27me3 axis, and downregulation of CDKN2A accelerates CRC proliferation and metastasis\[^{29}\]. However, the results of some other studies were opposite but consistent with our findings. A recent convincing study demonstrated that CDKN2A was a cancer-driver gene that could effectively predict the poor prognosis and clinical status of CRC patients\[^{6}\]. Concordant with this, several studies found that CDKN2A was a risk gene for overexpression in CRC and highlighted that increased CDKN2A protein expression, rather than loss of protein expression, was associated with poor prognosis in CRC\[^{3,19,25,30}\].

Possible explanations for these contradictory results are as follows: (1) It is well known that CDKN2A protein expression is affected by genomic deletions, point mutations, and promoter region hypermethylation\[^{28,31}\]. The promoter region of the CDKN2A gene was hypermethylated, combined with methylase, and thus could not bind to the RNA binding enzyme, resulting in decreased or silent protein expression. Therefore, we speculated that this result was due to hypermethylation of gene body regions rather than promoter regions, and CDKN2A protein expression was thus positively altered in the tumor with the help of histone modification\[^{32}\]; (2) An additional speculation was that CDKN2A protein expression was influenced by the stage of tumor development. CDKN2A is known to be involved in the epithelial-stromal microenvironment during CRC development, with different stages of tumor progression and diverse states of the tumor microenvironment, and CDKN2A protein expression thus varies substantially in multiple studies\[^{24}\]. It has also been proposed that the upregulation of CDKN2A protein expression is a consequence of tumor metastasis\[^{30}\]; and (3) The degree of cellular senescence varies, leading to different trends in the expression of CDKN2A and therefore to conflicting inferences about its role in tumors\[^{22}\]. Additionally, since the mRNA expression of CDKN2A could be promoted by nontumor cells present in the tumor microenvironment, interpreting of bulk transcriptional data remains challenging, requiring single-cell RNA-seq analysis to analyze population-specific transcription of this gene\[^{33}\]. Because of the limitations of the study design, small sample size, and publication bias, the mechanism of CDKN2A in CRC has not been fully elucidated despite multiple investigations being conducted. This problem needs to be resolved in the future to fully construct the genomic, transcriptomic, epigenetic and proteomic landscape of CDKN2A in CRC.

Our study more comprehensively revealed the proteomic signature of CRC, although not for the first time, and provided important biological and clinical insights. Of course, our study has some limitations. First, similar to the shortcomings of previous studies, this was a single-center study, and the findings may therefore not have general applicability. Second, the lack of genomic and epigenetic data from our own tissues prevented the complete elucidation of the gene-mRNA-protein chain. To some extent, it is possible to complement the understanding of the CRC mechanism at the protein level. Finally, to fully substantiate the tumor suppressor or cancer-promoting role of the CDKN2A gene, multicenter studies are needed.

**CONCLUSION**

In conclusion, this study more comprehensively revealed the proteomic signature of CRC. CDKN2A
was identified among all the differentially expressed proteins and shown to be involved in the cell cycle, p53 signaling pathway and other mechanisms. Moreover, CDKN2A is associated with poor overall survival and may serve as a prognostic biomarker and treatment target for CRC.

ARTICLE HIGHLIGHTS

Research background
Colorectal cancer (CRC) has become the second leading cause of cancer-related deaths worldwide; however, its specific pathogenic mechanism has not been elucidated until now. Exploring the proteomic features of CRC, mining protein prognostic biomarkers and identifying precise therapeutic targets are important for improving the prognosis of CRC patients.

Research motivation
Despite improvements in diagnosis and treatment, the overall survival of CRC patients is still not very satisfactory. In particular, the 5-year survival rate of patients with advanced CRC remains less than 20%. Therefore, there is an urgent need for the clinical discovery of novel biomarkers and therapeutic targets. With the development of proteomic technology, proteins are considered potential biomarkers and precision therapy targets in CRC.

Research objectives
To comprehensively characterize the proteomic features and identify novel prognostic biomarkers and precise therapeutic targets of CRC.

Research methods
The differentially expressed proteins (DEPs) were obtained by performing liquid chromatography–mass spectrometry detection of clinical samples, including colorectal cancer tissues and paired paracancerous tissues. Through further bioinformatic analysis, immunohistochemical (IHC) verification, and the correlation between DEPs and overall survival, protein prognostic biomarkers and therapeutic targets for CRC were identified.

Research results
The authors first provide a comprehensive characterization of the proteomic signature of CRC. Compared with normal tissues, 1115 proteins were upregulated and 705 proteins downregulated in CRC based on a $P_{adj} < 0.05$ and $|\log_{2} FC| > 2$ criteria, and the DEPs were involved in a variety of different molecular functions and signal transduction pathways. In addition, through IHC verification and survival analysis, we found that high expression of cyclin-dependent kinase inhibitor 2A (CDKN2A) protein was significantly correlated with poor prognosis in CRC. This demonstrated that CDKN2A could be used as a prognostic biomarker and a target for precision therapy in CRC.

Research conclusions
The proteomic signature of CRC has been comprehensively characterized, and CDKN2A has strong potential as a prognostic biomarker and a target for precision therapy in CRC.

Research perspectives
Novel protein prognostic biomarkers and precise therapeutic targets provide new opportunities to improve the prognosis of CRC patients.

ACKNOWLEDGEMENTS
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FOOTNOTES

Author contributions: Wang QQ performed the study, analyzed the data, and drafted the manuscript; Zhou YC and Zhou Ge JY collected samples from subjects; Qin G provided guidance on experimental procedures; Yin TF, Zhao DY, and Tan C collected the clinical data; Yao SK supervised the study performance, revised the manuscript, and obtained the funding; and All authors read and approved the final manuscript.

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Retrospective Cohort Study

Is anoplasty superior to scar revision surgery for post-hemorrhoidectomy anal stenosis? Six years of experience

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Abstract

BACKGROUND
Anal stenosis is a rare but frustrating condition that usually occurs as a complication of hemorrhoidectomy. The severity of anal stenosis can be classified into three categories: mild, moderate, and severe. There are two main surgical treatments for this condition: scar revision surgery and anoplasty; however, no studies have compared these two approaches, and it remains unclear which is preferable for stenoses of different severities.

AIM
To compare the outcomes of scar revision surgery and double diamond-shaped flap anoplasty.

METHODS
Patients with mild, moderate, or severe anal stenosis following hemorrhoidectomy procedures who were treated with either scar revision surgery or double diamond-shaped flap anoplasty at our institution between January 2010 and December 2015 were investigated and compared. The severity of stenosis was determined via anal examination performed digitally or using a Hill-Ferguson retractor. The explored patient characteristics included age, sex, preoperative severity of anal stenosis, preoperative symptoms, and preoperative adjuvant therapy; moreover, their postoperative quality of life was measured using a 10-point scale. Patients underwent proctologic follow-up examinations one, two, and four weeks after surgery.

RESULTS
We analyzed 60 consecutive patients, including 36 men (60%) and 24 women (40%). The mean operative time for scar revision surgery was significantly shorter than that for double diamond-shaped flap anoplasty (10.14 ± 2.31 [range: 7-15] min vs 21.62 ± 4.68 [range: 15-31] min; P < 0.001). The average length of hospital stay was also significantly shorter after scar revision surgery than after anoplasty (2.1 ± 0.3 vs 2.9 ± 0.4 d; P < 0.001). Postoperative satisfaction was categorized into four groups: 45 patients (75%) reported excellent satisfaction (scores of 8-10), 13 (21.7%) reported good satisfaction (scores of 6-7), two (3.3%) had no change in satisfaction (scores of 3-5), and none (0%) had scores indicating poor satisfaction (1-2). As such, most patients were satisfied with their quality of life after surgery other than the two who noticed no difference due owing to the fact that they experienced recurrences.

CONCLUSION
Scar revision surgery may be preferable for mild anal stenosis upon conservative treatment failure. Anoplasty is unavoidable for moderate or severe stenosis, where cicatrized tissue is extensive.

Key Words: Anal canal; Anoplasty; Scar revision; Stenosis; Surgery-induced tissue adhesions; Surgical flaps

Core Tip: The severity of anal stenosis can be classified into three categories: mild, moderate, and severe. According to our study, we drew an algorithm for the management of anal stenosis based on severity. For mild anal stenosis, scar revision surgery can be attempted first if nonsurgical methods fail, with anoplasty performed if recurrence occurs. For moderate and severe anal stenosis, opting for anoplasty from the outset is the best option to prevent subsequent surgeries.

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DOI: https://dx.doi.org/10.12998/wjcc.v10.i22.7698
severity of symptoms and recover normal anal function\cite{20,21}. Ideally, the selected procedure should be simple to perform and be well-tolerated, with a low complication rate and good long-term results without recurrence. However, there are no studies comparing the two aforementioned surgical approaches, and it remains unclear whether the choice of procedure depends on the severity of the stenosis. Therefore, we performed this retrospective study to compare patients who underwent scar revision surgery to those who underwent anoplasty over a six-year period.

**MATERIALS AND METHODS**

**Patients**
This retrospective cohort analysis included patients who were treated between January 2010 and December 2015 for mild-to-severe anal stenosis and who underwent scar revision surgery or double diamond-shaped flap at the Department of Surgery, Taiwan Adventist Hospital, Taipei, Taiwan (Figure 1). We included patients who were diagnosed with anal stenosis post-hemorrhoidectomy. Patients with this condition owing to other causes such as inflammatory bowel disease, tuberculosis, trauma, previous radiation therapy, and previous anal malignancy were excluded from the study, as were those who were lost to follow-up. Ultimately, 60 patients who fulfilled the selection criteria were included in the analysis.

**Preoperative management**
Preoperative evaluation included clinical and proctologic examinations. The following variables were collected during the clinical examination: age; sex; the preoperative severity of anal stenosis, symptoms, and adjuvant therapy. A proctologic examination was performed digitally or using a Hill-Ferguson retractor to determine the severity of the stenosis. All the patients had first attempted conservative management methods but were unsuccessful, thereby necessitating surgical intervention to ameliorate their discomfort. All data were inputted into an electronic database.

**Surgical technique**
Full bowel preparation was performed preoperatively, and the same team performed all surgical procedures for all the patients. Scar revision surgery or double diamond-shaped flap was chosen according to the surgeon’s experiences and preference. We performed these two procedures under intravenous general anesthesia; moreover, a single dose of intravenous antibiotics (cefazolin) was administered upon the induction of anesthesia as a prophylactic against wound infection. The patients were placed in the jackknife position, and the skin was sterilized and draped per standard protocol. For scar revision surgery, the scar was commonly found in the 3, 7, and 11 o’clock directions. We removed the scar with a longitudinal incision through the stricture while controlling bleeding with wet epinephrine tape. The wound was closed with a 3-0 catgut (transverse closure) and covered with gauze (Figure 2A). For the double diamond-shaped flap anoplasty, a diamond-shaped flap from the adjacent perianal skin was delineated and dissected together on both sides. The dissection was generally performed deep into the fascia to create a well-perfused, tension-free flap transposed into the anal canal. The flap was then introduced into the anal canal defect for wound coverage (Figures 2B and 3).

**Postoperative follow-up**
Before discharge, the operative time, length of hospital stay, and postoperative complications were recorded. The patients underwent scheduled clinical and proctologic examinations at the outpatient clinic 1, 2, and 4 wk after surgery. Subsequently, regular inspections were performed upon patient request. Patients were contacted by telephone after 6 mo and were invited to the outpatient clinic for a final follow-up evaluation. During their postoperative workups, the patients underwent clinical and proctologic evaluations during which the following variables were collected: postoperative symptoms, postoperative adjuvant therapy, recurrence, and postoperative quality of life. Recurrence was defined as experiencing symptoms of anal stenosis that could not relieved by conservative treatment. The patients’ postoperative quality of life was assessed using a satisfaction questionnaire that comprised a 10-point rating scale ranging from 1 (poor) to 10 (excellent). The satisfaction scores were grouped into four categories: excellent (8-10), good (6-7), same (3-5), and poor (1-2).

**Statistical analysis**
The patients’ characteristics are summarized as total numbers, percentages, and means ± standard deviations. Student’s \( t \)-test for paired samples was used to detect differences in the means of continuous variables over time. Statistical significance was set at a \( P \)-value < 0.05. The SPSS software for Windows, version 22.0 (IBM Corp., Armonk, NY, United States) was used to perform the statistical analyses.
Figure 1 Selection process of the patients in the study.

Figure 2 Surgical technique. A: Scar revision surgery. The scar is removed with a longitudinal incision through the stricture in the 3, 7, and 11 o’clock directions. The wound is then closed transversely; B: Double diamond-shaped flap. A diamond-shaped flap from the adjacent perianal skin is delineated, and the flap is introduced into the anal canal defect for wound coverage.

Approval and consent
The study protocol was reviewed and approved by the institutional review board of our hospital (approval No. 111-E-01). All procedures were performed under the ethical standards of the institutional research committee and those of the 1964 Helsinki Declaration and its later amendments, or comparable ethical standards. The requirement for informed consent was waived by the institutional review board of our hospital due to the retrospective nature of the study, and patient information was anonymized and de-identified prior to analysis.

RESULTS
The patients’ demographic data and characteristics are presented in Table 1. Thirty-six men (60%) and 24 women (40%) with anal stenosis underwent scar revision surgery or double diamond-shaped flap anoplasty between January 1, 2010 and December 31, 2015. Among them, 8 with moderate or severe anal stenosis had previously undergone scar revision surgery, but underwent diamond-shaped flap anoplasty owing to recurrence; these individuals were categorized into the diamond-shaped flap anoplasty group. The median patient age was 54.65 ± 12.65 years (range: 27-76 years). All patients had previously undergone hemorrhoidectomy, and all reported having a poor quality of life due to anal stenosis. In terms of severity, 48.33%, 33.33%, and 18.33% of the patients had mild, moderate, and severe conditions, respectively. All patients had strained defecation; other symptoms are shown in Table 1. All
Table 1 Demographic characteristics of patients who underwent surgery for hemorrhoidectomy-associated anal stenosis

<table>
<thead>
<tr>
<th></th>
<th>Scar revision surgery</th>
<th>Double diamond-shaped flap anoplasty</th>
<th>P value</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient numbers</td>
<td>21 (35%)</td>
<td>39 (65%)</td>
<td></td>
<td>60</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>54 ± 14.5</td>
<td>55 ± 11.8</td>
<td>0.777</td>
<td>54.65 ±12.65</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>13/8 (61.9%/38.09%)</td>
<td>23/16 (58.97%/41.03%)</td>
<td>0.825</td>
<td>36/24 (60%/40%)</td>
</tr>
<tr>
<td>Preoperative severity of anal stenosis</td>
<td>&lt; 0.001</td>
<td>Mild (80.95%)</td>
<td>17</td>
<td>12 (30.77%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moderate (19.05%)</td>
<td>4</td>
<td>16 (41.03%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Severe</td>
<td>0</td>
<td>11 (28.21%)</td>
</tr>
<tr>
<td>Preoperative symptoms</td>
<td></td>
<td>Strained defecation (100%)</td>
<td>21</td>
<td>39 (100%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Incomplete evacuation (61.9%)</td>
<td>13</td>
<td>26 (66.67%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Painful evacuation (19.04%)</td>
<td>4</td>
<td>25 (64.1%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Defecation bleeding</td>
<td>0</td>
<td>8 (20.51%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Incontinence</td>
<td>0</td>
<td>7 (17.95%)</td>
</tr>
<tr>
<td>Adjuvant therapy</td>
<td></td>
<td>Laxative medication (100%)</td>
<td>21</td>
<td>39 (100%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pain control medication (19.05%)</td>
<td>4</td>
<td>25 (64.1%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Digital dilatation (33.33%)</td>
<td>7</td>
<td>17 (43.59%)</td>
</tr>
</tbody>
</table>

Figure 3 Double diamond-shaped flap anoplasty. A: Intraoperative double diamond-shaped flap design; B: Postoperative double diamond-shaped flap.

patients had previously tried conservative management, and all were administered laxatives, while smaller proportions attempted other additional treatments. Ultimately, 21 patients (35%) underwent scar revision surgery while 39 (65%) underwent double diamond-shaped flap anoplasty.

The perioperative results are shown in Table 2. The mean operative times for scar revision surgery was significantly shorter for that for double diamond-shaped flap anoplasty (10.14 ± 2.31 [range: 7-15] min vs 21.62 ± 4.68 [range: 15-31] min; P < 0.001). The average of length of hospital stay was also significantly shorter in the former group (2.1 ± 0.3 d) than in the latter (2.9 ± 0.4 d; P < 0.001). Four patients in the double diamond-shaped flap group underwent urinary catheterization because of urinary retention, but the difference in this complication between the two groups was not significant (P = 0.129). None of the patients in our study experienced wound dehiscence, wound infection, postoperative fever, or postoperative bleeding.

Finally, we investigated the postoperative conditions of the patients after 6 mo (Table 3). Two patients of moderate anal stenosis in the scar revision surgery group had strained defecation and one had incomplete evacuation; these were considered recurrence. None of the patients in the anoplasty group...
Table 2 Surgical outcomes of patients treated surgically for anal stenosis

<table>
<thead>
<tr>
<th></th>
<th>21 (35%)</th>
<th>39 (65%)</th>
<th>&lt; 0.001</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operative time (min)</td>
<td>10.14 ± 2.31</td>
<td>21.62 ± 4.68</td>
<td>&lt; 0.001</td>
<td>17.6 ± 6.8</td>
</tr>
<tr>
<td>Length of hospital stay (d)</td>
<td>2.1 ± 0.3</td>
<td>2.9 ± 0.4</td>
<td>&lt; 0.001</td>
<td>2.62 ± 0.52</td>
</tr>
<tr>
<td>Complications</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute urinary retention</td>
<td>0</td>
<td>4 (10.3%)</td>
<td>-</td>
<td>4 (6.7%)</td>
</tr>
<tr>
<td>Wound dehiscence</td>
<td>0</td>
<td>0</td>
<td>0.129</td>
<td>0</td>
</tr>
<tr>
<td>Wound infection</td>
<td>0</td>
<td>0</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Postoperative fever</td>
<td>0</td>
<td>0</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Postoperative bleeding</td>
<td>0</td>
<td>0</td>
<td></td>
<td>0</td>
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</tbody>
</table>

Table 3 Postoperative 6-mo follow-up

<table>
<thead>
<tr>
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<th>Scar revision surgery</th>
<th>Double-diamond-shaped flap anoplasty</th>
<th>P value</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient numbers</td>
<td>21 (35%)</td>
<td>39 (65%)</td>
<td></td>
<td>60</td>
</tr>
<tr>
<td>Postoperative symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strained defecation</td>
<td>2 (9.52%)</td>
<td>0</td>
<td>0.05</td>
<td>2 (3.33%)</td>
</tr>
<tr>
<td>Incomplete evacuation</td>
<td>1 (4.76%)</td>
<td>0</td>
<td>0.169</td>
<td>1 (1.67%)</td>
</tr>
<tr>
<td>Painful evacuation</td>
<td>0</td>
<td>0</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Defecation bleeding</td>
<td>0</td>
<td>0</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Incontinence</td>
<td>0</td>
<td>0</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Adjuvant therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laxative medication</td>
<td>2 (9.52%)</td>
<td>0</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>Pain control medication</td>
<td>0</td>
<td>0</td>
<td>0.05</td>
<td>0</td>
</tr>
<tr>
<td>Digital dilatation</td>
<td>0</td>
<td>0</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Recurrence</td>
<td>2 (9.52%)</td>
<td>0</td>
<td>0.05</td>
<td>2 (3.33%)</td>
</tr>
<tr>
<td>Quality of life</td>
<td></td>
<td></td>
<td>0.035</td>
<td></td>
</tr>
<tr>
<td>Poor (1–2)</td>
<td>0</td>
<td>0</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Same (3–5)</td>
<td>2 (9.52%)</td>
<td>0</td>
<td></td>
<td>2 (3.33%)</td>
</tr>
<tr>
<td>Good (6–7)</td>
<td>6 (28.57%)</td>
<td>7 (17.95%)</td>
<td></td>
<td>13 (21.67%)</td>
</tr>
<tr>
<td>Excellent (8–10)</td>
<td>13 (61.90%)</td>
<td>32 (82.05%)</td>
<td></td>
<td>45 (75%)</td>
</tr>
</tbody>
</table>

had any postoperative symptoms or required adjuvant therapy (i.e., there were no recurrences in this group). On their postoperative satisfaction questionnaires, 45 patients (75%) reported excellent satisfaction scores, whereas 13 (21.7%) and 2 (3.3%) reported good satisfaction and no change, respectively; the latter two were those who experienced recurrences. Importantly, there were a significant difference in satisfaction between the two groups (P = 0.035), with more satisfaction in double diamond-shaped flap anoplasty group.

DISCUSSION

Anal stenosis is not uncommon after anal surgery; its rate has been reported to range from 1.2% to 10% in patients who have undergone hemorrhoidectomy[22]. As mentioned in the Introduction, there are numerous causes of anoderm tissue scarring that can lead to anal stenosis or stricture. Mild anal stenosis is defined as a stenotic anal canal that can still be examined using a well-lubricated index finger or medium-size Hill-Ferguson retractor[11]. Most patients with mild anal stenosis can be managed nonsurgically using methods such as increasing fiber-rich food in the diet or using stool softening or bulk-forming agents[11,23]. Daily gentle self-digital or instrumental dilation with Hegar dilators can also be
Weng et al. Scar revision vs anoplasty for anal stenosis

considered. Digital dilatation is a much simpler method and avoid the costs of Hegar dilators; however, patients may unintentionally injure the anal sphincter, resulting in further fibrosis and stricture and ultimately more serious stenosis[4,24]. Therefore, Hegar dilators used by surgeons while patients are under adequate anesthesia are a safer choice. Casadesus et al[3] described 4 patients who achieved satisfactory results with regular progressive self-dilatation using Hegar dilators. If conservative management fails, scar revision surgery ought to be the first choice; this simpler procedure can often achieve satisfactory outcomes and produce fewer complications. Scar revision surgery involved only the excision of the fibrotic tissue and suturing of the wound, causing less trauma to the anoderm and thus risks fewer postoperative complications than anoplasty. Most of our patients with mild anal stenosis in whom conservative treatment failed were satisfied with scar revision surgery, and had none complications or recurrences. Anoplasty is only indicated if scar revision surgery fails.

Moderate anal stenosis is defined as the ability of a lubricated index finger or medium-sized Hill-Ferguson retractor to penetrate the anus only after forceful dilatation[11]. Such patients usually require surgical intervention, as conservative management is likely to fail. In our study, 2 of the 4 patients with moderate anal stenosis reported no change in their postoperative quality of life after undergoing scar revision surgery; they still experienced strained defecation and incomplete evacuation, which we considered recurrences. Three and five patients in our study with moderate and severe anal stenosis, respectively, had previously undergone scar revision surgery before attempting diamond-shaped flap owing to recurrence; they also required adjuvant therapy such as laxatives, pain control medication, and/or self-digital dilatation. Accordingly, these findings suggest that patients with moderate anal stenosis should undergo anoplasty instead of scar revision surgery to avoid subsequent operations.

Severe anal stenosis is defined as the inability of either a lubricated little finger or a small Hill-Ferguson retractor to penetrate the anus[11]. As in patients with moderate stenosis, conservative management is not adequate for patients with severe stenosis. Moreover, scar revision surgery is not feasible owing to extensive cicatrized tissue. Therefore, we immediately opted for anoplasty for these patients. Anoplasty consists of excising the fibrotic tissue, dissecting the stricture, and increasing the dimension of the anal outlet using proximal or distal local flap advancement to restore normal anal function[20,21,25]. In our study, all patients with severe anal stenosis who underwent double diamond flap anoplasty achieved good outcomes; their postoperative quality of life improved significantly, and none required adjuvant therapy or experienced recurrence.

There are numerous procedures described in the literature regarding anoplasty for anal stenosis, and the choice of the surgery depends on the surgeon’s experience as well as the severity of the stricture[6,12,17,26]. No single procedure is superior to others, and it is difficult to evaluate the outcomes of the various techniques owing to the lack of adequate prospective trials[12]. We selected the double diamond flap anoplasty technique because of its good long-term results and low complication rates, as well as our departmental experience with this procedure. Moreover, this method is performed on both sides of the anus simultaneously, which can ameliorate the stenosis remarkably. After the anoplasty procedure, the postoperative quality of life improved greatly, and none of the patients required adjuvant therapy or experienced recurrences.

However, we found that the length of hospital stay was significantly longer in the double diamond flap anoplasty group than in the scar revision surgery group. Given that the anoplasty produced a larger operative wound, it is likely that more pain control medication is required in this group. The number of postoperative complications associated with urinary retention was also higher in the anoplasty group, even though this group experienced better performance than the scar revision surgery group in terms of quality of life improvement, recurrence rate, and the need for postoperative adjuvant therapy.

Based on our experience, we developed an algorithm for selecting the appropriate anal stenosis management methods according to severity (Figure 4). According to this algorithm, conservative management should considered first for mild anal stenosis; if non-operative approaches fail, scar revision surgery can then be performed. A simpler procedure can often achieve satisfactory outcomes and produce fewer complications. If the patient experiences recurrence after scar revision surgery, anoplasty is indicated. For patients with moderate or severe anal stenosis, conservative management or scar revision surgery may not be adequate first choices; rather, directly opting for anoplasty may be the best way to achieve satisfactory outcomes and avoid secondary operations.

There are some limitations in our study. First, some biases were inevitable because of the retrospective and single-hospital nature of this study. Second, it was small sample size because most of the patients with anal stenosis did not need surgical intervention, which were excluded in advance. Third, information on important confounders for the associated risks (e.g., smoking habits, consumption of alcohol, dietary patterns, type 2 diabetes mellitus, hypertension, and many other comorbidities) were not well-recorded. Finally, it was a retrospective cohort analysis. Further large-scale prospective studies are needed to investigate these results.
CONCLUSION

Anal stenosis can be managed effectively, with the optimal method based on the condition’s severity. For mild anal stenosis, scar revision surgery can be attempted first if nonsurgical methods fail, with anoplasty performed if recurrence occurs. For moderate and severe anal stenosis, opting for anoplasty from the outset is the best option to prevent subsequent surgeries.

ARTICLE HIGHLIGHTS

Research background
There are two main surgical treatments for anal stenosis: scar revision surgery and anoplasty. There were no studies comparing these two approaches, and it remains unclear which is preferrable for stenoses of different severities, including mild, moderate, and severe.

Research motivation
To compare the outcomes of scar revision surgery and double diamond-shaped flap anoplasty for anal stenosis.

Research objectives
To analyze which surgery have benefit to different severity of anal stenosis.

Research methods
Patients with anal stenosis following hemorrhoidectomy procedures who were treated with either scar revision surgery or double diamond-shaped flap anoplasty at our institution between January 2010 and December 2015 were investigated and compared.

Research results
The mean operative time for scar revision surgery was significantly shorter than that for double diamond-shaped flap anoplasty. The average of length of hospital stay was also significantly shorter after scar revision surgery than after anoplasty.

Research conclusions
Scar revision surgery may be preferable for mild anal stenosis upon conservative treatment failure. Anoplasty is unavoidable for moderate or severe stenosis, where cicatized tissue is extensive.

Research perspectives
Further study must conduct to analyze which surgery have benefit to different severity of anal stenosis.
FOOTNOTES

Author contributions: Weng YT contributed to this work; Weng YT, Jung CK, Lin KH, Chang CK, Kang JC, Chen CY, Hu JM, and Pu TW designed the research study; Weng YT, Jung CK and Pu TW performed the research; Weng YT and Lin KH contributed new reagents and analytic tools; Weng YT, Jung CK, Lin KH and Pu TW analyzed the data and wrote the manuscript; all authors have read and approve the final manuscript.

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Data sharing statement: No additional data are available.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

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REFERENCES


Retrospective Study

Short- (30-90 days) and mid-term (1-3 years) outcomes and prognostic factors of patients with esophageal cancer undergoing surgical treatments

Meng-Kun Shi, Yun-Qing Mei, Jia-Lun Shi

Abstract

BACKGROUND
The factors influencing the prognosis of patients with esophageal cancer vary among studies and are still poorly known.

AIM
To determine the factors associated with survival in patients with esophageal cancer.

METHODS
This retrospective study included patients with esophageal cancer admitted between January 2017 and March 2020 at Heping Hospital Affiliated to Changzhi Medical College. All patients were treated according to the available guidelines. Follow-up was censored in October 2020. Univariable and multivariable Cox regression analyses were used to determine the independent risk factors for overall survival (OS).

RESULTS
In total, 307 patients were included. Their median age was 64 (range, 44-79) years, 63.5% were male, and the median disease course was 2 (0.1-36) months. The median tumor size was 3 (0-10) cm. Most patients were T3 (29.6%), N0 (70.0%). Most tumors were grade 2 (48.2%), and 87.3% were squamous cell carcinoma. The in-hospital mortality was 16.9%, the 30-day mortality was 19.9%, and the 90-day mortality was 25.4%. The cumulative OS rates at the last follow-up were 82.1% (95%CI: 67.7%-96.5%) for stage 0/1/II and 47.4% (95%CI: 16.5-78.6%) for stage
III/IVA ($P < 0.001$). The multivariable analysis showed that creatinine levels (HR = 1.02, 95%CI: 1.00-1.03, $P = 0.050$), pTNM III/IVA (HR = 4.19, 95%CI: 2.19-8.01, $P < 0.001$), adjuvant radiotherapy and/or chemotherapy (HR = 0.23, 95%CI: 0.11-0.49), and the Comprehensive Complication Index (CCI) (HR = 1.02, 95%CI: 1.004-1.03, $P = 0.011$) were independently associated with OS.

**CONCLUSION**

The survival of patients with esophageal cancer is poor, especially those with pTNM III/IVA. pTNM stage III/IVA, CCI, and adjuvant therapy (radiotherapy and/or chemotherapy) are independently associated with OS.

**Key Words:** Esophageal cancer; Survival; Prognosis; Factors; Multivariable analysis

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**Core Tip:** The factors influencing prognosis in esophageal cancer vary among studies and are still poorly known. Therefore, this study aimed to determine the factors related to the survival of patients with esophageal cancer. The results showed that the in-hospital mortality was 16.9%, the 30-day mortality was 19.9%, and the 90-day mortality was 25.4%. Hence, the survival of patients with esophageal cancer is poor, especially those with pTNM III/IVA disease. pTNM stage III/IVA, Comprehensive Complication Index, and adjuvant therapy (radiotherapy and/or chemotherapy) are independently associated with overall survival. These results help delineate the factors associated with poor survival in patients with esophageal cancer.

**INTRODUCTION**

Esophageal cancer is the ninth cancer worldwide in terms of incidence but the sixth in mortality[1]. The most common histological subtypes of esophageal cancer include squamous cell carcinoma (SCC) and adenocarcinoma[2-5]. Worldwide, SCC comprises 90% of all esophageal cancer cases. In Western countries, the incidence of SCC is on the decline while adenocarcinoma incidence is rising; SCC is more common in Eastern Europe and Asia, while adenocarcinoma is more common in North America and Western Europe[3-5]. Most patients with esophageal cancer are > 50 years old[2,3], and both histologic subtypes are more common in men[4]. The most likely risk factors for esophageal cancer include tobacco use and excessive alcohol use (especially for the development of SCC), obesity (especially for the development of adenocarcinoma), and a history of gastroesophageal reflux disease (GERD) and/or Barrett esophagus (especially for the development of adenocarcinoma)[3,4].

Most tumors are diagnosed with regional or distant metastasis, and the 5-year overall survival (OS) is 39% in patients with a localized disease compared with 4% in patients with distant metastases[3]. Local recurrence after primary treatment with definitive chemoradiation may occur in 10%-30% of the patients within the first year[2]. Increased HER2-neu expression is associated with poor survival, particularly in patients with SCC[4]. The 5-year OS rate among patients treated with neoadjuvant chemotherapy for esophageal cancer in various studies ranges from 16% to 62%[6]. A Charlson score ≥ 2, history of myocardial infarction, and congestive heart failure may increase mortality risk following surgery for esophageal cancer[7]. Age > 70 years does not have prognostic significance after esophagectomy for esophageal cancer[8].

Some predictive models are available, but their value is limited. The Dutch nomogram is based on three variables and shows a concordance index of 0.76-0.77[9]. The POSSUM models can predict morbidity and mortality in patients undergoing gastroesophageal surgery, but they can overestimate the risks[10]. Other multivariable analysis studies reported various factors associated with poor prognosis[11-14]. However, beyond the traditional prognostic factors (e.g., histological grade and TNM staging[3-5,15,19]), the factors influencing prognosis in esophageal cancer are poorly known and vary among studies. Identification of the factors that could help refine prognostication is important since two patients with the same histological grade and TNM staging can have different survival.

Therefore, this study aimed to determine the factors related to the survival of esophageal cancer. The results could help delineate the factors associated with poor survival in patients with esophageal cancer.
MATERIAL AND METHODS

Study design and patients
This retrospective study included patients with esophageal cancer admitted between January 2017 and June 2020 at the Department of Gastrointestinal Surgery of Heping Hospital Affiliated to Changzhi Medical College. This study was approved by the Ethics Committee of Heping Hospital Affiliated to Changzhi Medical College [approval number: 2020 (037), approval date: July 22, 2020]. The requirement for informed consent was waived by the committee due to the retrospective study design. The inclusion criteria were: (1) > 18 years of age; (2) underwent surgical treatments; and (3) confirmed with esophageal cancer by postoperative pathological examination. The exclusion criteria were: (1) incomplete clinical data; and (2) follow-up < 90 days.

Treatments
Each patient was treated according to the available guidelines for the treatment of esophageal cancer[4, 5,15,16], the physicians’ clinical experience, and the discussion with the patient. The treatment regimens included radiotherapy alone, chemotherapy alone (paclitaxel + cisplatinum, paclitaxel + nedaplatin, oxaliplatin, tegafur/gimeracil/oteracil, oxaliplatin + docetaxel/tegafur/gimeracil/oteracil, and nedaplatin/docetaxel), and radiotherapy combined with chemotherapy.

The type of surgery was selected according to the tumor’s location and size (the most important factor), infiltration depth, invasive degree, and general condition of the patients (whether they could tolerate open surgery). The surgery methods included endoscopic submucosal dissection (ESD), mediastinoscopy/laparoscopy/thoracoscopy, laparothoracoscopy combined palliative resection of esophageal cancer, laparothoracoscopy combined esophageal cancer radical operation, and open surgery. All the procedures were performed by experienced surgeons and followed standard protocols.

Follow-up
The patients were followed at 1, 3, 6, 9, 12, 18, 24, 30, 36, 48, and 72 months after the operation. For this study, follow-up was censored in October 2020. The follow-up was completed by the investigators and the medical team routinely. Routine follow-up included telephone, SMS, email, and outpatient visits. All follow-up data were extracted from the patient charts. The patients were not contacted for the purpose of this study.

Data collection
The following data were collected from the medical records: demographic data, past medical history, and concomitant diseases; site, size, stage, and type of esophageal cancer; hematological examination results within 1 week before the operation, treatment strategies, operation-related parameters, postoperative complications, Comprehensive Complication Index (CCI)[20]; survival, recurrence, and metastasis.

Statistical analysis
The continuous variables were tested for normality using the Kolmogorov-Smirnov test. The continuous variables were not normally distributed in this study and are presented as medians (ranges). Categorical and ordinal variables are presented as frequencies and percentages. Univariable and multivariable Cox regression analyses (backward) were used to determine the independent risk factors for OS. The variables with P values < 0.10 in the univariable analysis were included in the multivariable analysis. The Kaplan-Meier curves of OS were plotted according to the pTNM staging results. All statistical analyses were two-sided. P values < 0.05 were considered statistically significant. SPSS 22.0 (IBM, Armonk, NY, United States) was used for statistical analyses.

RESULTS

Characteristics of the patients
Initially, 357 patients were included according to the inclusion criteria, but 26 with missing clinical information and 24 lost to follow-up were excluded, leaving 307 patients. As shown in Table 1, the median age at diagnosis was 64 (44-79) years, 63.5% were male, median BMI was 22.2 (14.9-31.6) kg/m², median disease course was 2 (0.1-36) months, 30.9% had a history of smoking, 6.5% had a history of drinking, and 75.9% were ASA II. Table 1 also presents the biochemical characteristics of the patients.

Characteristics of the tumors and treatments
Table 2 shows the characteristics of the tumors. Most tumors were in the middle part of the esophagus (55.7%). The median tumor size was 3 (0-10) cm. Most patients were T3 (29.6%) N0 (70.0%). Most tumors were grade 2 (48.2%), and 87.3% were SCC.
Table 1 Baseline characteristics of the patients (n = 307)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Median (range) / n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>64 (44, 79)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>22.2 (14.9, 31.6)</td>
</tr>
<tr>
<td>Disease course (months)</td>
<td>2 (0.1, 36)</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>195 (63.5%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>95 (30.9%)</td>
</tr>
<tr>
<td>Drinking</td>
<td>20 (6.5%)</td>
</tr>
<tr>
<td>Family history of esophageus cancer</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>112 (36.5%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>21 (6.8%)</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>16 (5.2%)</td>
</tr>
<tr>
<td>ASA stage</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>233 (75.9%)</td>
</tr>
<tr>
<td>III</td>
<td>73 (23.8%)</td>
</tr>
<tr>
<td>IV</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Hemoglobin (g/L)</td>
<td>141 (80, 180.4)</td>
</tr>
<tr>
<td>MCV (fl)</td>
<td>93.6 (71.1, 134.1)</td>
</tr>
<tr>
<td>Platelets (× 10⁹/L)</td>
<td>213 (60.3, 445.9)</td>
</tr>
<tr>
<td>Lymphocytes (× 10⁹/L)</td>
<td>1.56 (0.07, 7.42)</td>
</tr>
<tr>
<td>Monocytes (× 10⁹/L)</td>
<td>0.36 (0.05, 1.01)</td>
</tr>
<tr>
<td>Neutrophils (× 10⁹/L)</td>
<td>3.63 (1.15, 12.94)</td>
</tr>
<tr>
<td>PT (s)</td>
<td>13.8 (11.4, 31.9)</td>
</tr>
<tr>
<td>APTT (s)</td>
<td>31.4 (10.6, 51.7)</td>
</tr>
<tr>
<td>Fibrinogen (g/L)</td>
<td>3.79 (1.95, 6.3)</td>
</tr>
<tr>
<td>D-dimer (ng/mL)</td>
<td>130 (14, 3354)</td>
</tr>
<tr>
<td>Total protein (g/L)</td>
<td>71 (3.32, 88.1)</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>42.1 (26.1, 63.5)</td>
</tr>
<tr>
<td>Creatinine (µmol/L)</td>
<td>63 (36, 187)</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>46.6 (28.2, 64.5)</td>
</tr>
</tbody>
</table>

ASA: American Society of Anesthesiologists; MCV: Mean corpuscular volume; PT: Prothrombin time; APTT: Activated partial thromboplastin time.

Among the 307 patients, 16.6% received neoadjuvant treatments, 84.0% underwent mediastinoscopy/laparoscopy/thoracoscopy, 8.8% underwent open surgery, and 7.2% underwent ESD. An R0 resection was achieved in 99.0% of the patients. Operation time was 270 (36-485) min, and blood loss was 150 (2-1000) mL. Lymph node dissection was performed in 92.2% of the patients, and the median number of positive lymph nodes was 0 (0-8). Most patients (69.4%) received no adjuvant treatments, 2.3% received radiotherapy alone, 25.1% received chemotherapy alone, and 3.3% received radiotherapy and chemotherapy.

Table 3 presents the complications observed. Among the 307 patients, 35.5% had no complications, while 64.5% had complications. The in-hospital mortality was 16.9%, the 30-day mortality was 19.9%, and the 90-day mortality was 25.4%.

**Survival**

The 1-year cumulative OS rates were 93.7% (95%CI: 88.3%-99.1%) for stage 0/I/II and 72.4% (95%CI: 57.7%-87.1%) for stage III/IVA. The 2-year cumulative OS rates were 87.8% (95%CI: 79.1%-96.5%) for stage 0/I/II and 60.2% (95%CI: 41.6%-78.8%) for stage III/IVA. The 3-year cumulative OS rates were 85.5% (95%CI: 74.7%-96.3%) for stage 0/I/II and 56.9% (95%CI: 36.8%-77.0%) for stage III/IVA. The
<table>
<thead>
<tr>
<th>Variables</th>
<th>Median (range) / n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tumor location</strong></td>
<td></td>
</tr>
<tr>
<td>Upper</td>
<td>15 (4.9%)</td>
</tr>
<tr>
<td>Middle to upper</td>
<td>21 (6.8%)</td>
</tr>
<tr>
<td>Middle</td>
<td>171 (55.7%)</td>
</tr>
<tr>
<td>Middle to lower</td>
<td>43 (14.0%)</td>
</tr>
<tr>
<td>Lower</td>
<td>57 (18.6%)</td>
</tr>
<tr>
<td><strong>Tumor diameter (cm)</strong></td>
<td>3 (0, 10)</td>
</tr>
<tr>
<td><strong>T stage</strong></td>
<td></td>
</tr>
<tr>
<td>Tis</td>
<td>30 (9.8%)</td>
</tr>
<tr>
<td>1a</td>
<td>4 (1.3%)</td>
</tr>
<tr>
<td>1b</td>
<td>69 (22.5%)</td>
</tr>
<tr>
<td>2</td>
<td>75 (24.4%)</td>
</tr>
<tr>
<td>3</td>
<td>91 (29.6%)</td>
</tr>
<tr>
<td>4a</td>
<td>36 (11.7%)</td>
</tr>
<tr>
<td>4b</td>
<td>2 (0.7%)</td>
</tr>
<tr>
<td><strong>N stage</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>215 (70.0%)</td>
</tr>
<tr>
<td>1</td>
<td>61 (19.9%)</td>
</tr>
<tr>
<td>2</td>
<td>28 (9.1%)</td>
</tr>
<tr>
<td>3</td>
<td>3 (1.0%)</td>
</tr>
<tr>
<td><strong>G stage</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>30 (9.8%)</td>
</tr>
<tr>
<td>1</td>
<td>21 (6.8%)</td>
</tr>
<tr>
<td>1-2</td>
<td>73 (23.8%)</td>
</tr>
<tr>
<td>2</td>
<td>148 (48.2%)</td>
</tr>
<tr>
<td>2-3</td>
<td>24 (7.8%)</td>
</tr>
<tr>
<td>3</td>
<td>11 (3.6%)</td>
</tr>
<tr>
<td><strong>pTNM</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>30 (9.8%)</td>
</tr>
<tr>
<td>I</td>
<td>108 (35.2%)</td>
</tr>
<tr>
<td>II</td>
<td>71 (23.1%)</td>
</tr>
<tr>
<td>III</td>
<td>87 (28.3%)</td>
</tr>
<tr>
<td>IVA</td>
<td>11 (3.6%)</td>
</tr>
<tr>
<td><strong>Pathological type</strong></td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>268 (87.3%)</td>
</tr>
<tr>
<td>Intraepithelial neoplasia</td>
<td>30 (9.8%)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>8 (2.6%)</td>
</tr>
<tr>
<td>Signet-ring cell carcinoma</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Neoadjuvant radiotherapy and/or chemotherapy</td>
<td>51 (16.6%)</td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
</tr>
<tr>
<td>Mediastinoscopy/ laparoscopy/thoracoscopy</td>
<td>258 (84.0%)</td>
</tr>
</tbody>
</table>
cumulative OS rates at the last follow-up were 82.1% (95%CI: 67.7%-96.5%) for stage 0/I/II and 47.4% (95%CI: 16.5%-78.6%) for stage III/IVA. The Kaplan-Meier analysis shows that the differences in survival were significant \( P < 0.001 \) (Figure 1).

**Multivariable analysis of OS**

Table 4 shows that creatinine levels \( P = 0.020 \), tumor size \( P = 0.002 \), T3-4 \( P = 0.003 \), N1-3 \( P < 0.001 \),

<table>
<thead>
<tr>
<th>Variables</th>
<th>Median (range) / n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clavien-Dindo stage</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>109 (35.5%)</td>
</tr>
<tr>
<td>I</td>
<td>27 (8.8%)</td>
</tr>
<tr>
<td>II</td>
<td>121 (39.4%)</td>
</tr>
<tr>
<td>IIIa</td>
<td>28 (9.1%)</td>
</tr>
<tr>
<td>IIIb</td>
<td>4 (1.3%)</td>
</tr>
<tr>
<td>IV</td>
<td>4 (1.3%)</td>
</tr>
<tr>
<td>IVa</td>
<td>8 (2.6%)</td>
</tr>
<tr>
<td>IVb</td>
<td>6 (2.0%)</td>
</tr>
<tr>
<td>CCI, median (range)</td>
<td>20.9 (0, 96.6)</td>
</tr>
<tr>
<td>Anastomotic leakage</td>
<td>75 (24.4%)</td>
</tr>
<tr>
<td>Secondary operation</td>
<td>7 (2.3%)</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>88 (28.7%)</td>
</tr>
<tr>
<td>Pulmonary infection</td>
<td>68 (22.1%)</td>
</tr>
<tr>
<td>Recurrence</td>
<td>11 (3.6%)</td>
</tr>
<tr>
<td>Metastasis</td>
<td>21 (6.8%)</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>52 (16.9%)</td>
</tr>
<tr>
<td>30-day mortality</td>
<td>61 (19.9%)</td>
</tr>
<tr>
<td>90-day mortality</td>
<td>78 (25.4%)</td>
</tr>
</tbody>
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CCI: Charlson comorbidity index.
### Table 4 Univariable and multivariable Cox regression analyses of overall survival

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<tr>
<th></th>
<th>Univariable</th>
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<td>95%CI</td>
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<td>Age</td>
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<td>Male</td>
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<td>Body mass index &lt; 28</td>
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<td>≥ 28</td>
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<td>Smoking</td>
<td>1.185</td>
<td>0.663, 2.118</td>
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<td>0.545, 3.452</td>
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<td>Hypertension</td>
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<td>Diabetes</td>
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<td>0.810, 4.449</td>
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<td>Hemoglobin</td>
<td>0.987</td>
<td>0.971, 1.004</td>
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<td>D-dimer</td>
<td>1.000</td>
<td>0.999, 1.001</td>
<td>0.782</td>
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<td>Albumin</td>
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<td>0.945, 1.067</td>
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<td>Creatinine</td>
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<td>Tumor diameter</td>
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<td>1.083, 1.429</td>
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<td>3-4</td>
<td>2.327</td>
<td>1.331, 4.068</td>
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<td>1-3</td>
<td>2.869</td>
<td>1.659, 4.962</td>
<td>&lt; 0.001</td>
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<td>&lt; 2</td>
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<tr>
<td>≥ 2</td>
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<td>1.062, 3.73</td>
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<td>pTNM stage</td>
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<tr>
<td>III/IVA</td>
<td>4.117</td>
<td>2.349, 7.213</td>
<td>&lt; 0.001</td>
<td>4.189</td>
<td>2.190, 8.012</td>
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<td>Pathological type</td>
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<td>Others</td>
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<td>0.222, 1.711</td>
<td>0.353</td>
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<td>Received preoperative radiotherapy or chemotherapy</td>
<td>1.157</td>
<td>0.592, 2.261</td>
<td>0.669</td>
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<td>Operation method</td>
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<td>Thoracotomy/laparotomy</td>
<td>0.867</td>
<td>0.312, 2.405</td>
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<td>Lymph node dissection</td>
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<td>Postoperative radiotherapy and/ or chemotherapy</td>
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<td>0.234</td>
<td>0.112, 0.488</td>
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<td>Number of metastatic lymph nodes</td>
<td>1.277</td>
<td>1.109, 1.471</td>
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<tr>
<td>CCI</td>
<td>1.029</td>
<td>1.014, 1.044</td>
<td>&lt; 0.001</td>
<td>1.018</td>
<td>1.004, 1.032</td>
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</table>
DISCUSSION

The factors influencing prognosis in esophageal cancer are still poorly known and vary among studies. Therefore, this study aimed to determine the factors related to the survival of patients with esophageal cancer. The results show that the survival of patients with esophageal cancer is poor, especially those with pTNM stage III/IVA. pTNM stage III/IVA, CCI, and adjuvant therapy (radiotherapy and/or chemotherapy) are independently associated with OS. This indicates that early clinical stage, fewer postoperative complications, and adjuvant therapy might be related to a better prognosis in patients with esophageal cancer after surgery. This study showed that the CCI is an independent risk factor affecting prognosis, indicating that postoperative nursing care to reduce postoperative complications might be helpful to improve the survival rate, while many surgeons tend to focus on surgery instead of postoperative nursing. Science-based postoperative management to reduce complications is also very important.

In this study, the 3-year cumulative OS rates were 85.5% for stage 0/1/II and 56.9% for stage III/IVA. This is consistent with the literature, as the studies indicate that a more advanced disease is associated with poorer survival[3-5,15-18]. Regarding the adjuvant treatments, this association is not surprising since the efficacy of adjuvant treatments to prevent recurrence and metastasis, and improve survival is the reason for giving adjuvant therapy in the first place[3-5,15,16,21]. Regarding the CCI, Bernardi et al [22] showed that patients with esophageal cancer who completed their treatment plan had a lower CCI than those who eventually dropped out, affecting the prognosis. Yamashita et al[23] and Aoyama et al [24] showed that the CCI was correlated with the prognosis of patients who undergo curative resection of esophageal carcinoma.

Nevertheless, a wide variety of other factors are associated with esophageal cancer prognosis in various studies. The Dutch nomogram is based on three variables independently associated with esophageal carcinoma: T stage, number of positive lymph nodes, and lymph node involvement[9]. The POSSUM score is a complex scoring system designed to determine the short-term postoperative mortality and includes 19 clinical, biochemical, and operative variables independently associated with prognosis[10]. Kawakita et al[25] showed that C-reactive protein levels and platelet distribution width...
Shi et al. Prognosis of esophageal cancer

could predict survival in patients with esophageal cancer. In esophageal SCC, which was the main histological subtype in the present study, Kim et al.\[26\] showed that only the CCI was associated with survival, supporting the present study. In the study by Hauge et al.\[19\], only the pTNM stage was independently associated with OS, supporting the present study. Hauge et al.\[19\] also suggested that patients with R0 resection and who received adjuvant therapy had a better survival than the other subgroups of patients, but, in the present study, the number of patients with R1 resection was too small for subgroup analyses. A large meta-analysis (171 studies and 73629 patients) indicated that the factors associated with OS were the pT stage, pN stage, perineural invasion, circumferential resection margin, poor tumor grade, and a high neutrophil-to-lymphocyte ratio\[27\]. The differences among studies are highly dependent upon the study populations, data available for analysis (especially retrospective studies, local practice, and the treatment periods. However, specific factors identified by multiple studies might be considered more reliable, but validation studies are necessary from multiple centers.

Of note, in this study, creatinine levels were independently associated with the prognosis of esophageal cancer, but the P-value was borderline, and it is unknown whether including more patients would tip the balance one way or the other. Creatinine levels have been reported to be independently associated with prognosis in gynecological\[28,29\] and colorectal\[30\] cancers, but no previous studies have reported such an association in esophageal cancer. Further study is required to clarify this issue.

This study has limitations. First, it was a retrospective study, and some data were not collected (e.g., the patients’ postoperative nutritional status, which is known to influence prognosis\[31\]). In addition, the follow-up data were from the charts, and there is a possibility of unreported events. Second, the factors related to recurrence-free survival (RFS) could not be analyzed due to incomplete data. Third, it was a single-center study, and it is unknown whether the results are valid externally.

CONCLUSION

In conclusion, the pTNM stage, CCI, and postoperative radiotherapy and/or chemotherapy are independently associated with OS. The survival of patients with pTNM III/IVA disease is worse than that of patients with pTNM I/II disease. Fewer complications and adjuvant therapy are associated with better survival.

ARTICLE HIGHLIGHTS

Research background
Esophageal cancer is the ninth cancer worldwide in terms of incidence but the sixth in mortality. The prognosis of esophageal cancer is poor.

Research motivation
The factors influencing the prognosis of patients with esophageal cancer vary among studies and are still poorly known. Some predictive models are available, but their value is limited.

Research objectives
This study aimed to determine the factors related to the survival of patients with esophageal cancer.

Research methods
This retrospective study included patients with esophageal cancer admitted between January 2017 and March 2020 at Heping Hospital Affiliated to Changzhi Medical College. All patients were treated according to the available guidelines. Follow-up was censored in October 2020. Univariable and multivariable Cox regression analyses were used to determine the independent risk factors for overall survival (OS).

Research results
Among 307 patients, the in-hospital mortality was 16.9%, the 30-day mortality was 19.9%, and the 90-day mortality was 25.4%. The patients showed a cumulative OS rate at the last follow-up of 82.1% (95%CI: 67.7%-96.5%) for stage 0/II and 47.4% (95%CI: 16.5%-78.6%) for stage III/IVA (P < 0.001). Creatinine levels (HR = 1.02, 95%CI: 1.00-1.03, P = 0.050), pTNM III/IVA (HR = 4.19, 95%CI: 2.19-8.01, P < 0.001), adjuvant radiotherapy and/or chemotherapy (HR = 0.23, 95%CI: 0.11-0.49), and the Comprehensive Complication Index (CCI) (HR = 1.02, 95%CI: 1.004-1.03, P = 0.011) were independently associated with OS.

Research conclusions
The survival of patients with esophageal cancer is poor, especially those with pTNM III/IVA. pTNM
stage III/IVA, CCI, and adjuvant therapy (radiotherapy and/or chemotherapy) are independently associated with OS. These results could help manage patients by identifying those needing closer follow-up.

**Research perspectives**
These results could help delineate the factors associated with poor survival in patients with esophageal cancer. Identification of the factors that could help refine prognostication is important since two patients with the same histological grade and TNM staging can have different survival. These results should be validated in large cohorts of patients from multiple centers.

**FOOTNOTES**

**Author contributions:** Shi MK contributed to conceptualization, methodology, data curation and analysis, writing (original draft), and visualization; Mei YQ contributed to writing (review and editing) and supervision; Shi JL contributed to writing (review and editing), acquisition of data, and supervision; all authors have read and approved the final manuscript.

**Institutional review board statement:** This study was approved by the Ethics Committee of Heping Hospital Affiliated to Changzhi Medical College (approval number: 2020 (037), approval date: July 22, 2020).

**Informed consent statement:** The requirement for informed consent was waived by the committee due to the retrospective study design.

**Conflict-of-interest statement:** We have no financial relationships to disclose.

**Data sharing statement:** The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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**Country/Territory of origin:** China

**ORCID number:** Meng-Kun Shi 0000-0001-8270-6784; Yun-Qing Mei 0000-0002-5269-2067; Jia-Lun Shi 0000-0003-2760-6064.

**REFERENCES**


Shi et al. Prognosis of esophageal cancer


Effectiveness of pulsed radiofrequency on the medial cervical branches for cervical facet joint pain

Min Cheol Chang, Seoyon Yang

BACKGROUND
Cervical facet joint pain (CFP) is one of the most common causes of neck pain and headache. Persistent CFP deteriorates the quality of life of patients and reduces their productivity at work.

AIM
To investigate the effectiveness of pulsed radiofrequency (PRF) stimulation of cervical medial branches in patients with chronic CFP.

METHODS
We retrospectively included 21 consecutive patients (age = 50.9 ± 15.3 years, range 26-79 years; male: female = 8:13; pain duration = 7.7 ± 5.0 mo) with chronic CFP, defined as ≥ 4 on the numeric rating scale (NRS). We performed PRF stimulation on the cervical medial branches. The outcomes of the PRF procedure were evaluated by comparing the NRS scores for CFP before treatment and 1 and 3 mo after treatment. Successful pain relief was defined as a ≥ 50% reduction in the NRS score at 3 mo when compared with the pretreatment NRS score.

RESULTS
No patient had immediate or late adverse effects following PRF. The average NRS score for CFP decreased from 5.3 ± 1.1 at pre-treatment to 2.4 ± 0.6 at the 1 mo follow-up, and 3.1 ± 1.1 at the 3 mo follow-up. Compared to the NRS scores before PRF stimulation, those at 1 and 3 mo after PRF stimulation had significantly decreased. Eleven of the 21 patients (52.4%) reported successful pain relief 3 mo after the PRF procedure. PRF stimulation on cervical medial branches may be a useful therapeutic option to control chronic CFP.
CONCLUSION
PRF stimulation of the cervical medial branches may be used as an alternative treatment method in patients with CFP. PRF can effectively alleviate CFP, and is safe to perform.

Key Words: Pulsed radiofrequency treatment; Zygapophyseal joint; Chronic pain; Pain; Neck pain; Pain management

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Core Tip: This is a retrospective study to investigate the effectiveness of pulsed radiofrequency (PRF) stimulation of cervical medial branches in patients with chronic cervical facet pain (CFP). Eleven of the 21 patients (52.4%) reported successful pain relief 3 mo after the PRF procedure. Compared to the numeric rating scale scores for CFP before PRF stimulation, those at 1 and 3 mo after PRF stimulation had significantly decreased after 1-month and 3-month follow-up. PRF stimulation on cervical medial branches may be a useful therapeutic option to control chronic CFP.

Comparison:
Chang MC, Yang S. Effectiveness of pulsed radiofrequency on the medial cervical branches for cervical facet joint pain. World J Clin Cases 2022; 10(22): 7720-7727
URL: https://www.wjgnet.com/2307-8960/full/v10/i22/7720.htm
DOI: https://dx.doi.org/10.12998/wjcc.v10.i22.7720

INTRODUCTION
Cervical facet joint pain (CFP) is one of the most common causes of neck pain and headache[1,2]. Clinicians frequently encounter patients with CFP, the prevalence of which ranges from 36% to 55%[1]. If CFP persists and progresses to chronic pain, its management becomes difficult[3]. Persistent CFP deteriorates the quality of life of patients and reduces their productivity at work[4]. Furthermore, it can cause affective disorders, such as depression and anxiety, and sleep disturbance[5]. Therefore, clinicians should actively control CFP.

Several treatments, such as facet joint injection of corticosteroids, oral medication, and physical therapy, have been used to control CFP[6-8]. However, despite these treatments, many patients complain of persistent CFP. Conventional radiofrequency (CRF) stimulation of the cervical medial branch has also been used to control CFP[9,10]. This involves continuous stimulation, which causes the ablation of nerves and tissues by frictional heat from a catheter needle[6,7]. Due to this characteristic of CRF, neuropathic pain following the ablation of nerves can occur, and electrical burns after the procedure have been reported[10,11]. In contrast to CRF, pulsed radiofrequency (PRF) is a useful tool to alleviate chronic pain. This uses a brief stimulation, followed by a long resting phase[12]. PRF exposes the target nerves and tissues to an electric field, and rarely damages these structures[12]. Because of this minimal tissue-destructive characteristic, PRF has been rapidly adopted in clinical practice for the treatment of several types of pain, including neuralgia, joint pain, and myofascial pain[12-16]. Recently, several studies have reported a positive effect of PRF on medial branches in the spine to manage facet pain[17,18]. However, little is known about its effect on the cervical medial branch in the management of CFP.

In the current study, we evaluated the effectiveness of PRF stimulation of cervical medial branches in patients with chronic CFP.

MATERIALS AND METHODS
Study design
This study was conducted retrospectively. We consecutively recruited patients who received PRF stimulation of the cervical medial branches under fluoroscopy in a pain clinic at a single university hospital from January 2014 to December 2019. The inclusion criteria were as follows: (1) PRF stimulation of cervical medial branches performed to control CFP; (2) Aged between 20 and 79 years; (3) ≥ 3 mo history of axial cervical pain without radicular symptoms; (4) ≥ 80% temporary pain relief following a diagnostic cervical medial branch block with 0.5 mL of 1% lidocaine for each level prior to PRF stimulation of cervical medial branches; (5) ≥ 4 points on the Numeric Rating Scale (NRS, 0 = no pain, 10 = worst pain imaginable) prior to PRF stimulation of the cervical medial branches; and (6) No procedure to treat CFP performed ≥ 3 mo prior to the PRF stimulation. Each patient underwent cervical
spine magnetic resonance imaging. We excluded patients who experienced cervical radicular pain due to disc herniation or foraminal stenosis and neck pain due to cervical canal stenosis. We retrospectively reviewed the medical records of 90 patients and included 21 patients (age = 50.9 ± 15.3 years, range 26-79 years; male: female = 8:13; pain duration = 7.7 ± 5.0 mo) in the analysis. A putatively painful cervical facet joint was selected on the basis of the distribution of pain and the location of tenderness.[12] All the included patients agreed to undergo PRF stimulation of cervical medial branches prior to the procedure. The Institutional Review Board of Yeungnam university hospital approved this study, and the need for written informed consent was waived due to the retrospective design of the study.

**Procedure**
An aseptic technique was adopted for PRF stimulation of the cervical medial branches using a posterior approach. For the procedure, patients were placed in a prone position, with the chest supported by a pillow, and the head slightly bent. Under the guidance of C-arm fluoroscopy (Siemens), a 22-gauge cannula (SMK Pole needle, 100 mm with a 10 mm active tip, Cotop International BV) was inserted in a posterior to anterior direction, and its tip was placed around the cervical medial branches, just lateral to the posterolateral center of the C2-3 facet joint for the superficial medial branch of the third cervical spinal dorsal ramus (third occipital nerve), waists of the articular pillars of C3-C6 for C3-6 medial branches, and the apex of the superior articular process of C7 for the C7 medial branch (Figure 1). PRF stimulation of the superficial medial branch of the third cervical spinal dorsal ramus was conducted to control the C2-3 facet joint pain (third occipital nerve). For C3-4, C4-5, and C6-7 facet joint pain, the two vertically adjacent spinal medial branches, the C3 (deep medial branch of the third cervical spinal dorsal ramus) and C4, C4 and C5, and C6 and C7 medial branches were stimulated, respectively (Table 1).[19]
Once the needle tip was at the target site of the medial cervical branch, the needle was repositioned until the patient reported pain or a pressure sensation similar to the pain they usually experienced at less than 0.5 V to confirm the proximity to the medial cervical branch. An electrode was connected to the cannula, and the thoracic medial branch was stimulated (G4 radiofrequency generator; Cosman Medical Inc., Burlington, MA, United States). PRF treatment was administered at 5 Hz, with a 5-millisecond pulsed width for 360 s at 45 V under the condition that the electrode tip temperature did not exceed 42 °C.

**Outcome measures**
Pain intensities were assessed using the NRS pain scores before and 1 and 3 mo after PRF treatment. Successful pain relief was defined as ≥ 50% reduction in the NRS score at 3 mo as compared with the pretreatment NRS score. Changes in NRS scores were also calculated as the difference between the pretreatment and 3 mo post treatment scores, to validate the degree of change in pain reduction [change in NRS (%) = (pretreatment score - scores at 3 mo post treatment)/pretreatment score × 100]. After 3 mo, the patient global perceived effect (GPE) was assessed using a 7-point Likert scale (Table 2).[20,21]
Patients reporting very good (score = 7) or good results (score = 6) were considered to be satisfied with the procedure.

**Statistical analysis**
Statistical analysis was performed with SPSS, version 23.0 (IBM Corporation, Armonk, NY, United States) for Windows (Microsoft Corporation, Redmond, WA, United States). The overall change in NRS scores over time was evaluated using a repeated-measures one-factor analysis. Multiple comparison results were obtained with Bonferroni correction. Statistical significance was set at \( P < 0.05 \).

**RESULTS**
None of the patients presented immediate or late adverse effects following the PRF procedure. The average NRS score for CFP declined from 5.3 ± 1.1 at pre-treatment to 2.4 ± 0.6 at the 1 mo follow-up and 3.1 ± 1.1 at the 3 mo follow-up. The NRS scores significantly changed over time (\( P < 0.001; \) Figure 2). Compared to the NRS scores before PRF stimulation, those at 1 and 3 mo after PRF stimulation were significantly decreased (\( P < 0.001 \)). Eleven of the 21 patients (52.4%) reported successful pain relief (≥ 50%) at 3 mo after PRF stimulation.
On the 7-point Likert scale, Good (score = 6) and fairly good results (score = 5) were observed in 11 (52.4%) and 5 patients (23.8%), respectively. However, no change in results (score = 4) was observed in 5 patients (23.8%). Accordingly, 11 patients (52.4%) were satisfied with the results 3 mo after the PRF procedure. Very good (score = 7), fairly bad (score = 3), bad (score = 2), and very bad (score = 1) scores were not reported. These findings demonstrated that PRF stimulation was effective at alleviating CFP, and more than half of patients who received the treatment were satisfied with the results of this treatment.
Table 1 The cervical medial branches on which pulsed radiofrequency was applied

<table>
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<th>Patient</th>
<th>Stimulated level</th>
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<tr>
<td>1</td>
<td>Lt. C4, 5, 6</td>
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<td>Rt. C3, 4</td>
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<td>12</td>
<td>Lt. C5, 6, 7</td>
</tr>
</tbody>
</table>

TON: Third occipital nerve.

Table 2 Global perceived effect according to a Likert scale

<table>
<thead>
<tr>
<th>Score</th>
<th>% Change</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>≥ 75 improvement</td>
<td>Very good</td>
</tr>
<tr>
<td>6</td>
<td>50-74 improvement</td>
<td>Good</td>
</tr>
<tr>
<td>5</td>
<td>25-49 improvement</td>
<td>Fairly good</td>
</tr>
<tr>
<td>4</td>
<td>0-24 improvement or worse</td>
<td>Same as before</td>
</tr>
<tr>
<td>3</td>
<td>25-49 worse</td>
<td>Fairly bad</td>
</tr>
<tr>
<td>2</td>
<td>50-74 worse</td>
<td>Bad</td>
</tr>
<tr>
<td>1</td>
<td>≥ 75 worse</td>
<td>Very bad</td>
</tr>
</tbody>
</table>

DISCUSSION

In the current study, we found that PRF simulation of the cervical medical branches could effectively control chronic CFP. After undergoing PRF stimulation of the cervical medial branch, significant pain relief was observed in patients with CFP, and approximately half of the patients reported successful pain relief (≥ 50% pain reduction); this effect lasted for at least 3 mo. Furthermore, about half of the patients reported successful pain relief and satisfaction with the results following PRF stimulation.

Facet joints are true synovial joints. It is assumed that the production of inflammatory cytokines and matrix-degrading enzymes disturbs chondrocyte metabolism, leading to cartilage degradation, as in other osteoarthritic joints\[22\]. Repetitive chemical and mechanical stress on cervical facet joints causes inflammation and narrowing of the capsule, resulting in osteoarthritis and chronic CFP\[23\]. Additionally, facet joint injury can occur due to whiplash injury following a sudden acceleration-deceleration force, which is a common cause of chronic CFP\[19\].

Medial branch nerves are very small nerve branches that carry pain signals from facet joints to the brain. There are various treatment methods for CFP. Physical therapy, manipulation, mobilization, oral medication, and cognitive behavioral therapy may all be applied, but their pain-reducing effect is controversial\[24\]. Three types of interventions for the treatment of CFP include intraarticular facet...
injections, medial branch blocks (MBBs), and neurolysis of medial branch nerves using radiofrequency [25]. The MBB is performed with corticosteroids and local anesthetics to reduce CFP. This may provide pain relief by suppressing nociceptive discharges and blocking the axonal transport and sympathetic reflex arc, thereby exerting anti-inflammatory effects[17]. However, local anesthetics can cause various adverse effects, such as hypotension, dizziness, nausea, seizures, and cardiac arrest[26]. Moreover, repeated corticosteroid injections can cause hyperglycemia, suppression of the hypothalamic-pituitary-adrenal axis, and osteoporosis[27]. To avoid the side effects of local anesthetics and corticosteroids, PRF stimulation was suggested as an alternative treatment method for CFP. No previous study has yet directly compared the effect of PRF stimulation to the cervical medial branches with other treatment methods for non-traumatic facet pain. Therefore, this study aimed to investigate whether PRF stimulation was effective in the management of chronic CFP.

PRF stimulation is a minimally neuro-destructive treatment applied in clinical practice to treat pain related to the facet joint, without inducing any significant complications[9]. The main advantages of PRF stimulation are that the procedure is painless and does not induce thermal damage to the tissues. PRF produces an electric field, which exerts a local or regional effect on immune cells, thus preventing progression to chronic pain[28,29]. The nociceptive inputs may be reduced along the pain pathways, and the electrical fields produced by PRF may alter the synaptic signal transmission[12]. Furthermore, PRF stimulation is reported to decrease microglia activity in the spinal dorsal horn[28]. Because microglia release several cytokines and chemokines that are associated with progression to chronic pain, the down-regulation of microglia activity can control pain[28]. Additionally, PRF stimulation may cause microscopic damage to unmyelinated C fibers that transfer the pain sensation[30].

The effect of PRF stimulation on the management of patients with CFP was documented in two studies. Mikeladze et al[30] investigated the effect of PRF on patients with cervical or lumbar facet joint pain. More than half of the patients (68 out of 114 patients) reported pain relief of 50% or more after PRF stimulation at 42 °C for 120 s. Liliang et al[31] enrolled patients with whiplash-related chronic CFP, and showed that PRF stimulation of the cervical medial branches relieved pain and reduced medication requirement. Our study included patients with only CFP, and the enrolled patients were not confined to...
those with a history of trauma. In line with these previous studies, the results of our study support the fact that PRF stimulation is safe and might effectively relieve CFP. In our study, PRF simulation was performed by a single physician with approximately 20 years of spinal intervention experience. Therefore, the risk of operator bias is low. Five patients in our study showed no improvement in CFP after PRF stimulation. This may be due to different underlying mechanisms involved in the development of chronic pain, which may be varied and complex\[32\]. Individualized treatment plans are required for the appropriate management of CFP.

However, there are several limitations to this study. First, the sample size was small. Second, this study lacked a placebo-controlled group. However, there are ethical considerations regarding the use of placebo in a controlled trial with patients who suffer from moderate to severe pain. Third, this study was conducted retrospectively. Fourth, the level of the origin of CFP was determined on the basis of distribution of pain, potentially adding a subjective component to our study. Fifth, we did not measure a beneficial effect on the quality of life. Further studies, including randomized controlled trials, are needed to compensate for these limitations. Authors should discuss the results and how they can be interpreted from the perspective of previous studies and of the working hypotheses. The findings and their implications should be discussed in the broadest context possible. Future research directions may also be highlighted.

**CONCLUSION**

In conclusion, we found that CFP was significantly reduced at 1 and 3 mo after PRF stimulation. The rate of successful pain relief and patient satisfaction at 3 mo after PRF stimulation was found to be 52.4%. In the current study, we showed that PRF stimulation of the cervical medial branches may be used as an alternative treatment method in patients with CFP. PRF may alleviate CFP effectively and is safe to perform.

**ARTICLE HIGHLIGHTS**

**Research background**
Cervical facet joint pain (CFP) is one of the most common causes of neck pain and headache. Persistent CFP deteriorates the quality of life of patients and reduces their productivity at work.

**Research motivation**
In order to investigate the effectiveness of pulsed radiofrequency (PRF) stimulation of cervical medial branches in patients with chronic CFP.

**Research objectives**
The authors aim to investigate the effectiveness of PRF stimulation of cervical medial branches in patients with chronic CFP.

**Research methods**
The authors retrospectively included 21 consecutive patients (age = 50.9 ± 15.3 years, range 26-79 years; male: female = 8:13; pain duration = 7.7 ± 5.0 mo) with chronic CFP, defined as ≥ 4 on the numeric rating scale (NRS). The authors performed PRF stimulation on the cervical medial branches.

**Research results**
The outcomes of the PRF procedure were evaluated by comparing the NRS scores for CFP before treatment and 1 and 3 mo after treatment. Successful pain relief was defined as a ≥ 50% reduction in the NRS score at 3 mo when compared with the pretreatment NRS score.

**Research conclusions**
PRF stimulation of the cervical medial branches may be used as an alternative treatment method in patients with CFP. PRF can effectively alleviate CFP, and is safe to perform.

**Research perspectives**
PRF stimulation on cervical medial branches may be a useful therapeutic option to control chronic CFP.
FOOTNOTES

Author contributions: Chang MC conceived and designed the paper; Yang S collected the data; both Chang MC and Yang S analyzed the data, contributed to the writing of the manuscript, and approved the final draft of the manuscript; and All authors have read and agreed to the submitted version of the manuscript.

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Informed consent statement: This study was conducted retrospectively, and there was the need for written informed consent was waived.

Conflict-of-interest statement: The authors declare no conflict of interest.

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Clinical performance evaluation of O-Ring Halcyon Linac: A real-world study

Guang-Yu Wang, Qi-Zhen Zhu, He-Ling Zhu, Ling-Juan Jiang, Nan Zhao, Zhi-Kai Liu, Fu-Quan Zhang

Abstract

BACKGROUND

Radiation therapy, especially the development of linear accelerators, plays a key role in cancer management. The fast-rotating coplanar O-ring Halcyon Linac has demonstrated many advantages. The previous literature has mainly focused on the machine parameters and plan quality of Halcyon, with a lack of relevant research on its clinical application.

AIM

To evaluate the clinical performance of the O-ring Halcyon treatment system in a real-world application setting.

METHODS

Data from sixty-one patients who were treated with the Halcyon system throughout the entire radiotherapy process in Peking Union Medical College Hospital between August 2019 and September 2020 were retrospectively reviewed. We evaluated the target tumour response to radiotherapy and irradiation toxicity from 1 to 3 mo after treatment. Dosimetric verification of Halcyon plans was performed using a quality assurance procedure, including portal dosimetry, ArcCHECK and point dose measurements for verification of the system delivery accuracy.
RESULTS
Of the 61 patients in the five groups, 16, 12, 7 and 26 patients had complete response, partial response, progressive disease and stable disease, respectively. No increase in the irradiated target tumour volume was observed when separately evaluating the local response. Regarding irradiation toxicity, no radiation-induced deaths were observed. Thirty-eight percent (23/61 patients) had no radiation toxicity after radiotherapy, 56% (34/61 patients) experienced radiation toxicity that resolved after treatment, and 6% (4/61 patients) had irreversible adverse reactions. The average gamma passing rates with a 2% dose difference and 2-mm distance to agreement for IMRT/VMAT/SRT plans were ArcCHECK at 96.4% and portal dosimetry at 96.7%, respectively. All of the validated clinical plans were within 3% for point dose measurements, and Halcyon’s ArcCHECK demonstrated a high pass rate of 99.1% ± 1.1% for clinical gamma passing criteria of 3%/3 mm.

CONCLUSION
The O-ring Halcyon Linac could achieve a better therapeutic effect on the target volume by providing accurate treatment delivery plans with tolerable irradiation toxicity.

Key Words: Halcyon; Response evaluation; Irradiation toxicity; Dosimetric verification

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Core Tip: The fast-rotating coplanar O-ring Halcyon Linac has demonstrated many advantages in radiation therapy. Unlike previous studies, which focused more on the machine parameters and quality control aspects of the O-ring Halcyon Linac, our institution evaluated Halcyon more from the perspective of practical clinical applications concerning radiotherapy effects and irradiation toxicity. The O-ring Halcyon Linac can generate desired treatment plans that meet clinically accepted constraints, pass routine patient-specific quality assurance for delivery accuracy verification, and present acceptable radiation toxicity under prospective yield.

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DOI: https://dx.doi.org/10.12998/wjcc.v10.i22.7728

INTRODUCTION
With the development and advancement of precision radiotherapy and intelligent radiotherapy, the requirements of radiotherapy equipment are also increasing. Rapid technology evolution and updated radiotherapy equipment can better protect organs at risk (OARs) and deliver highly accurate treatment to the target tissue[1,2]. A commercially available, fast-rotating coplanar O-ring linear accelerator (Linac) Halcyon treatment platform was launched by Varian Medical Systems (Palo Alto, CA, United States) in China in 2019. This machine is equipped with a single-energy six-megavolt (6 MV) flattening filter-free (FFF) beam with a dual-layer staggered 1 cm-wide Multi-Leaf Collimator (MLC) and compulsive image guide, which can achieve higher dose rates, reduce the out-of-field dose, and decrease head scatter and electron contamination compared to traditional flattened beams[3,4]. With an O-ring gantry and a rapid gantry rotation speed of 4 revolutions per minute (RPM), this Linac can greatly reduce the scanning time for cone beam computed tomography (CBCT), which can in turn generate more patient throughput[5]. Halcyon image-guided radiation therapy (IGRT) treatments are equipped with fast kilovoltage cone beam CT (kV-CBCT) and support an iterative CBCT reconstruction algorithm (iCBCT) that can provide better soft tissue display resolution[6,7] so that practitioners can obtain more information from the collected images.

In terms of the plan quality and machine parameters of Halcyon, previous studies have focused more on comparisons with C-arm Linac[5,8,9]. In contrast to C-arm Truebeam Linac (Varian Medical Systems, Palo Alto, CA, United States), Halcyon has the highest achievable maximal dose rate of 800 MU/min, with two times faster leaf speed (5 cm/s), four times faster collimator rotation (2.5 RPM), and four times faster gantry speed (4 RPM)[10]. In addition, the Halcyon system supports automatic couch shifting to replace manual isocentre shifting and faster image-guided procedures, which can compensate for the time needed, further improving daily treatment delivery accuracy, as well as patient compliance and safety. These factors explain why C-arm Truebeam Linac has a higher maximum available dose rate
setting (1400 MU/min) than Halcyon Linac (800 MU/min), but the overall treatment time for Truebeam is no longer than that for Halcyon.

The Halcyon system theoretically improves the quality of radiotherapy planning, improves the positioning accuracy, shortens the treatment time, and has potential radiobiology advantages, but what does it look like in practice? Halcyon version 2.0 was implemented in our institution and the modulation resolution of MLC was 0.5 cm. Initial acceptance testing and commissioning data confirmed that the machine met the manufacturer specifications described above. After using this machine for a certain period, our institution has certain clinical experience and research foundations for its use. This study therefore intends to retrospectively analyse patients treated with the Halcyon Linac at our institution and evaluate the effectiveness, safety, and quality assurance of Halcyon products in clinical application to provide a reference and suggestions for oncologists using Halcyon equipment.

**MATERIALS AND METHODS**

**Patients**

We retrospectively obtained data from sixty-one patients who were treated with the Halcyon system throughout the entire radiotherapy process at the Department of Radiation Oncology, Peking Union Medical College Hospital, between August 2019 and September 2020. According to treatment area, the identified patients were divided into five groups, including the head and neck group, chest group, abdomen group, pelvic group, and spine and bone group. The inclusion criteria were as follows: full use of the Halcyon system throughout the entire radiotherapy process; completion of the radiotherapy plan; a clear and evaluable target volume; and complete patient medical records, radiotherapy data and follow-up information. Patients with the following clinical scenarios were excluded: other types of Linac systems used during irradiation of the target volume; failure to complete the radiotherapy plan for various reasons; loss to follow-up or a lack of patient clinical data; and no evaluation of the lesion. Demographic and clinical information, including sex, race, age, clinical diagnosis, pathological type, radiotherapy plan scheduling, course timeline, treatment progress, target volume, OARs, radiotherapy positioning, dose, and concurrent therapy, were retrieved from electronic medical records and Linac systems. At the same time, imaging evaluation data from before and after treatment and equipment operation records, such as machine failure records and maintenance records, were consulted. This study was reviewed and approved by the Institutional Review Board of Peking Union Medical College Hospital (No. S-K1883).

**Treatment approaches and follow-up**

Radiotherapy was administered to patients according to the pathological characteristics of the lesion, the patient’s physical status and willingness, and the doctor’s preference. Radiotherapy was performed using a 6-MV X-ray Halcyon linear accelerator and intensity modulated radiotherapy (IMRT), volumetric modulated arc therapy (VMAT) or stereotactic radiotherapy (SRT) modalities. All of the patients met the indications for radiotherapy. All of the patients were scanned by a Philips Brilliance Big Bore CT scanner to obtain CT-based simulation images, and the images were transmitted to an Eclipse15.5 treatment planning system (Varian, United States). The doctors drew the target volumes and OARs, the physicists designed the plan, and the therapists operated the equipment. CBCT examination was performed before every treatment, and then radiotherapy was completed with the Halcyon Linac. The imaging data of patients from 1 to 3 mo after treatment with the Halcyon Linac were reviewed and compared with imaging data before treatment to evaluate the target tumour response after radiation treatment. Tumour response was evaluated according to the Response Evaluation Criteria in Solid Tumours (RECIST), except for bone metastasis. Bone tumour response was assessed using criteria developed by the M.D. Anderson Cancer Center (MDA). Systemic progression, such as distant metastasis, was recorded. All of the patients were followed up for 1 to 3 mo after radiotherapy by outpatient, inpatient or telephone visits to evaluate them for irradiation toxicity. Toxicities, such as acute skin reactions, myelosuppression, mucosal reactions, radiation pneumonia or gastrointestinal disorders, were evaluated using the Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE 4.0).

**Quality assurance**

Dosimetric verification of Halcyon plans was performed using quality assurance procedures such as portal dosimetry, ArcCHECK and point dose measurements to verify the system delivery accuracy[11]. The treatment delivery accuracy was evaluated by delivering a plan in quality assurance measurement mode to the Linac via an on-board electronic portal imaging device (EPID) imager and recording the gamma analysis pass rates via portal dosimetry. For portal dosimetry, gamma evaluation criteria of 2%/2 mm with a 10% low dose threshold were used. A cube solid water phantom with multiple water-equivalent plastic blocks and spacers was used to verify the dose distributions for the clinical plans[12], and the measured point doses were compared to point doses calculated at the same location. Then, percent differences were reported. ArcCHECK (SunNuclear, FL, United States) used 3%/3 mm and 2%/2 mm gamma evaluation criteria with low dose thresholds of 5% and 10%, respectively, to compare
RESULTS

Patient characteristics
Between August 2019 and September 2020, a total of 61 patients who completed radiotherapy by Halcyon were enrolled. There were 12 patients in the head and neck group, 13 in the chest group, 10 in the abdomen group, 14 in the pelvic group, and 12 in the spine and bone group. Among them, cervical cancer was the most common cancer type (18%; 11 patients). One patient was treated with SRT, 21 patients with IMRT, and 39 patients with VMAT. Regarding the irradiated site, 56% of patients were treated for a primary tumour, 1% for recurrence in situ postoperatively, and 43% for metastasis. Table 1 summarizes the clinical characteristics of the enrolled patients.

Effects of radiotherapy
By comparing the imaging data of patients before and 1-3 mo after treatment and the results of other auxiliary examination methods, the changes in the tumour size of the irradiated site before and after treatment were evaluated. The detailed response evaluations and the time intervals for evaluation are shown in Table 2. The irradiated lesions of most patients were evaluated for nearly 1 mo after radiotherapy. The most effective response, reported complete response (CR), was in the pelvic group, with nine cases of cervical cancer. Seven patients experienced distant metastasis within 1 to 3 mo after the completion of radiotherapy, indicating progressive disease (PD). In the abdomen and spine and bone groups, the results showed that the majority of patients had stable disease.

Irradiation toxicity
All of the patients completed the prescription dose of radiotherapy. Regarding toxicity, no radiation-induced deaths were observed. According to the outpatient, inpatient or telephone follow-up records, none of the patients felt discomfort during radiotherapy. Thirty-eight percent (23/61 patients) had no radiation toxicity after radiotherapy, 56% (34/61 patients) had radiation toxicities that resolved after treatment, and 6% (4/61 patients) had irreversible adverse reactions. The most common adverse effect was a haematological reaction (57%; 35/61 patients). Among the patients experiencing haematological reactions, 26 patients had grade 1-2 myelosuppression, but no patients had grade 4 myelosuppression during follow-up. In the head and neck group, the radiation toxicities observed after subsequent treatment were hypogeusia (2 patients), oral ulceration (3 patients), dysphagia (2 patients), and increased and sticky pharyngeal secretion (1 patient), which resolved after treatment. In the chest group, the radiation toxicities that resolved after treatment included radiation pneumonitis, radiodermatitis, cutaneous pigmentation, chest and back pain (one case of each). There were few adverse reactions other than myelosuppression, urinary tract reactions and gastrointestinal tract reactions in the abdomen, pelvic, spine and bone groups. Regarding long-term complications, two patients from the head and neck group had xerostomia, one patient with brain metastases receiving SRT had hypomnesia, and one patient with lung cancer developed radiation pulmonary fibrosis.

Quality assurance
Table 3 shows the mean values of the treatment delivery parameter (and range) differences, including point dose measurements, ArcCHECK (2 mm/2%), ArcCHECK (3 mm/3%) and portal dosimetry. A total of 61 plans were generated in the Eclipse15.5 treatment planning system, and we performed 29, 20, 23, and 16 dosimetric verifications of the Halcyon plans for the above treatment delivery parameters. All of the ArcCHECK results were greater than 95% with 3 mm/3% gamma criteria, and only two portal dosimetry (88.6% and 89.7%) results were less than the 10% low dose threshold. The results of point dose measurements were all controlled at 3%. Figure 1 shows an example of the predicted dose compared with the detected dose.

DISCUSSION
We explored the effectiveness, safety, and quality assurance of Halcyon in clinical application between June 2015 and July 2018 by analysing 61 patients subdivided into five groups. Our results showed that O-ring Halcyon Linac could achieve a better therapeutic effect on the target volume by providing accurate treatment delivery plans with tolerable toxicity of irradiation. For clinics that use Halcyon for treatment delivery, administering radiotherapy with this system is feasible and safe.

According to previous studies, the Halcyon treatment platform showed good performance for radiotherapy modalities. An early study by Cozzi et al[13] reported that Halcyon could deliver radiotherapy to conventionally fractionated breast, head and neck, and high-risk prostate tissue quickly and effectively with plans of similarly high clinical quality when compared to the C-arm Linac. Pokhrel
et al [14] reported an analysis of stereotactic body radiation therapy (SBRT) treatment of abdominal and pelvic oligometastatic lymph nodes with single-isocentre VMAT using Halcyon. They showed that acceptable plan quality and effective treatment delivery could be achieved for SBRT using the Halcyon Linac. These studies demonstrate that the Halcyon platform can generate treatment plans that meet clinically accepted constraints and pass routine patient-specific quality assurance testing for delivery accuracy verification. Compared with these previous studies, which mostly reported product performance from plan quality and machine parameters, we focused more on the effectiveness and safety of the Halcyon system in clinical practice applications. In our study, patients were divided into five groups according to the irradiated site and received mainly conventional fraction dose radiotherapy using IMRT and VMAT, which is closely related to daily clinical application.

Assessment of solid tumour response, except for in the spine and bone group, was performed using criteria developed by RECIST, version 1.1 [15]. Four patients were evaluated as having PD due to distant metastasis, but no increase in the irradiated target tumour volume was observed when separately evaluating the local response. This finding demonstrated the effectiveness of Halcyon for the local control of cancer. In the previous literature, there have been few evaluations of the efficacy of a specific machine in the field of radiotherapy. Early disease-control outcomes in patients treated with Halcyon were comparable to published reports with no recurrences in the radiation field, although with a
Table 2 Response evaluation and time interval for evaluation

<table>
<thead>
<tr>
<th>Group</th>
<th>The time interval for evaluation (n)</th>
<th>Response evaluation (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 mo</td>
<td>2 mo</td>
</tr>
<tr>
<td>Head and neck</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Chest</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Abdomen</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Pelvic</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Spine and bone</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>37</td>
<td>21</td>
</tr>
</tbody>
</table>


Table 3 mean ± SD values of treatment delivery parameters (and range)

<table>
<thead>
<tr>
<th>Dosimetric verification</th>
<th>Point dose measurements (%)</th>
<th>ArcCHECK (2%/2 mm) (%)</th>
<th>ArcCHECK (3%/3 mm) (%)</th>
<th>Portal dosimetry (2%/2 mm) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head and neck</td>
<td>0.26 ± 1.1 (-0.22-1.92)</td>
<td>95.5 ± 1.8 (93.2-97.7)</td>
<td>99.4 ± 0.5 (98.8-100)</td>
<td>97.8 ± 2.4 (93.3-100)</td>
</tr>
<tr>
<td>Chest</td>
<td>1 ± 0.6 (0.45-2.18)</td>
<td>97.63 ± 1.1 (96.1-98.4)</td>
<td>99.2 ± 0.8 (97.9-100)</td>
<td>89.7</td>
</tr>
<tr>
<td>Abdomen</td>
<td>1.11 ± 0.7 (0.23-2.01)</td>
<td>97.1 ± 2.0 (95.5-99.3)</td>
<td>98.8 ± 1.5 (96.5-99.7)</td>
<td>96</td>
</tr>
<tr>
<td>Pelvic</td>
<td>-0.15 ± 0.7 (-0.99-1.38)</td>
<td>96.0 ± 2.2 (94.2-99.2)</td>
<td>99 ± 1.4 (96.3-100)</td>
<td>98.4 ± 2.4 (98.1-98.6)</td>
</tr>
<tr>
<td>Spine and bone</td>
<td>0.2 ± 1.8 (-1.8-2.72)</td>
<td>96.5 ± 1.8 (93.6-97.8)</td>
<td>99.2 ± 0.9 (97.9-100)</td>
<td>93.2 ± 6.4 (88.6-97.7)</td>
</tr>
<tr>
<td>Total</td>
<td>0.42 ± 1 (-1.8-2.72)</td>
<td>96.4 ± 1.8 (93.3-99.3)</td>
<td>99.1 ± 1.1 (96.3-100)</td>
<td>96.7 ± 3.4 (88.6-100)</td>
</tr>
</tbody>
</table>

Figure 1 Portal dosimetry: Examples of a cervical cancer patient treated with pelvic lymph nodes region radiotherapy. Portal dosimetry demonstrated a high pass rate of 98.6% for clinical gamma passing criteria of 2%/2 mm with the predicted dose (left side) and detected dose (right side).

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relatively short median follow-up[16,17]. Gupta et al[18] found 13.56% local (with or without distant metastasis) first recurrence in neoadjuvant chemotherapy followed by concomitant chemoradiation for cervical cancer. The small cohort of cervical cancer patients in our abdomen group all showed CR, demonstrating a good start to long-term survival. Most of the patients with PD were in the chest group (3/4 patients). Three patients (two with small cell lung cancer and one with oesophageal squamous carcinoma) in the chest group with PD were closely related to the strong biologic invasiveness of these two tumours and the tendency for distant metastasis[19,20]. This finding serves as a reminder that radiotherapy, as a topical treatment for cancer patients, is not a replacement for systemic treatment. In the efficacy evaluation of irradiation response, the patients with cervical cancer achieved the most CR among the enrolled patients (9/16 patients), with a significant advantage compared with other diseases. This finding is closely related to China having made great progress in cervical cancer treatment, with a nearly five percent increase in five-year overall survival compared to that in the United States[21]. Our institution has conducted in-depth basic and clinical research in the field of radiotherapy for cervical
cancer and established a model of precise radiotherapy for cervical cancer[22-24].

Bone is one of the most common sites of metastasis, and external beam radiotherapy is an important treatment modality that plays a key role in controlling lesion progression[25,26]. For the evaluation of bone tumour response, we did not use the International Union Against Cancer (UICC) or WHO criteria, which define bone tumour response by plain radiography and skeletal scintigraphy[27,28], or the RECIST criteria, which regard bone metastases as unmeasurable lesions[15]. In our study, we referred to a revised set of response criteria for bone metastases proposed by the MDA[29], which presents a practical approach for the diagnosis and assessment of bone metastasis. For all twelve patients in the spine and bone group, the target volumes were bone metastases, and three patients had PD because of distant metastasis. When we evaluated the bone response to radiotherapy, there was fill-in or sclerosis of lytic lesions, normalization of osteoblastic lesions, no increase in the size of any existing measurable lesions in the irradiated sites, and other similar imaging findings, regarded as no local lesion progression following the MDA criteria.

In terms of safety, this study examined outpatient and inpatient records and performed telephone follow-up. The results showed that acute toxicities were well tolerated in all patients, and no patients felt discomfort during radiotherapy. Most patients had radiation toxicities related to haematological reactions, but their symptoms subsided over time. Myelosuppression was closely related to the irradiation site, and the main reason for the occurrence of myelosuppression in most patients is likely the administration of concurrent chemotherapy or other therapies, which definitely exacerbate haematological toxicity[30,31]. Although we made great efforts in the planning design and machine performance, late toxic reactions are inevitable due to the physics of radiation and the proximity to OARs[32,33]. Among the patients with irreversible adverse reactions, most patients experienced xerostomia as a long-term side effect (50%; 2/4 patients), which was closely related to the inevitable damage to the parotid gland caused by the physical characteristics of the radiation dose reduction and tumour location during radiotherapy for head and neck tumour patients[34].

To obtain a better radiotherapy effect and achieve uniform coverage while maintaining safe doses to the target volume, steep dose gradients must be achieved with precise dose delivery. Quality assurance, especially for dosimetric verification, is required to ensure accurate plan delivery. According to previous studies, Halcyon has demonstrated great quality assurance results. Pokhrel et al[35] described the plan quality, treatment delivery efficacy and accuracy of SBRT treatments using the O-ring Halcyon Linac via VMAT. Petroccia et al[10] reported that Halcyon could potentially reduce the dose to OARs while simultaneously increasing the dose delivered to the tumour. We also performed some dosimetric verification of Halcyon plans, and the results were within the acceptable range, except for two portal dosimetry (88.6% and 89.7%) results. We redesigned the treatment plan, performed dosimetric verification again for these two patients, and treated them after the verification results passed the set low dose threshold. In addition, Halcyon’s ArcCHECK and portal dosimetry demonstrated high gamma passing rates greater than an average of 95% with criteria of 2%/2 mm and 3%/3 mm. All of the validated clinical plans were within 3% for point dose measurements. These quality assurance measurements verified that accurate delivery could be achieved with Halcyon.

Some of the limitations of this study are as follows. First, the incidence of radiation toxicities might have been underestimated because of the retrospective nature of the study, most of the patients being outpatients, and the short-term telephone follow-up, which might not illustrate the full picture. Second, as a retrospective, single-centre study, selection bias might exist. Nonetheless, our sample size was sufficiently large when compared to analogous studies. Third, unlike previous research on machine features and parameters, this study was a descriptive study that focused more on Halcyon products in clinical treatment applications; thus, we did not include controls.

CONCLUSION

In summary, we evaluated the clinical performance of the Halcyon treatment system in a real-world application setting by analysing patients who received Halcyon Linac throughout the entire radiotherapy process. The results of this study indicate that the Halcyon platform can generate treatment plans that meet clinically accepted constraints, can pass routine patient-specific quality assurance evaluations for delivery accuracy verification, and has acceptable radiation toxicities under prospective yield.

ARTICLE HIGHLIGHTS

Research background

Radiation therapy is commonly used in cancer management. Halcyon, a novel 6MV-flattening-filter-free O-ring linear accelerator (6X-FFF ORL), was designed to deliver treatment with greater speed than a traditional C-arm Linac, demonstrating great advantages.
**Research motivation**
The development of linear accelerators has played a key role in cancer management. Halcyon, as a new accelerator with many breakthrough innovations, is worthy of further exploration for clinical application. Previous studies have mainly focused on the machine parameters and plan quality of Halcyon, while relevant research on its clinical application has been lacking.

**Research objectives**
To evaluate the clinical performance of the O-ring Halcyon treatment system in a real-world application setting and share our clinical experience with 6X-FFF ORL radiation therapy for cancer management.

**Research methods**
Patients who were treated with the Halcyon system throughout the entire radiotherapy process were retrospectively reviewed. We evaluated the Halcyon from three aspects: effects of radiotherapy, irradiation toxicity and quality assurance. Dosimetric verification of Halcyon plans was performed using quality assurance procedures such as portal dosimetry, ArcCHECK and point dose measurements to verify the system delivery accuracy.

**Research results**
Of the 61 patients in the five groups, no increase in the irradiated target tumour volume was observed when separately evaluating local response. Regarding irradiation toxicity, thirty-eight percent (23/61 patients) had no radiation toxicity after radiotherapy, 56% (34/61 patients) experienced radiation toxicity that resolved after treatment, and 6% (4/61 patients) had irreversible adverse reactions. All of the validated clinical plans were within 3% for point dose measurements, and the average gamma passing rates with a 2% dose difference and 2-mm distance to agreement for IMRT/VMAT/SRT plans were ArcCHECK at 96.4% and portal dosimetry at 96.7%, respectively.

**Research conclusions**
We showed that the Halcyon platform can generate treatment plans that meet clinically accepted constraints and pass routine patient-specific quality assurance for delivery accuracy verification. For clinics that choose Halcyon as the treatment delivery option, administering VMAT and IMRT is feasible and safe.

**Research perspectives**
Further follow-up is needed to assess late toxicity and long-term outcomes.

**FOOTNOTES**

**Author contributions:** Wang GY designed and performed the research and wrote the paper; Liu ZK and Zhang FQ designed the research and supervised the report; Zhu QZ and Zhu HL performed the research; Jiang LJ and Zhao N supervised the report.

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REFERENCES


**Retrospective Study**

**Correlation between the warning symptoms and prognosis of cardiac arrest**

Kang Zheng, Yi Bai, Qiang-Rong Zhai, Lan-Fang Du, Hong-Xia Ge, Guo-Xing Wang, Qing-Bian Ma

**Abstract**

**BACKGROUND**
A low survival rate in patients with cardiac arrest is associated with failure to recognize the condition in its initial stage. Therefore, recognizing the warning symptoms of cardiac arrest in the early stage may play an important role in survival.

**AIM**
To investigate the warning symptoms of cardiac arrest and to determine the correlation between the symptoms and outcomes.

**METHODS**
We included all adult patients with all-cause cardiac arrest who visited Peking University Third Hospital or Beijing Friendship Hospital between January 2012 and December 2014. Data on population, symptoms, resuscitation parameters, and outcomes were analysed.

**RESULTS**
Of the 1021 patients in the study, 65.9% had symptoms that presented before cardiac arrest, 25.2% achieved restoration of spontaneous circulation (ROSC), and 7.2% survived to discharge. The patients with symptoms had higher rates of an initial shockable rhythm (12.2% vs 7.5%, \( P = 0.020 \)), ROSC (29.1% vs 17.5%, \( P = 0.001 \)) and survival (9.2% vs 2.6%, \( P = 0.001 \)) than patients without symptoms. Compared with the out-of-hospital cardiac arrest (OHCA) without symptoms subgroup, the OHCA with symptoms subgroup had a higher rate of calls before arrest (81.6% vs 0.0%, \( P < 0.001 \)), health care provider-witnessed arrest (13.0% vs 1.4%, \( P = 0.001 \)) and bystander cardiopulmonary resuscitation (15.5% vs 4.9%, \( P = 0.002 \)); a shorter no flow time (11.7% vs 2.8%, \( P = 0.002 \)) and a higher ROSC rate.
Over 60% of SCA events occur under in-hospital patients under monitoring and are known as in-hospital cardiac arrest (IHCA) patients. In contrast, many SCA events occur outside the hospital and is known as out-of-hospital cardiac arrest (OHCA). In these situations, bystanders are usually not trained in CPR procedures, a primary problem that increases the difficulty of treatment and reduces the survival rate.

Core Tip: This was a retrospective study to investigate the correlation between the symptoms and the outcomes in cardiac arrest patients. A total of 65.9% of patients had symptoms before arrest. Dyspnea, chest pain, and unconsciousness were the most common symptoms. The patients with symptoms had a higher rate of initial shockable rhythm, restoration of spontaneous circulation (ROSC) and survival than patients without symptoms. The out-of-hospital cardiac arrest symptoms subgroup had a higher rate of bystander cardiopulmonary resuscitation, a shorter no flow time, and a higher ROSC rate. The in-hospital cardiac arrest symptoms subgroup had higher ROSC and survival rates. Immediate recognition of symptoms and activation of the emergency medical system could prevent resuscitation delay and improve the survival rate.

INTRODUCTION

Sudden cardiac arrest (SCA) is commonly defined as an unexpected loss of pulse, which causes the patient to rapidly collapse. SCA has become a major issue in the field of emergency medicine over the past decades[1]. SCA patients may survive with timely cardiopulmonary resuscitation (CPR). Patients in the end-stage of cardiac arrest and those with pre-existing illnesses, such as terminal cancer, nonresponding pneumonia, end-stage cirrhosis, or massive cerebral hemorrhage, are generally untreatable, so cardiac arrest is predictable and death is inevitable[2]. However, if a patient is not in the end stage, regardless of the etiology and location of the cardiac arrest, high-quality basic life support and advanced cardiovascular life support could save the patient’s life[3].

Important progress has been made in resuscitation science over the last two decades. Smartphone applications can be used to activate the emergency response system[4,5]. There are more specific recommendations for high-quality chest compression, including an adequate compression rate and depth, full chest recoil, and the minimization of interruptions. Extracorporeal CPR may be considered for select cardiac arrest patients[6]. However, despite major progress in public-access defibrillation and resuscitation techniques, survival after SCA remains very low, at approximately 10% in developed countries and less than 1% in China and other developing countries[7,8]. The unpredictability of SCA is a primary problem that increases the difficulty of treatment and reduces the survival rate[7].

Over 60% of SCA events occur under in hospitalized patients under monitoring[7,9]. In a hospital, health care providers can arrive at the site within a few minutes, and the rapid response team can begin treatment immediately, which may contribute to the higher survival rate of in-hospital cardiac arrest (IHCA) patients[10]. In contrast, many SCA events occur outside the hospital and is known as out-of-hospital cardiac arrest (OHCA). In these situations, bystanders are usually not trained in CPR[11]. An immediately activated emergency response system is the first part of the “chain of survival” for OHCA.
patients, as emphasized by CPR guidelines in recent years[12]. However, most patients who experience cardiac arrest in public do not receive adequate treatment in China. The most common public response is “wait and see”, and treatment initiation by emergency medical services (EMS) can also be influenced by factors such as traffic jams and response time, that is, the time from answering the call to EMS arrival on site, which is largely determined by the availability of dispatching resources[8]. All the above can result in missing the ideal time to rescue a cardiac arrest patient. Thus, the rate of survival to discharge in OHCA patients in China has remained low for many years.

Regardless of OHCA or IHCA, clinicians need to develop methods to identify high-risk patients who suffer cardiac arrest. Warning symptoms are defined as signs that appear before SCA and have a causal relationship, including chest pain, dyspnea, palpitation, unconsciousness, and paralysis[13].

We hypothesized that different etiologies of SCA correlate with certain symptoms and that the immediate and correct recognition of symptoms and etiology can improve patient survival. We sought to investigate the characteristics of the warning symptoms of cardiac arrest, and to determine the correlation between cardiac arrest symptoms and patient prognosis.

**MATERIALS AND METHODS**

**Setting**
Two medical centers participated in this study: Perking University Third Hospital and Beijing Friendship Hospital. Both are general hospitals, and the number of emergency visits exceeds 10000 per year in each of the two hospitals, which is the highest in Beijing.

**Study design and data collection**
We included all adult patients with all-cause cardiac arrest who visited Perking University Third Hospital or Beijing Friendship Hospital between January 2012 and December 2014. The exclusion criteria were as follows: Younger than 18 years old, showing obvious signs of irreversible disease (e.g., terminal cancer) and have a Do Not Resuscitate (DNR) declaration. Using the personal identification number provided to all emergency patients, electronic medical records in the hospital information systems were reviewed.

Data on patient characteristics, including pre-existing illnesses, warning symptoms within 24 h before SCA, call for EMS, the presence of a witness at the scene, time from cardiac arrest to contact with a health care provider, time from cardiac arrest to effective CPR (as defined by trained public rescuer or health care provider), initial rhythm, administration of defibrillation, restoration of spontaneous circulation (ROSC) (defined as a brief ROSC that provides evidence of more than an occasional gasp), and survival to discharge, were obtained. This study was approved by the Peking University Third Hospital Medical Science Research Ethics Committee.

**Statistical analysis**
Continuous variables are presented as the mean ± SD and were compared using a t-test. Categorical variables are presented as numbers (%) and were compared using the chi-square test or Fisher’s exact test as appropriate. A P value < 0.05 was considered statistically significant. All data were analysed using the statistical software package SPSS (IBM Corp. IBM SPSS Statistics for Windows, Version 25.0. Armonk, New York, United States).

**RESULTS**

**Study population**
During the 36-mo study period, a total of 32743 patients visited the emergency departments. Of these patients, 2556 suffered cardiac arrest. One hundred eighteen patients were excluded because of incomplete information, and an additional 1417 were excluded for end-stage disease or DNR requests. A total of 1021 patients were ultimately included in this study. Among the included patients, 673 (65.9%) had warning symptoms, and 348 (34.1%) patients had no symptoms (Figure 1).

The included patients had a mean age of 64.1 ± 16.7 years; 68.4% were male, 37.8% had a cardiac etiology, 10.6% had an initial shockable rhythm, 25.2% achieved ROSC, and 7.0% survived to discharge. Of the 1021 patients, 770 (75.4%) had pre-existing illnesses. The top five pre-existing illnesses were hypertension (33.6%), coronary heart disease (23.3%), diabetes (20.0%), cerebral vascular disease (13.7%), and malignancy (8.8%). Other pre-existing illnesses included chronic kidney disease, chronic obstructive pulmonary disease, asthma, interstitial lung disease, valvular heart disease, cardiomyopathy, and cirrhosis.
Zheng K et al. Warning symptoms in cardiac arrest

Characteristics and outcomes of the patients with and those without symptoms

The patients with symptoms had a higher mean age (65.2 ± 16.2 vs 61.8 ± 17.4 years, \( P = 0.002 \)) and had higher rates of initial shockable rhythm (12.2% vs 7.5%, \( P = 0.020 \)), ROSC (29.1% vs 17.5%, \( P = 0.001 \)) and survival (9.2% vs 2.6%, \( P = 0.001 \)) than the patients without symptoms. Regarding other factors, such as sex, pre-existing illnesses, arrest location and etiology, there were no significant differences between the two groups (Table 1).

Patients were divided into OHCA or IHCA groups according to the cardiac arrest location, and then each group was divided into subgroups according to the presence or absence of symptoms (Table 2). The OHCA with symptoms subgroup had higher proportions of calls before arrest (81.6% vs 0.0%, \( P < 0.001 \)), health care provider-witnessed arrest (13.0% vs 1.4%, \( P = 0.001 \)), bystander CPR administration (15.5% vs 4.9%, \( P = 0.002 \)), no flow time for 1 to 4 min (11.7% vs 2.8%, \( P = 0.002 \)), and ROSC (23.8% vs 13.2%, \( P = 0.011 \)) than the OHCA without symptoms subgroup. In comparison to the IHCA without symptoms subgroup, the IHCA with symptoms group had a higher mean age (66.2 ± 15.2 vs 62.5 ± 16.3 years, \( P = 0.005 \)) and higher proportions of ROSC (32.0% vs 20.6%, \( P = 0.003 \)) and survival to discharge (10.6% vs 2.5%, \( P < 0.001 \)); there were no significant differences in any resuscitation parameters.

Warning symptoms among cardiac arrest patients

Six hundred seventy-three patients (65.9%) had warning symptoms before SCA. The top five symptoms were dyspnea (48.7%), chest pain (18.3%), unconsciousness (15.2%), paralysis (4.3%), and vomiting (4.0%). Other symptoms included abdominal pain, seizure, dysphonia, palpitation, dizziness, syncope, and headache (Figure 2).

Four hundred sixty male patients had warning symptoms. The top three symptoms were dyspnea (45.9%), chest pain (20.9%) and unconsciousness (14.6%). Two hundred thirteen female patients had warning symptoms. The top three symptoms were dyspnea (54.9%), unconsciousness (16.4%) and chest pain (12.7%). Chest pain was more common in males (20.9% vs 12.7%, \( P = 0.011 \)), whereas dyspnea was more common in females (54.9% vs 45.9%, \( P = 0.029 \)). There was no significant difference in the other symptoms between the two groups (Table 3).

Among the patients who were younger than 60 years old, 225 patients had warning symptoms. The top three symptoms were dyspnea (44.9%), chest pain (22.2%) and unconsciousness (16.9%). Among the patients who were aged 60 years and older, 448 patients had warning symptoms. The top three symptoms were dyspnea (50.7%), chest pain (16.3%) and unconsciousness (14.3%). No significant difference was observed in these age groups (Table 3).

Two hundred sixty-four patients with a cardiac etiology had warning symptoms. The top three symptoms were chest pain (44.3%), dyspnea (41.7%) and unconsciousness (7.3%). Two hundred one patients with a noncardiac etiology had warning symptoms. The top three symptoms were dyspnea (53.3%), unconsciousness (20.3%) and paralysis (6.4%). Symptoms of dyspnea (53.3% vs 41.7%, \( P = 0.003 \)), unconsciousness (20.3% vs 7.2%, \( P < 0.001 \)), paralysis (6.4% vs 1.1%, \( P = 0.001 \)), vomiting (5.4% vs 1.9%, \( P = 0.025 \)), abdominal pain (3.9% vs 0.8%, \( P = 0.013 \)) and dysphonia (2.9% vs 0.4%, \( P = 0.019 \)) were
Table 1 Characteristics of the patients with and without symptoms

<table>
<thead>
<tr>
<th></th>
<th>All (n = 1021)</th>
<th>No symptoms (n = 348)</th>
<th>Symptoms (n = 673)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, mean ± SD</strong></td>
<td>64.1 ± 16.7</td>
<td>61.8 ± 17.4</td>
<td>65.2 ± 16.2</td>
<td>0.002*</td>
</tr>
<tr>
<td><strong>Male, n (%)</strong></td>
<td>698 (68.4)</td>
<td>238 (68.4)</td>
<td>460 (68.4)</td>
<td>0.990</td>
</tr>
<tr>
<td><strong>Pre-existing illness, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>343 (33.6)</td>
<td>120 (31.3)</td>
<td>223 (33.1)</td>
<td>0.666</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>238 (23.3)</td>
<td>72 (18.8)</td>
<td>166 (24.7)</td>
<td>0.154</td>
</tr>
<tr>
<td>Diabetes</td>
<td>204 (20.0)</td>
<td>67 (17.4)</td>
<td>137 (20.4)</td>
<td>0.676</td>
</tr>
<tr>
<td>Cerebral vascular disease</td>
<td>140 (13.7)</td>
<td>40 (10.4)</td>
<td>100 (14.9)</td>
<td>0.139</td>
</tr>
<tr>
<td>Malignancy</td>
<td>90 (8.8)</td>
<td>27 (7.0)</td>
<td>63 (9.4)</td>
<td>0.392</td>
</tr>
<tr>
<td>1 pre-existing illness</td>
<td>341 (33.4)</td>
<td>105 (24.7)</td>
<td>236 (35.1)</td>
<td>0.116</td>
</tr>
<tr>
<td>2 pre-existing illnesses</td>
<td>209 (20.5)</td>
<td>74 (19.5)</td>
<td>135 (20.1)</td>
<td>0.651</td>
</tr>
<tr>
<td>≥3 pre-existing illnesses</td>
<td>83 (8.1)</td>
<td>24 (6.3)</td>
<td>59 (8.8)</td>
<td>0.300</td>
</tr>
<tr>
<td><strong>Location of SCA, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.066</td>
</tr>
<tr>
<td>Out of hospital</td>
<td>383 (37.5)</td>
<td>144 (41.4)</td>
<td>239 (35.5)</td>
<td></td>
</tr>
<tr>
<td>In hospital</td>
<td>638 (62.5)</td>
<td>204 (58.6)</td>
<td>434 (64.5)</td>
<td></td>
</tr>
<tr>
<td><strong>Initial shockable rhythm, n (%)</strong></td>
<td>108 (10.6)</td>
<td>26 (7.5)</td>
<td>82 (12.2)</td>
<td>0.020*</td>
</tr>
<tr>
<td><strong>Cardiac etiology, n (%)</strong></td>
<td>386 (37.8)</td>
<td>122 (35.1)</td>
<td>264 (39.2)</td>
<td>0.193</td>
</tr>
<tr>
<td>ROSC, n (%)</td>
<td>257 (25.2)</td>
<td>61 (17.5)</td>
<td>196 (29.1)</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Survival to discharge, n (%)</td>
<td>71 (7.0)</td>
<td>9 (2.6)</td>
<td>62 (9.2)</td>
<td>&lt; 0.001*</td>
</tr>
</tbody>
</table>

*P < 0.05.

SCA: Sudden cardiac arrest; ROSC: Restoration of spontaneous circulation.

Figure 2 Warning symptoms in patients with sudden cardiac arrest.

more common in the noncardiac etiology group. In contrast, chest pain was more common in the cardiac etiology group (44.3% vs 1.5%, P < 0.001). There were no significant differences in other symptoms between the two groups (Table 3).

Sixty-two surviving patients had warning symptoms. The top three symptoms were (43.5%), chest pain (33.9%) and unconsciousness (12.9%). Among the 621 patients who did not survive, the top three symptoms were dyspnea (49.3%), chest pain (16.7%) and unconsciousness (15.4%). Chest pain was more common in the surviving patients (33.9% vs 16.7%, P = 0.001). There were no significant differences in the other symptoms between the two groups (Table 3).
### Table 2 Resuscitation parameters and prognosis in patients with and without symptoms

<table>
<thead>
<tr>
<th></th>
<th>OHCA</th>
<th>IHCA</th>
<th><strong>P</strong> value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, (mean ± SD)</strong></td>
<td>60.8 ± 18.8</td>
<td>63.4 ± 17.7</td>
<td>0.174</td>
</tr>
<tr>
<td><strong>Male, n (%)</strong></td>
<td>106 (73.6)</td>
<td>175 (73.2)</td>
<td>0.933</td>
</tr>
<tr>
<td><strong>Call before arrest, n (%)</strong></td>
<td>0 (0.0)</td>
<td>195 (81.6)</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td><strong>Witness of cardiac arrest, n (%)</strong></td>
<td>&lt; 0.001*</td>
<td>194 (95.1)</td>
<td>0.299</td>
</tr>
<tr>
<td><strong>No symptoms (n = 144)</strong></td>
<td></td>
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<td></td>
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<tr>
<td><strong>Symptoms (n = 239)</strong></td>
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<tr>
<td><strong>No symptoms (n = 204)</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Symptoms (n = 434)</strong></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
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<tr>
<td><strong>Male, n (%)</strong></td>
<td>106 (73.6)</td>
<td>175 (73.2)</td>
<td>0.933</td>
</tr>
<tr>
<td><strong>Call before arrest, n (%)</strong></td>
<td>0 (0.0)</td>
<td>195 (81.6)</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td><strong>Witness of cardiac arrest, n (%)</strong></td>
<td>&lt; 0.001*</td>
<td>194 (95.1)</td>
<td>0.299</td>
</tr>
<tr>
<td><strong>No flow time, n (%)</strong></td>
<td>0.002*</td>
<td>194 (95.1)</td>
<td>0.299</td>
</tr>
<tr>
<td><strong>1 to 4 min</strong></td>
<td>4 (2.8)</td>
<td>26 (11.7)</td>
<td>0.002*</td>
</tr>
<tr>
<td><strong>5 to 10 min</strong></td>
<td>4 (2.8)</td>
<td>16 (6.7)</td>
<td>0.095</td>
</tr>
<tr>
<td><strong>&gt; 10 min</strong></td>
<td>136 (94.4)</td>
<td>195 (81.6)</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td><strong>Initial shockable rhythm, n (%)</strong></td>
<td>7 (4.9)</td>
<td>19 (7.9)</td>
<td>0.244</td>
</tr>
<tr>
<td><strong>Cardiac etiology, n (%)</strong></td>
<td>77 (53.5)</td>
<td>140 (58.6)</td>
<td>0.329</td>
</tr>
<tr>
<td><strong>ROSC, n (%)</strong></td>
<td>19 (13.2)</td>
<td>57 (23.8)</td>
<td>0.011*</td>
</tr>
<tr>
<td><strong>Survival to discharge, n (%)</strong></td>
<td>49 (2.8)</td>
<td>16 (6.7)</td>
<td>0.095</td>
</tr>
</tbody>
</table>

*P < 0.05.

**OHCA**: Out-of-hospital cardiac arrest; **IHCA**: In-hospital cardiac arrest; **CPR**: Cardiopulmonary resuscitation; **ROSC**: Restoration of spontaneous circulation.

### DISCUSSION

Most patients had warning symptoms before SCA. Warning symptoms frequently occurred before SCA, and most symptoms recurred during the 24-hour period before SCA[13]. Unfortunately, more than two-thirds of patients and their families ignore the symptoms until cardiac arrest occurs[14]. In our study, it was remarkable that 65.9% of the patients had warning symptoms. Once warning symptoms appear, immediate activation of EMS could help patients receive treatment as early as possible. Emergency calls before patient collapse was associated with an increase in the proportions of EMS-witnessed cases and survival[4]. In our study, it was remarkable that the patients with symptoms had a better prognosis. The rate of bystander CPR in China is less than 20%. Most victims received appropriate treatment only when EMS personnel arrived at the scene[15]. In the large cities of China, the average time from the emergency call to EMS arrival was 10 minutes[8]. Due to the low rate of bystander CPR and lack of CPR knowledge, improving the public’s immediate recognition of cardiac arrest and activation of emergency response are the most important components of OHCA survival in China. In our study, we found that the OHCA patients with symptoms subgroup had higher proportions of emergency calls before arrest, health care provider-witnessed arrest and no flow time for 1 to 4 minutes. This means that if people could promptly recognize the warning symptoms of cardiac arrest and call EMS immediately, most patients could be treated as early as possible, which may improve the prognosis of cardiac arrest.

Pre-existing illnesses are generally associated with unfavorable outcomes[16]. However, the correlation between pre-existing illnesses and warning symptoms is not clear[13]. In our study, more than 50% of the patients had pre-existing illnesses, regardless of the presence of symptoms. Hypertension and coronary heart disease were the most common pre-existing illnesses. This discovery indicated that patients with cardiovascular illnesses had a high risk of cardiac arrest and thus should be the focus in hospitals. It should be noted that there was no relationship between pre-existing illnesses and warning symptoms, nor were there significant differences between patients with and without warning symptoms.

In our study, dyspnea, chest pain and unconsciousness were the top three warning symptoms, which accounted for 82.2% of symptoms, and dyspnea, at 48.7%, was the most common. Other studies also
Table 3 Warning symptoms in patients with sudden cardiac arrest

<table>
<thead>
<tr>
<th>Symptom, n (%)</th>
<th>Sex</th>
<th>Age</th>
<th>Etiology</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male (n = 460)</td>
<td>Female (n = 213)</td>
<td>P value</td>
<td>&lt; 60 yr (n = 225)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>211 (45.9)</td>
<td>117 (54.9)</td>
<td>0.029&lt;sup&gt;a&lt;/sup&gt;</td>
<td>101 (44.9)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>96 (20.9)</td>
<td>27 (12.7)</td>
<td>0.011&lt;sup&gt;a&lt;/sup&gt;</td>
<td>50 (22.2)</td>
</tr>
<tr>
<td>Unconsciousness</td>
<td>67 (14.6)</td>
<td>35 (16.4)</td>
<td>0.530</td>
<td>38 (16.9)</td>
</tr>
<tr>
<td>Paralysis</td>
<td>23 (5.0)</td>
<td>6 (2.8)</td>
<td>0.195</td>
<td>9 (4.0)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>20 (4.3)</td>
<td>7 (3.3)</td>
<td>0.514</td>
<td>7 (3.1)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>10 (2.2)</td>
<td>8 (3.8)</td>
<td>0.237</td>
<td>4 (1.8)</td>
</tr>
<tr>
<td>Seizure</td>
<td>13 (2.8)</td>
<td>2 (0.9)</td>
<td>0.123</td>
<td>6 (2.7)</td>
</tr>
<tr>
<td>Dysphonia</td>
<td>6 (1.3)</td>
<td>7 (3.3)</td>
<td>0.082</td>
<td>4 (1.8)</td>
</tr>
<tr>
<td>Palpitation</td>
<td>8 (1.7)</td>
<td>2 (0.9)</td>
<td>0.425</td>
<td>3 (1.3)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>4 (0.9)</td>
<td>1 (0.5)</td>
<td>0.574</td>
<td>2 (0.9)</td>
</tr>
<tr>
<td>Syncope</td>
<td>1 (0.2)</td>
<td>1 (0.5)</td>
<td>0.576</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (0.2)</td>
<td>0 (0.0)</td>
<td>0.496</td>
<td>1 (0.4)</td>
</tr>
</tbody>
</table>

<sup>a</sup>P < 0.05.

reported that these three symptoms were the most common complaints of all the patients who experienced cardiac arrest[13,17]. Therefore, health care providers should focus on patients with these symptoms, do their best to recognize critically ill patients in the triage area, and treat them in the appropriate medical units.

In males and females, dyspnea, chest pain, and unconsciousness were the top three most common warning symptoms, but the presence of a pre-existing illness may induce different clinical manifestations; for example, acute myocardial infarction usually presents as chest pain in males but not in females[18-20]. Our results were typical in that chest pain was more common in male patients. Based on these results, more information about other clinical manifestations should be collected, including electrocardiogram findings and myocardial injury markers, to make a correct diagnosis, especially in female patients with suspected acute myocardial infarction but without typical ischemic chest pain.

Younger patients (younger than 60 years of age) and elderly patients (older than 60 years of age) are known to have different disease spectra[7,21,22]. In our study, there were no differences in the warning symptoms that presented in the younger patients compared to the elderly patients; however, because of more comorbidities and longer disease durations, elderly patients usually received more attention from...
health care providers when they visit emergency departments. In contrast, younger patients received less attention because of their health histories and lack of regular health check-ups. As this may result in misdiagnosis, which can have serious consequences, more attention should be given to younger SCA patients in emergency departments.

The etiology of cardiac arrest was categorized as cardiac or noncardiac. The most common cardiac etiologies were acute myocardial infarction and heart failure, both of which include chest pain and dyspnea\cite{7,23,24}. In our study, chest pain and dyspnea were the most important warning symptoms in patients with a cardiogenic etiology, accounting for 86.0% of all symptoms. In contrast, noncardiac etiologies include several diseases that include a variety of clinical manifestations, such as dyspnea, unconsciousness, paralysis, vomiting, and abdominal pain\cite{17,25}. During CPR, the health care provider should give special treatment for the specific etiology if it is known\cite{22,26-28}. That is, analyzing a patient’s symptoms to make an initial diagnosis and initiating appropriate treatment measures may be helpful in improving the ROSC rate. It is worth noting, however, that dyspnea was common in SCA due to both cardiac and noncardiac etiologies (41.7% vs 53.3%), with a variety of mechanisms contributing to the dyspnea in different situations, such as shock or poisoning. Therefore, when managing patients with dyspnea as a warning symptom, additional clinical information should be collected for the differential diagnosis.

In this study, chest pain was the most common warning symptom of SCA with a cardiac etiology, and patients with chest pain had a higher rate of survival. Considering that acute myocardial infarction is the most common cardiac cause of cardiac arrest, which is the primary cause of malignant arrhythmia, including ventricular fibrillation and pulseless ventricular tachycardia, early defibrillation can terminate arrhythmia, and ROSC can be achieved\cite{29-31}. Consequently, when treating cardiac arrest patients with chest pain, a warning symptom, evaluating their initial rhythm and administering defibrillation to restore rhythm as soon as possible during CPR is an important method of improving the survival rate.

CONCLUSION

In this study, most patients had warning symptoms before cardiac arrest. Dyspnea, chest pain and unconsciousness were the most common symptoms, and patterns of symptoms differed by etiology and sex. The characteristics of the warning symptoms may be helpful in identifying the etiology and allowing the initiation of targeted treatment during CPR. Early warning signs of cardiac arrest were similar in patients of different ages, and clinicians should focus on younger patients as well as elderly patients. Finally, because of the low rate of bystander CPR and their lack of CPR knowledge, immediate recognition of cardiac arrest and activation of EMS should prevent CPR delay and increase the survival rate of OHCA patients.

ARTICLE HIGHLIGHTS

Research background
The characteristics of early warning symptoms need further research. Especially the point of time, frequency and severity of warning symptoms before cardiac arrest occur.

Research motivation
Most patients had warning symptoms before cardiac arrest. Dyspnea, chest pain, and unconsciousness were the most common symptoms. The characteristics of the warning symptoms may be helpful in identifying the etiology and allowing the initiation of targeted treatment during cardipulmonary resuscitation.

Research objectives
A total of 65.9% of patients had symptoms before arrest. Dyspnea, chest pain, and unconsciousness were the most common symptoms. The patients with symptoms had a higher rate of initial shockable rhythm, restoration of spontaneous circulation (ROSC) and survival than patients without symptoms. The out-of-hospital cardiac arrest symptoms subgroup had a higher rate of bystander cardipulmonary resuscitation, a shorter no flow time, and a higher ROSC rate. The in-hospital cardiac arrest symptoms subgroup had higher ROSC and survival rates.

Research methods
This was a retrospective study. We included all adult patients with all-cause cardiac arrest who visited Peking University Third Hospital or Beijing Friendship Hospital between January 2012 and December 2014. Data on population, symptoms, resuscitation parameters, and outcomes were analysed and compared between cardiac arrest patients with warning symptoms and those without warning.
symptoms.

**Research results**
We sought to investigate the characteristics of the warning symptoms of cardiac arrest, and to determine the correlation between cardiac arrest symptoms and patient prognosis.

**Research conclusions**
We found that different etiologies of sudden cardiac arrest correlate with certain symptoms and that the immediate and correct recognition of symptoms and etiology can improve patient survival.

**Research perspectives**
In the future, we should carry out more research on the characteristics of symptoms, such as the point of time, frequency and severity of warning symptoms.

**FOOTNOTES**

**Author contributions:** Zheng K and Ma QB designed the study; Zheng K and Bai Y participated in the acquisition, analysis, and interpretation of the data, and drafted the initial manuscript; Zhai QR, Du LF, Ge HX and Wang GX participated in the acquisition and analysis of the data; Ma QB revised the article critically for important intellectual content; all authors have read and approve the final manuscript.

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**Data sharing statement:** Technical appendix, statistical code, and dataset available from the corresponding author at maqingbian@bjmu.edu.cn.

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**L-Editor:** A
**P-Editor:** Fan JR

**REFERENCES**


Zheng K et al. Warning symptoms in cardiac arrest


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Retrospective Study

Serum ferritin levels in children with attention deficit hyperactivity disorder and tic disorder

Cai-Yun Tang, Fang Wen

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Abstract

BACKGROUND
Iron plays an important role in neurodevelopmental functions in the brain. Serum ferritin levels are different in children with attention deficit hyperactivity disorder and tic disorder than in healthy children.

AIM
To explore the current status of iron deficiency in children with neurodevelopmental disorders and its sex and age effects.

METHODS
A total of 1565 children with attention deficit hyperactivity disorder (ADHD), 1694 children with tic disorder (TD), 93 children with ASD and 1997 healthy control children were included between January 1, 2020, and December 31, 2021 at Beijing Children’s Hospital. We describe the differences in age levels and ferritin levels between different disease groups and their sex differences. The differences between the sexes in each disease were analyzed using the t test. The incidence rate of low serum ferritin was used to describe the differences between different diseases and different age groups. A chi-square test was used to analyze the difference in the incidence of low serum ferritin between the disease group and the control group. Analysis of variance was used for comparisons between subgroups, and regression analysis was used for confounding factor control.

RESULTS
A total of 1565 ADHD patients aged 5-12 years were included in this study, and the average serum ferritin levels of male and female children were 36.82 ± 20.64 μg/L and 35.64 ± 18.56 μg/L, respectively. A total of 1694 TD patients aged 5-12 years were included in this study, and the average serum ferritin levels of male and female children were 35.72 ± 20.15 μg/L and 34.54 ± 22.12 μg/L, respectively. As age increased, the incidence of low serum ferritin in ADHD and TD first decreased and then increased, and 10 years old was the turning point of rising
levels. The incidence of ADHD with low serum ferritin was 8.37%, the incidence of TD with low serum ferritin was 11.04%, and the incidence of the healthy control group with low serum ferritin was 8.61%, among which male children with TD accounted for 9.25% and female children with TD accounted for 11.62%. There was a significant difference among the three groups ($P < 0.05$). In addition, there were 93 children with ASD with an average serum ferritin level of $30.99 \pm 18.11 \mu g/L$ and a serum ferritin incidence of $15.05\%$.

**CONCLUSION**

In conclusion, low serum ferritin is not a risk factor for ADHD or TD. The incidence of low serum ferritin levels in children with ADHD and TD between 5 and 12 years old decreases first and then increases with age.

**Key Words:** Iron deficiency; Attention deficit hyperactivity disorder; Tic disorder; Serum ferritin levels; Retrospective study

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**Core Tip:** By investigating the status of iron deficiency in children with neurodevelopmental disorders and its influence on gender and age, it is suggested to check the serum ferritin level and related hematological indexes of children with neurodevelopmental disorders at the age of 5-10 years, and make necessary iron supplementation.

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**URL:** https://www.wjgnet.com/2307-8960/full/v10/i22/7749.htm

**DOI:** https://dx.doi.org/10.12998/wjcc.v10.i22.7749

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**INTRODUCTION**

Iron deficiency in early childhood can lead to developmental abnormalities in gene expression, neurotransmitter function, neurometabolism and other aspects related to brain development, which in turn affects children’s sensorimotor functions, growth and development, cognitive language, social emotions, the development of learning and memory, and so on[1]. Iron deficiency can also lead to a decrease in iron content in the brain, which can cause central nervous system dysfunction and ultimately lead to neuropsychiatric symptoms[2]. Iron participates in several basic biochemical functions in the brain, is a cofactor for many metabolic processes and material synthesis and has important effects on neurodevelopmental functions such as myelination, transmitter transmission, and gene expression[3].

Notably, it has been reported that iron deficiency in children is associated with neurodevelopmental diseases, leading to abnormalities in growth and development, learning behavior, motor function, social emotion, intellectual development, cognitive ability, language function, sleep cycle, etc.[4-6]. Ferritin is an objective and sensitive indicator for the investigation and study of iron deficiency because serum ferritin is an important iron storage protein that is crucial for iron homeostasis and participates in a variety of physiological and pathological processes. Serum ferritin is one of the most reliable and widely used markers of iron storage status in the body[7]. The variability of serum ferritin levels is lower than that of serum iron levels, and when iron reserves are depleted, the decline of serum ferritin precedes the decline of serum iron[8].

Neurodevelopmental outcomes include attention deficit disorder hyperactivity (ADHD), tic disorders (TD) and autism spectrum disorders (ASD). The incidence of neurodevelopmental disorders in children is also increasing year by year[8]. The following will introduce iron deficiency-related research on these three diseases. First, a study of ADHD confirmed that the serum ferritin level of children with ADHD was significantly lower than that of the control group[9]. Mahmoud *et al* studied 58 untreated children with ADHD and found that the serum ferritin level of children with ADHD was significantly lower than that of the control group[10]. There are also studies on the serum ferritin level and the Conners Parental Rating Scale (CPRS) total score. There is a significant negative correlation between serum ferritin levels and scores on the Conners Teacher Rating Scale (CTRS)[11,12]. This suggests that iron deficiency may indicate more severe ADHD symptoms. It should be emphasized that iron supplementation can also improve ADHD symptoms[13,14]. Studies have also found that iron supplementation is related to the increase in serum ferritin levels and the parallel reduction in the severity of ADHD symptoms assessed by the parents’ Conners score[15]. Second, studies on TD have shown that children and adults with
mature Tourette syndrome have reduced serum ferritin[3]. A large-scale epidemiological study showed that children with iron deficiency anemia are at increased risk of tic disorder, iron storage status may be related to children’s tics, and low ferritin levels may be the result of pediatric tic risk factors for the development of the disease or predictors of the severity of tics in children[16]. A study of 107 children and adults found that ferritin levels were significantly reduced. Compared with the control group, the caudate nucleus and putamen nucleus of TS patients were larger[17]. Lower iron reserves may help to reduce the size of the caudate and putamen nuclei, thereby increasing the susceptibility to tics[18].

Third, research on ASD has shown that anemia diagnosed earlier in pregnancy was associated with an increased risk of the development of ASD, ADHD, and particularly ID in offspring[19]. In a study that investigated iron levels in ASD patients aged 19 mo to 13 years, 52% of ASD children developed ID[20]. Another study showed that 8.3% of autistic children aged 1 to 2 years, 14.2% of autistic children aged 3 to 5 years, and 20% of autistic children aged 6 to 10 years had below-normal serum ferritin levels[21].

Other studies have shown that children with ASD have significantly lower serum hemoglobin, hematocrit, iron, and mean corpuscular volume levels than healthy children, but these are not enough to cause anemia[22]. However, meta-analyses have shown that the available evidence is inconsistent with regard to whether iron levels are lower in children with ASD[23].

There is a lack of cohort studies on the status of iron deficiency and iron supplementation in children with ADHD, TD and ASD among Chinese children and adolescents. The sex and age effects of iron deficiency and the critical period of iron supplementation are unclear. In conclusion, the level of iron deficiency in neurodevelopmental disorders of ADHD, TD and ASD and the status of sex-age effects are still unclear, and data from Chinese samples are lacking. This study will adopt the thinking of retrospective research and investigation by enrolling ADHD, TD and ASD children in the psychiatric department of Beijing Children's Hospital as the sample. The sample size is large, and more attention can be paid to the comparison of the difference in serum ferritin levels of ADHD, TD and ASD children with respect to gender and age than previous studies. This study will explore the current status of iron deficiency in children with neurodevelopmental disorders and its influence on sex and age, providing an important reference for the correlation between neurodevelopmental disorders and ferritin and necessary iron supplementation.

**MATERIALS AND METHODS**

**Participants**
We retrospectively reviewed data from Beijing Children's Hospital for consecutive diagnoses of ADHD, TD, and ASD between January 1, 2020, and December 31, 2021. This study was in accordance with the Declaration of Helsinki and approved by the Institutional Ethics Committee of Beijing Children's Hospital (No. IEC-C-006-A04-V.06). We confirmed that all patient data were anonymous in this study. Additionally, children with normal physical examinations were selected as a healthy control group. The possible influencing factors of ferritin results should be strictly controlled, and drug use and comorbidities of patients should be thoroughly analyzed to prevent drugs and other diseases from affecting the results of ferritin examination of patients. There were also strict admission and exclusion criteria. The diagnosis of neurodevelopmental disorders was carried out by professional psychiatrists. More details are provided in Figure 1.

**Inclusion criteria and exclusion criteria**
Inclusion criteria: (1) Children who met the DSM-V diagnostic criteria for ADHD, TD and ASD; and (2) Children who had completed the ferritin test during the visit were included in the study. Exclusion criteria: Patients suffering from other movement disorders, epilepsy, malabsorption-related disorders, low serum hemoglobin levels and/or receiving iron supplements, acute febrile disease, malignancy and autoimmune diseases.

**Methods for ferritin analysis**
Serum ferritin was detected by a Beckman DXI800 automatic immune electrochemiluminescence analyzer and an original matching serum ferritin detection kit. After all children washed their hands with soap, 1 mL of venous blood was collected, and serum samples were separated for detection and tested by full-time staff in the biochemical room of the hospital testing center. The experimental process was strictly controlled by quality and tested in accordance with the operating procedures. The standard of low serum ferritin was 15 μg/L[23].

**Data extraction and bias control**
We extracted the identity, sex, age, diagnosis and ferritin level of subjects from the test bank based on the records of the Psychiatric Department of Beijing Children's Hospital. Considering the possible bias caused by the small sample size, our criterion for the inclusion of subjects is that when the ferritin test amount of the age group of the child needs to involve more than 50 cases, the subjects of this age group
should be included.

In order to avoid the bias of retrospective study to the greatest extent, the inclusion criteria and exclusion criteria of research objects are restricted to narrow the differences between research objects. A case-control study was used to control confounding factors. The age of confounding factors was stratified and then treated with corresponding statistical methods. Analysis of variance was used for comparisons between subgroups. Linear regression and logistic regression models were used to control the confounding bias.

**Data analysis**

SPSS version 23 was used for statistical analysis. We used the mean, standard deviation, and 95% confidence intervals to describe age levels, ferritin levels, and sex differences between disease groups. A test was used to analyze the sex difference in each disease, and the chi-square test was used to analyze the difference in the low incidence of serum ferritin between the disease group and the control group, with $P = 0.05$ considered as significant. Analysis of variance was used for comparisons between subgroups, and regression analysis was used for confounding factor control. The low incidence of serum ferritin was used to describe differences between disease and age groups.

**RESULTS**

**Patient characteristics**

A total of 1565 children with ADHD, 1694 TD children, 93 ASD children and 1997 healthy control children were included in this study. The age range was from 5 to 12 years old. In the ADHD group, 1317 children (84.15%) were male, and 248 children (15.85%) were female. The average age of the children was 7.92 ± 1.85 years. The average serum ferritin of the children was 36.63 ± 20.32 μg/L. The average serum ferritin levels of male and female children were 36.82 ± 20.64 μg/L and 35.64 ± 18.56 μg/L, respectively. There was no significant difference in the average age of male and female children ($P > 0.05$). In the TD group, 1282 children (64.2%) were male, and 412 children (35.8%) were female. The average age of the children was 7.61 ± 2.03 years. The average serum ferritin of the children was 35.43 ± 20.64 μg/L. The average serum ferritin levels of male and female children were 35.72 ± 20.15 μg/L and 34.54 ± 22.12 μg/L, respectively. There was no significant difference in the average age of male and female children ($P > 0.05$). In the ASD group, 83 children (89.25%) were male, and 10 children (10.75%) were female. The average age of the children was 6.14 ± 2.88 years. The average serum ferritin of the children was 30.99 ± 18.11 μg/L. The average serum ferritin levels of male and female children were 31.42 ± 18.58 μg/L and 27.42 ± 13.73 μg/L, respectively. There was no significant difference in the average age of male and female children ($P > 0.05$). In the healthy control group, 979 children (49.02%)...
were male, and 1018 children (50.98%) were female. The average age of the children was 7.61 ± 2.03 years. The average serum ferritin of the children was 71.66 ± 51.99 μg/L. The average serum ferritin levels of male and female children were 74.34 ± 51.19 μg/L and 69.08 ± 52.64 μg/L, respectively. There was a significant difference in the average age of male and female children (P < 0.05).

The results showed that the incidence of ADHD with low serum ferritin was 8.37% (131/1565), the incidence of TD with low serum ferritin was 11.04% (182/1649), and the incidence of ASD with low serum ferritin was 15.05% (14/93). The incidence in the healthy control group with low serum ferritin was 8.61% (172/1997). There was a significant difference among the four groups (P < 0.05). More details are provided in Tables 1 and 2.

**Regression analysis**

In the liner regression using the fitting least square method, ADHD (β = -0.110, P < 0.001) and TD (β = -0.114, P < 0.001) were both associated with lower level of serum ferritin even after age and sex (see Table 3). In logistic regression analyses, ADHD and TD were not significantly associated with low serum ferritin concentration in univariate models. And the associations were still not statistically significant in multivariate models. Besides, we found sex 2 was related to the increased risk of low serum ferritin concentration with adjusted OR of 1.38 (95% CI, 1.08-1.75) (see Table 4).

**Comparison of serum ferritin in different age groups**

To better present the ferritin levels of children with ADHD and TD in different age groups, we first conducted analysis of variance for different subgroups of different disease groups according to age and found that ferritin levels in different age groups of different disease groups were statistically significant. ASD data were not included in this analysis because of the small sample size of ASD patients grouped by age. More details are provided in Table 5.

Next, we calculated the incidence of low serum ferritin in different age groups of 5-12 years old and found that in ADHD, TD and healthy controls, as age increased, the incidence of low serum ferritin first decreased and then increased. The high trend, at 10 years old, was the turning point of rising levels. ASD data were not included in this analysis because of the small sample size of ASD patients grouped by age. More details are provided in Figure 2.

**DISCUSSION**

This study mainly explores the level of ferritin in children with ADHD and TD and its effects on sex and age. This study is currently the largest sample size study in China to explore ADHD and TD iron deficiency. This study shows that serum ferritin levels are significantly correlated with sex, age and disease type, which is inconsistent with most previous research results on ADHD and TD ferritin levels at home and abroad[9,12,24]. This may be due to the further research results obtained on the basis of fully controlling confounding factors by using more scientific statistical methods. The results showed that the incidence of ADHD with low serum ferritin was 8.37%, and the incidence of TD with low serum ferritin was 11.04%. The incidence of low serum ferritin in ASD was 15.05%, but low serum ferritin was not a risk factor for ADHD or TD. The results are consistent with previous studies[25-27]. At the same time, we reported ferritin levels of children of different ages and sexes, which can provide an important reference for follow-up studies of iron deficiency in children with ADHD and TD.

The results of this study show that the incidence of low serum ferritin deficiency in children 5-12 years old with ADHD is 8.37%, and the incidence of low serum ferritin deficiency in children 5-12 years old with TD is 11.04%, which is related to the normal control group. This is lower than the results of similar studies at home and abroad[12,28]. Low serum ferritin was not a risk factor for ADHD or TD. The possible reason is that the reference value ranges used in different studies are different. This study uses the World Health Organization guidelines and expert consensus on the diagnosis and treatment of iron deficiency in China. The reference value limit is 15 μg/L[29], and the reference value range used in domestic studies on ADHD serum ferritin is 24 μg/L or 30 μg/L[25,27]. In related foreign studies, the limit of ADHD serum ferritin is set higher[12]. Thus, when the cutoff value of serum ferritin levels in children with ADHD is different, the incidence of low serum ferritin is also different. This highlights the lack of ferritin norms in children with ADHD. Therefore, in future studies, it is necessary to establish serum ferritin standards based on Chinese ADHD samples to provide a more detailed and substantial basis and recommendations for the supplementation of ferritin in children with ADHD.

The results of this study showed that ferritin levels were different at different ages of ADHD and TD, and the incidence of low serum ferritin levels in children with ADHD and TD between 5 and 12 years old decreases first and then increases with age. Ten years old is the turning point. Generally, the age range of 5-10 years old is a period of high incidence for ADHD and TD visits, as well as a period of high incidence of iron deficiency. This suggests that the relationship between iron deficiency and ADHD and TD still needs to be further explored. Although there are many qualitative studies on the relationship between the two[12], there are few studies on the levels of serum ferritin in different age groups. Therefore, based on this research, this study recommends that at the age of 5-10 years, special attention...
Table 1 Characteristics of patients and control subjects

<table>
<thead>
<tr>
<th></th>
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<th>TD</th>
<th>ASD</th>
</tr>
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<tr>
<td>n</td>
<td>1997</td>
<td>1565</td>
<td>1694</td>
<td>93</td>
</tr>
<tr>
<td>(M/F)</td>
<td>(979/1018)</td>
<td>(1317/246)</td>
<td>(1282/412)</td>
<td>(83/10)</td>
</tr>
<tr>
<td>%</td>
<td>49.02/50.98</td>
<td>84.15/15.85</td>
<td>64.2/35.8</td>
<td>89.25/10.75</td>
</tr>
<tr>
<td>Age</td>
<td>8.57 ± 2.28</td>
<td>7.92 ± 1.85</td>
<td>7.61 ± 2.03</td>
<td>6.14 ± 2.88</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>74.34 ± 51.19(^a)</td>
<td>36.82 ± 20.64</td>
<td>35.72 ± 20.15</td>
<td>31.42 ± 18.58</td>
</tr>
<tr>
<td>Female</td>
<td>69.08 ± 52.64(^a)</td>
<td>35.64 ± 18.56</td>
<td>34.54 ± 22.12</td>
<td>27.42 ± 13.73</td>
</tr>
<tr>
<td>SF</td>
<td>71.66 ± 51.99</td>
<td>36.63 ± 20.32</td>
<td>35.43 ± 20.64</td>
<td>30.99 ± 18.11</td>
</tr>
<tr>
<td>F (%)</td>
<td>8.61(^a)</td>
<td>8.37(^a)</td>
<td>11.04(^a)</td>
<td>15.05(^a)</td>
</tr>
</tbody>
</table>

\(^a\)P < 0.05.

HC: Healthy control; ADHD: Attention deficit hyperactivity disorder; TD: Tic disorder; ASD: Autism spectrum disorders; SF: Serum ferritin; F: Incidence of low serum ferritin.

Table 2 Description of the average distribution of age and serum ferritin level

<table>
<thead>
<tr>
<th>Grouping</th>
<th>Mini</th>
<th>Max</th>
<th>Mean</th>
<th>SD</th>
<th>Skewness</th>
<th>Kurtosis</th>
<th>95%CI lower</th>
<th>95%CI upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>HC age</td>
<td>5.00</td>
<td>12.00</td>
<td>8.57</td>
<td>2.28</td>
<td>-0.03</td>
<td>-1.26</td>
<td>8.47</td>
<td>8.67</td>
</tr>
<tr>
<td>HC SF</td>
<td>1.30</td>
<td>200.00</td>
<td>71.66</td>
<td>51.99</td>
<td>0.76</td>
<td>-0.51</td>
<td>69.38</td>
<td>50.63</td>
</tr>
<tr>
<td>ADHD age</td>
<td>5.00</td>
<td>12.00</td>
<td>7.92</td>
<td>1.85</td>
<td>0.47</td>
<td>-0.65</td>
<td>7.83</td>
<td>8.01</td>
</tr>
<tr>
<td>ADHD SF</td>
<td>2.60</td>
<td>148.60</td>
<td>36.63</td>
<td>20.32</td>
<td>1.53</td>
<td>3.42</td>
<td>35.62</td>
<td>37.64</td>
</tr>
<tr>
<td>TD age</td>
<td>5.00</td>
<td>12.00</td>
<td>7.61</td>
<td>2.03</td>
<td>0.49</td>
<td>-0.76</td>
<td>7.52</td>
<td>7.71</td>
</tr>
<tr>
<td>TD SF</td>
<td>2.90</td>
<td>262.70</td>
<td>35.43</td>
<td>20.64</td>
<td>2.66</td>
<td>15.31</td>
<td>34.45</td>
<td>36.41</td>
</tr>
<tr>
<td>ASD age</td>
<td>1</td>
<td>14.00</td>
<td>6.14</td>
<td>2.88</td>
<td>0.47</td>
<td>0.35</td>
<td>5.55</td>
<td>6.73</td>
</tr>
<tr>
<td>ASD SF</td>
<td>4.7</td>
<td>89.6</td>
<td>30.98</td>
<td>18.11</td>
<td>1.25</td>
<td>1.41</td>
<td>27.26</td>
<td>34.71</td>
</tr>
</tbody>
</table>

HC: Healthy control; ADHD: Attention deficit hyperactivity disorder; TD: Tic disorder; ASD: Autism spectrum disorders; SF: Serum ferritin.

should be given to the assessment of serum ferritin levels in children with ADHD and TD. It is necessary to pay attention to differences in different age groups and determine whether it is possible to establish reference intervals for different age groups of ADHD and TD based on different serum ferritin levels to facilitate more sensitive detection of these levels and timely supplementation. Achieving the greatest improvement in ADHD and TD symptoms will be an important research direction for future ADHD and TD ferritin deficiency investigations and follow-up interventions.

The etiological and physiological mechanisms of ADHD and TD caused by iron deficiency are as follows: First, this metal plays an active role in the anabolism of neurotransmitters, the activity of dopamine D2 receptors, and the concentration of basal ganglia (especially the Globus pallidus). Iron is a cofactor of enzymes necessary for the synthesis and catabolism of monoaminergic neurotransmitters[12, 30]. Monoamine neurotransmitters mainly include epinephrine and norepinephrine, 5-hydroxytryptamine, and dopamine. Dopamine neurotransmitters act on the prefrontal lobe and striatum, and dysfunction of the prefrontal striatum plays an important role in the pathogenesis of ADHD. Iron deficiency is related to a decrease in dopamine transporter expression[18], the gene of dopamine transporter is related to the genetic susceptibility of ADHD[31]. Second, iron is a part of neuron development, myelination, DNA synthesis/repair and phospholipid metabolism[1], which is the basis for the neurodevelopmental disease ADHD in children. Third, iron deficiency leads to residual structural defects and the neurological function-related gene imbalance hypothesis[6]. Early nutrient intake (such as malnutrition) during the critical period of life will lead to abnormal structural development, ranging from overall structural abnormalities to fine ultrastructural changes. Therefore, in future research, we need to further explore the inner link between iron deficiency and the occurrence of ADHD symptoms and provide a new perspective for the exploration of the pathophysiological mechanism of ADHD and TD[32].
Table 3 The β of attention deficit hyperactivity disorder/tic disorder for the level of serum ferritin among children

<table>
<thead>
<tr>
<th></th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
<td>P</td>
<td>β</td>
</tr>
<tr>
<td>Among children with ADHD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADHD</td>
<td>-0.107</td>
<td>&lt; 0.001</td>
<td>-0.107</td>
</tr>
<tr>
<td>Age</td>
<td>0.011</td>
<td>&lt; 0.001</td>
<td>0.011</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Among children with TD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TD</td>
<td>-0.113</td>
<td>&lt; 0.001</td>
<td>-0.108</td>
</tr>
<tr>
<td>Age</td>
<td>0.001</td>
<td>&lt; 0.001</td>
<td>0.010</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Model 1 was not adjusted for any other variables; Model 2 was further adjusted for age; Model 3 was further adjusted for age and sex. ADHD: Attention deficit hyperactivity disorder; TD: Tic disorder.

Table 4 Odds ratio of attention deficit hyperactivity disorder/tic disorder for low serum ferritin among children

<table>
<thead>
<tr>
<th></th>
<th>Model 1, OR (95%CI)</th>
<th>Model 2, OR (95%CI)</th>
<th>Model 3, OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Among children with ADHD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADHD</td>
<td>0.94 (0.74-1.19)</td>
<td>0.90 (0.71-1.15)</td>
<td>0.82 (0.63-1.06)</td>
</tr>
<tr>
<td>Age</td>
<td>0.68 (0.46-1.01)</td>
<td>0.68 (0.46-1.01)</td>
<td>1.22 (0.94-1.56)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Among children with TD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TD</td>
<td>0.97 (0.77-1.22)</td>
<td>0.91 (0.72-1.15)</td>
<td>0.99 (0.78-1.28)</td>
</tr>
<tr>
<td>Age</td>
<td>0.65 (0.93-1.56)</td>
<td>0.65 (0.95-1.53)</td>
<td>1.38 (1.08-1.75)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ADHD: Attention deficit hyperactivity disorder; TD: Tic disorder; OR: Odds ratio. Model 1 was not adjusted for any other variables. Model 2 was further adjusted for age. Model 3 was further adjusted for age and sex.

Future research directions of ADHD and TD iron deficiency are discussed in the following. After combining ADHD and TD ferritin research, ADHD and TD iron deficiency research can be carried out from the following three aspects in the future. First, the sensitivity index and cutoff value of ADHD and TD iron deficiency, or the establishment of a cutoff value of serum ferritin levels in different age groups, can be used to formulate specific guidelines for screening and appropriate iron supplementation. Second, most studies evaluating iron status in ADHD and TD are based on measurements of serum ferritin levels, but there is no strong evidence that serum ferritin is a highly reliable marker of brain iron. Brain iron affects nerve function and white matter myelination. The degree of correlation between serum ferritin and brain iron levels is unclear [29,33]. Therefore, in addition to evaluating the surrounding iron markers, the evaluation of brain iron levels is essential to determine the possible role of iron deficiency in the pathophysiology of ADHD and TD. Third, regarding whether iron supplementation can alleviate the symptoms of ADHD, related research results are inconsistent, and some studies have shown that iron supplementation can improve ADHD and TD [13]. Studies have also found that iron supplementation is related to the increase in serum ferritin levels and the parallel reduction in the severity of ADHD and TD symptoms as assessed by the parents’ Conner’s score [13]. These aspects need to be validated further. Therefore, future investigations should include iron-supplemented ADHD and TD cohort studies to provide a new perspective for ADHD and TD intervention research. In terms of iron supplementation, the course, safety and compliance of iron supplementation are also very important references [32,33].

The advantage of our research lies in the extraction of large samples of data. At the same time, the average serum ferritin levels of children with ADHD and TD at 5-12 years of age were analyzed, which is a measure of the serum ferritin levels of children with ADHD and TD at different ages. These measurements can provide a reference for iron supplementation. Some limitations of our study need to
### Table 5 Comparison of serum ferritin in different age groups

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>HC</th>
<th>ADHD</th>
<th>TD</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>63.15 ± 52.54</td>
<td>28.77 ± 17.54</td>
<td>29.73 ± 21.55</td>
</tr>
<tr>
<td>6</td>
<td>65.05 ± 48.64</td>
<td>31.66 ± 16.38</td>
<td>32.68 ± 16.54</td>
</tr>
<tr>
<td>7</td>
<td>75.24 ± 55.18</td>
<td>33.78 ± 19.16</td>
<td>33.99 ± 19.48</td>
</tr>
<tr>
<td>8</td>
<td>79.05 ± 53.37</td>
<td>37.93 ± 20.34</td>
<td>36.63 ± 16.76</td>
</tr>
<tr>
<td>9</td>
<td>77.88 ± 52.77</td>
<td>43.27 ± 22.41</td>
<td>41.92 ± 23.44</td>
</tr>
<tr>
<td>10</td>
<td>77.10 ± 49.96</td>
<td>43.59 ± 21.15</td>
<td>40.74 ± 18.28</td>
</tr>
<tr>
<td>11</td>
<td>68.65 ± 49.32</td>
<td>42.36 ± 24.06</td>
<td>38.17 ± 25.55</td>
</tr>
<tr>
<td>12</td>
<td>66.85 ± 52.22</td>
<td>32.66 ± 18.77</td>
<td>39.16 ± 28.08</td>
</tr>
<tr>
<td>F</td>
<td>3.651</td>
<td>14.206</td>
<td>9.381</td>
</tr>
<tr>
<td>P</td>
<td>0.001</td>
<td>0.000</td>
<td>0.000</td>
</tr>
</tbody>
</table>

HC: Healthy control; ADHD: Attention deficit hyperactivity disorder; TD: Tic disorder.

---

**Figure 2** Comparison of the incidence of low serum ferritin in different age groups and diseases between 5-12 years old. ADHD: Attention deficit hyperactivity disorder; TD: Tic disorder; HC: Healthy control.

---

be pointed out. First, neurodevelopmental disorders were studied in outpatient cases, and only individuals who used medical resources to seek psychiatric care were identified. Our sampling method involves convenience sampling. There may be some selection bias in the sample; however, the patients included in our study were diagnosed by professional psychiatrists, and the diagnoses were more reliable than self-reported diagnoses. Second, serum ferritin concentrations may be related to inappropriate dietary habits, and the link between neurodevelopmental disorders and altered dietary patterns remains unclear. Third, we did not have personal information that would help us understand patients' risk of mental disorders, such as environmental factors (long-term life stress, traumatic experiences) and a family history of mental disorders. Fourth, our study cannot prove a causal relationship between low serum ferritin and neurodevelopmental disease, although our results suggest a significant association between neurodevelopmental disease and serum ferritin.

---

**CONCLUSION**

Neurodevelopmental disorders (ADHD, TD and ASD) are heterogeneous diseases. The relationship
between ADHD and TD and serum ferritin needs further exploration. We found that the incidence of low serum ferritin levels in children with ADHD and TD between 5-12 years old was 8.37% and 11.04%, respectively. The incidence of ASD with low serum ferritin was 15.05%. It is recommended to routinely check the serum ferritin levels and related hematological indicators of children with ADHD, TD and ASD and to perform necessary iron supplementation. In particular, children with ADHD and TD aged 5-10 years were diagnosed. In the future, we need to conduct cohort studies to further consolidate the evidence of iron deficiency in children with ADHD, TD and ASD and carry out necessary iron intervention studies to explore the underlying mechanisms.

**ARTICLE HIGHLIGHTS**

**Research background**
Iron deficiency in early childhood can lead to developmental abnormalities in gene expression, neurotransmitter function, neurometabolism and other aspects related to brain development. It has been reported that iron deficiency in children is associated with neurodevelopmental diseases. Serum ferritin is one of the most reliable and widely used markers of iron storage status in the body. This study will explore the current status of iron deficiency in children with neurodevelopmental disorders and its influence on sex and age, providing an important reference for the correlation between neurodevelopmental disorders and ferritin and necessary iron supplementation.

**Research motivation**
The level of iron deficiency in neurodevelopmental disorders of attention deficit disorder hyperactivity (ADHD), tic disorder (TD) and autism spectrum disorders (ASD) and the status of sex-age effects are still unclear, and data from Chinese samples are lacking. This study will adopt the thinking of retrospective research and investigation by enrolling ADHD, TD and ASD children in the psychiatric department of Beijing Children’s Hospital as the sample. The sample size is large, and more attention can be paid to the comparison of the difference in serum ferritin levels of ADHD, TD and ASD children with respect to gender and age than previous studies.

**Research objectives**
This study will explore the current status of iron deficiency in children with neurodevelopmental disorders and its influence on sex and age, providing an important reference for the correlation between neurodevelopmental disorders and ferritin and necessary iron supplementation.

**Research methods**
A total of 1565 children with ADHD, 1694 children with TD, 93 children with ASD and 1997 healthy control children were included between January 1, 2020, and December 31, 2021 at Beijing Children's Hospital. We describe the differences in age levels and ferritin levels between different disease groups and their sex differences. T test, Chi-square analysis, variance analysis and regression analysis were used for statistical processing of the data.

**Research results**
The average serum ferritin levels of male and female children were 36.82 ± 20.64 μg/L and 35.64 ± 18.56 μg/L in 1565 ADHD patients. The average serum ferritin levels of male and female children were 35.72 ± 20.15 μg/L and 34.54 ± 22.12 μg/L in 1694 TD patients. As age increased, the incidence of low serum ferritin in ADHD and TD first decreased and then increased, and 10 years old was the turning point of rising levels. The incidence of ADHD with low serum ferritin was 8.37%, the incidence of TD with low serum ferritin was 11.04%, and the incidence of the healthy control group with low serum ferritin was 8.61% \((P < 0.05)\). There may be some selection bias and confounding factors such as diet, environmental factors and family history in the sample, and our study cannot prove a causal relationship between low serum ferritin and neurodevelopmental disease.

**Research conclusions**
Neurodevelopmental disorders (ADHD, TD and ASD) are heterogeneous diseases. We found that the incidence of low serum ferritin levels in children with ADHD and TD between 5-12 years old was 8.37% and 11.04%, respectively. The incidence of ASD with low serum ferritin was 15.05%. It is recommended to routinely check the serum ferritin levels and related hematological indicators of children with ADHD, TD and ASD and to perform necessary iron supplementation. In particular, children with ADHD and TD aged 5-10 years were diagnosed.

**Research perspectives**
In the future, we need to conduct cohort studies to further consolidate the evidence of iron deficiency in children with ADHD, TD and ASD and carry out necessary iron intervention studies to explore the
underlying mechanisms.

FOOTNOTES

Author contributions: Wen F gave suggestions for writing, analysis and revised the manuscript; Tang CY did substantial contributions to the conception and design of the work; and the acquisition, analysis, or interpretation of data for the work and drafted the manuscript.

Institutional review board statement: This study was in accordance with the Declaration of Helsinki and approved by the Institutional Ethics Committee of Beijing Children's Hospital, No. IEC-C-006-A04-V.06.

Conflict-of-interest statement: All of the authors declare that they have no competing interests.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at wenfang0812@163.com. Participants gave informed consent for data sharing, but the presented data are anonymized and risk of identification is low. No additional data are available.

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L-Editor: A
P-Editor: Wu YXJ

REFERENCES


Retrospective Study

Application of metagenomic next-generation sequencing in the diagnosis of infectious diseases of the central nervous system after empirical treatment

Ying-Ying Chen, Yan Guo, Xin-Hong Xue, Feng Pang

Abstract

BACKGROUND
The diagnostic value of metagenomic next-generation sequencing (mNGS) in central nervous system (CNS) infectious diseases after empirical treatment has not been reported.

AIM
To investigate the diagnostic value of mNGS of cerebrospinal fluid (CSF) in the empirically treated CNS infectious diseases.

METHODS
A total of 262 CSF samples from patients with suspected CNS infections were collected between August 2020 and December 2021. Both mNGS and conventional methods were used for testing. The conventional methods included microbial culture, smear, polymerase chain reaction, etc.

RESULTS
Among 262 suspected cases, 183 cases (69.84%) were diagnosed as CNS infection, including 86 cases of virus infection (47.00%), 70 cases of bacterial infection (38.25%) and 27 cases of fungal infection (14.76%). The sensitivity and specificity of mNGS were 65.6% (95%CI: 58.2%-72.3%) and 89.6% (95%CI: 79.1%-95.3%), respectively. The PPV of mNGS was 94.5% (95%CI: 88.6%-97.6%), and the NPV was 48.8% (95%CI: 39.7%-57.9%). The pathogen detective sensitivity and accuracy of mNGS were higher than those of conventional methods (Sensitivity: 65.6% vs 37.2%; P < 0.001; Accuracy: 72.0% vs 50%, P < 0.001). The results showed that compared with conventional methods, mNGS technology was a more sensitive...
method for the diagnosis of CNS infection after empirical treatment.

**CONCLUSION**

mNGS can be a better method applied in the diagnosis of CNS infection after empirical treatment.

**Key Words:** Metagenomic next-generation sequencing; Cerebrospinal fluid; Central nervous system infection; Pathogenic culture

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**Core Tip:** The study found that metagenomic next-generation sequencing (mNGS) had a higher sensitivity than the conventional methods in the diagnosis of infectious diseases of the central nervous system after empirical treatment. mNGS has significant clinical value and should be used mainly in early pathogen diagnosis in the future.

**INTRODUCTION**

Infectious diseases of the central nervous system (CNS) are acute or chronic inflammatory (or noninflammatory) diseases caused by pathogenic microorganisms that invade the parenchyma, meninges and blood vessels of the CNS[1]. The pathogenic microorganisms include viruses, bacteria, fungi, mycobacterium tuberculosis, spirochetes, parasites, etc. The infections are characterized by high morbidity, rapid disease progression, and high rates of disability and death. With the exception of stroke, meningitis ranks first in terms of disability and second in terms of mortality among neurological diseases. The pathogenic diagnosis of CNS infections mainly relies on cerebrospinal fluid (CSF) smear microscopy, pathogen culture, antigen-antibody tests, polymerase chain reaction (PCR) tests, etc. Early diagnosis of this disease is difficult to realize and it always followed by poor curative effects and prognosis[2,3]. In view of this, it is important for us to find a way to diagnose, identify and treat CNS infections at an early stage, which is also the topic of our research.

As an emerging pathogen detection method, metagenomic next-generation sequencing (mNGS) is of increasing interest to researchers, as it is able to detect all potential pathogens in a single test[4,5]. In recent years, mNGS has been proven to be outstanding in the diagnosis of infectious diseases, especially in the infections of blood, respiratory tract and CNS. Studies have reported that mNGS can increase the diagnosis rate of CNS infections by 25%[6-8]. The application of mNGS can improve and optimize the diagnostic strategy for infectious encephalitis/meningitis. However, the clinical value of mNGS in diagnosing CNS infection after empirical treatment remains to be discussed. In this study, we compared the differences of mNGS and conventional methods in the detection of pathogens including viruses, bacteria, and fungi in CNS infections after empirical therapy.

**MATERIALS AND METHODS**

According to standard procedures, we recruited 262 patients with suspected CNS infections who visited our hospital from August 2020 to December 2021 as study subjects. The inclusion criteria were high-level clinical suspicion of CNS infectious diseases (e.g., fever, impaired consciousness, manifestations of increased intracranial pressure, signs of meningeal irritation, etc.). Exclusion criteria were refusal of lumbar puncture to obtain CSF or bloody CSF. Specimens from all patients were routinely tested for pathogens, including culture of bacteria and fungi from CSF, detection of bacteria on the stained CSF smear, serology test and PCR. CSF specimens were collected simultaneously for mNGS, and the clinical and laboratory data of the patients were recorded. The 262 patients enrolled in this study were diagnosed by three chief neurologists based on their clinical presentation, imaging findings, response to antibiotic treatment, follow-up results, and pathogenic evidence. Among them, 195 patients were diagnosed with CNS infections (183 infections with viruses, bacteria, and fungi and 12 other infections). The remaining 67 patients were diagnosed with noninfectious diseases, including autoimmune enceph-
alitis, malignancy and venous sinus thrombosis. The study conforms to the principles of the Declaration of Helsinki and received ethical approval from the Ethics Committee of Liaocheng People’s Hospital. Patients or their families gave informed consent to the diagnosis and treatment and signed the informed consent form.

**CSF next-generation sequencing and data extraction**

CSF was extracted from each patient and tested in our laboratory (provided by Shenzhen UW Medical Laboratory Co., Ltd.) under aseptic conditions. The procedures of nucleic acid extraction and second-generation sequencing were as follows: Add 0.3 mL of 0.5 mm diameter glass beads to the broken wall tube, and then add 0.6 mL of specimen. Shake the tube at 2800-3200 r/min for 20 min at high speed, and then the 300 µL of nucleic acid is extracted. The DNA was extracted using the TINAamp Micro DNA Kit (DP316, Tiangen Biochemical Technology Co., Ltd., China) according to the standard operation.

The DNA libraries were constructed according to the following steps: Firstly, randomly cut the DNA into fragments, then perform the end-repair and adaptor ligation. Finally, the DNA fragments after ligation were amplified by PCR. The libraries were quality-controlled using Agilent 2100 (Agilent Technologies, United States) and Qubit 2.0 (Invitrogen, United States). The double-stranded DNA was converted to single-stranded circular DNA by DNA degradation and cyclization, and the DNA nanoballs (DNBs) were generated by rolling circle amplification (RCA) technology. The Qubit 2.0 was used for quality control of the DNBs. The qualified DNBs were loaded onto chips and sequenced on the BGISEQ-50 platform (BGI Genetics Ltd., China) with 20 mol/L of sequencing data.

After removing low-quality short reads (length < 35 bp) to obtain sequencing data with high-quality, the high-quality reads were aligned to the human reference genome (hg19) sequence by BWA. Then the low-complexity reads were removed. The remaining reads were simultaneously aligned with four microbial genomic databases, which mainly composed of viruses, bacteria, fungi, and parasites. These database were downloaded from the National Center for Biotechnology Information (ftp://ftp.ncbi.nlm.nih.gov/genomes/), which mainly contain 1979 DNA viral whole-genome sequences, 6350 bacterial genomes, 1064 fungal genomes associated with human infections, and 234 parasite genome sequences associated with human diseases.

**Threshold criteria for positive mNGS results**

The final sequencing data were obtained by removing common background microorganisms and suspected pathogenic microorganisms that appeared in > 50% of the samples in the past 3 mo.

For viruses and bacteria, the positive criteria were mapped when the reads of one microorganism (species level) were 10 times greater than those of any other microorganism. For fungi, the coverage (species level) of one fungus was 5 times wider than that of any other fungus. The positive criteria in this study were as follows: (1) After excluding the microorganisms from normal skin and other flora, the top 5 genera with a relative high abundance were selected, and the top 2 species in each genus were selected; (2) Viruses, bacteria and fungi were considered positive when their number of specific sequences was ≥ 3 reads; (3) The clinical manifestations and imaging changes of the patients were discussed by experienced physicians and excluded the possible colonization and contamination cases; and (4) The condition of the patient improved after a targeted treatment. Consistent with clinical judgment or targeted treatment from three experienced senior physicians.

Results of mNGS or conventional methods were considered positive only if the pathogen tested corresponding to the final clinical diagnosis. If the patient’s final clinical diagnosis was a non-CNS infection, a positive test result was considered a false positive, and a negative result was considered a true negative. If the patient’s final clinical diagnosis was a CNS infectious disease, a positive result was considered a true positive, and a negative test was considered a false negative.

**Statistical analysis**

Using the final clinical diagnosis as the gold standard (the final clinical diagnosis was determined by three chief physicians based on the imaging, clinical manifestation, response to the medical therapy, and follow-up of the patient) to divide the subject patients into CNS infection and non-CNS infection groups. Differences in continuous variables between the groups were calculated using t tests and χ² tests. P values <0.05 was considered as statistically significant. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy (ACC) were calculated, and the χ² test was used to compare the sensitivity and specificity of mNGS with conventional pathogen detection methods. All statistics were reported as absolute values with 95% confidence intervals (CIs), and the SPSS 25.0 was used for statistics analysis.

**General characteristics**

A total of 262 patients were involved in this study, only 195 cases of them were diagnosed with CNS infections and the remaining 67 cases were diagnosed with non-CNS infectious diseases. The patients with CNS infections included 183 cases of viral, bacterial, and fungal infections and 12 cases of parasitic infections with 95 males and 97 females and an average age of 41.2 (14-91) years. All patients had received empirical treatment prior to CSF collections. The final CNS infections were classified as viral,
bacterial, fungal, other infections, and noninfectious diseases. The non-CNS infections included autoimmune encephalitis, malignancy, and venous sinus thrombosis.

RESULTS

The diagnostic values of mNGS and conventional methods in the CNS virus infections are compared as follows

Comparison of the diagnostic performance of mNGS and conventional methods: Based on the final clinical diagnosis, 86 of the 121 patients with suspected viral infections were diagnosed with viral encephalitis or meningitis, and all 121 patients were given empirical antiviral therapy. A total of 135 CSF specimens were tested by mNGS and conventional methods respectively (serology and PCR) (5 of these patients underwent multiple mNGS tests). Compared with the conventional methods, the mNGS had a subtle advantage of detective sensitivity (66.3% vs 53.5%, P = 0.087), specificity (88.6% vs 85.7%, P = 1.00), accuracy (72.7% vs 62.8%, P = 0.009), positive predictive value (93.4% vs 90.2%, P = 0.779), and negative predictive value (51.7% vs 42.9%, P = 0.316) (Table 1).

Inconsistency between mNGS and conventional methods for virus detection: Among 86 specimens of CSF from patients with confirmed viral infection, 29 specimens were tested negative by mNGS while 40 were tested negative by conventional methods. In addition, mNGS confirmed the diagnosis of viral infection in 19 of the specimens that tested negative by conventional methods. Among these specimens that tested negative by mNGS, only 7 cases were confirmed by conventional methods (Table 2).

Consistency between mNGS and conventional methods for virus detection: Thirty-eight of 86 (11.43%) cases were tested both positive by mNGS and conventional methods and 22 of 86 (32.86%) cases were tested both negative by these two methods respectively. Moreover, 19 cases (52.86%) were tested positive only by mNGS and 7 (32.86%) were tested positive only by conventional methods (Figure 1A).

Comparison of pathogenic detection between mNGS and conventional methods: The positive detection rate of mNGS in CNS viral infections was 57/86 (66.28%), and the top 3 pathogens with the highest detection rate were herpes simplex virus type 3, cytomegalovirus, and herpes simplex virus type 1. The positive detection rate of conventional methods was 46/86 (53.49%), and the top 3 pathogens with the highest detection rate were cytomegalovirus, herpes simplex virus type 3, and herpes simplex virus type 1. A total of 17 pathogenic viruses were detected by mNGS, and 8 by conventional methods (Figure 2A). That means the mNGS can detect a wider range of pathogens than conventional methods.

The diagnostic values of mNGS and conventional methods in the CNS bacterial infections are compared as follows

Comparison of the diagnostic performance of mNGS and conventional methods: Based on the final clinical diagnosis, 96 patients with suspected bacterial infections were given empirical antibiotics, and finally, 70 patients were diagnosed with bacterial meningitis or encephalitis. A total of 110 specimens were prepared for mNGS and bacterial smear-culture respectively (6 of these patients underwent multiple mNGS tests). Compared with the conventional methods, the mNGS had a distinct advantage of detective sensitivity (65.7% vs 14.3%, P < 0.001), specificity (88.5% vs 84.6%, P = 1.000), accuracy (71.9% vs 33.3%, P < 0.001), positive predictive value (93.9% vs 71.4%, P = 0.061), and negative predictive value (48.9% vs 26.8%, P = 0.011) (Table 3).

Inconsistency between mNGS and conventional methods for bacterial detection: Among the 70 confirmed CSF specimens, 24 of them were tested negative by mNGS and 60 were tested negative by conventional methods. Moreover, mNGS confirmed the bacterial infections in 37 specimens that were tested negative by conventional methods. Among these specimens that tested negative by mNGS, only 2 cases were confirmed by conventional methods (Table 4).

Consistency between mNGS and conventional methods for bacterial detection: Eight of 70 (11.43%) cases were tested both positive by mNGS and conventional methods and 23 of 70 (32.86%) cases were tested both negative by these two methods respectively. Moreover, 37 cases (52.86%) were tested positive only by mNGS and 2 (2.86%) were tested positive only by conventional methods (Figure 1B).

Comparison of pathogenic detection between mNGS and conventional methods: The mNGS positive detection rate of mNGS in CNS bacterial infections was 46/70 (65.71%) and the top 3 pathogens with the highest detection rate were Streptococcus pneumoniae, Haemophilus influenzae, and Klebsiella pneumoniae. The positive detection rate of conventional methods was 10/70 (14.29%), and the top 3 pathogens with the highest detection rate were S. pneumoniae, Staphylococcus aureus, and K. pneumoniae. A total of 13 pathogenic bacteria were detected by mNGS, and 5 by conventional methods (Figure 2B). That means the mNGS can detect a wider range of pathogens than conventional methods.
Table 1 The performance of metagenomic next-generation sequencing and the conventional methods in the diagnosis of central nervous system virus infections

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Accuracy</th>
<th>Positive predictive value</th>
<th>Negative predictive value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional methods</td>
<td>53.5% (42.7%, 64.2%)</td>
<td>85.7% (69.0%, 94.6%)</td>
<td>62.8% (53.5%, 71.3%)</td>
<td>90.2% (77.8%, 96.3%)</td>
<td>42.9% (31.3%, 55.2%)</td>
</tr>
<tr>
<td>mNGS</td>
<td>66.3% (55.2%, 75.9%)</td>
<td>88.6% (72.3%, 96.3%)</td>
<td>72.7% (63.7%, 80.2%)</td>
<td>93.4% (83.3%, 97.9%)</td>
<td>51.7% (38.5%, 64.6%)</td>
</tr>
<tr>
<td>P value</td>
<td>0.087</td>
<td>1.000</td>
<td>0.099</td>
<td>0.779</td>
<td>0.316</td>
</tr>
</tbody>
</table>

Table 2 Inconsistency between metagenomic next-generation sequencing and conventional methods in diagnosing central nervous system virus infections

<table>
<thead>
<tr>
<th>mNGS</th>
<th>Conventional methods (+, -)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>38, 19</td>
<td>57</td>
</tr>
<tr>
<td>-</td>
<td>7, 22</td>
<td>29</td>
</tr>
<tr>
<td>Total</td>
<td>45, 41</td>
<td>86</td>
</tr>
</tbody>
</table>

mNGS: Metagenomic next-generation sequencing; +: Positive; -: Negative.

Table 3 Performance of metagenomic next-generation sequencing and the conventional methods in the diagnosis of central nervous system bacterial infections

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Accuracy</th>
<th>Positive predictive value</th>
<th>Negative predictive value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional methods</td>
<td>14.3% (8.5%, 23.6%)</td>
<td>84.6% (64.3%, 95.0%)</td>
<td>33.3% (24.2%, 43.8%)</td>
<td>71.4% (42.0%, 90.4%)</td>
<td>26.8% (17.9%, 37.9%)</td>
</tr>
<tr>
<td>mNGS</td>
<td>65.7% (53.3%, 76.4%)</td>
<td>88.5% (68.7%, 97.0%)</td>
<td>71.9% (61.6%, 80.3%)</td>
<td>93.9% (82.1%, 98.4%)</td>
<td>48.9% (34.3%, 63.7%)</td>
</tr>
<tr>
<td>P value</td>
<td>&lt; 0.001</td>
<td>1.000</td>
<td>&lt; 0.001</td>
<td>0.061</td>
<td>0.011</td>
</tr>
</tbody>
</table>

Table 4 Inconsistency of metagenomic next-generation sequencing and conventional methods in diagnosing central nervous system bacterial infections

<table>
<thead>
<tr>
<th>mNGS</th>
<th>Conventional test (+, -)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>8, 37</td>
<td>45</td>
</tr>
<tr>
<td>-</td>
<td>2, 23</td>
<td>25</td>
</tr>
<tr>
<td>Total</td>
<td>10, 60</td>
<td>70</td>
</tr>
</tbody>
</table>

mNGS: Metagenomic next-generation sequencing; +: Positive; -: Negative.

The diagnostic values of mNGS and conventional methods in the CNS fungal infections are compared as follows

Comparison of the diagnostic performance of mNGS and conventional methods: Based on the final clinical diagnosis, 33 patients with suspected fungal infections were given antifungal treatment, and finally, 27 patients were diagnosed with fungal infections. A total of 27 CSF specimens were prepared for mNGS and fungal culture respectively. Compared with the conventional methods, the mNGS had a slight advantage of detective sensitivity (63.0% vs 44.4%, P = 0.127), specificity (100% vs 83.3%, P = 0.01), accuracy (69.7% vs 51.5%, P = 0.131), positive predictive value (100% vs 92.3%, P = 0.433), and negative predictive value (37.5% vs 25.0%, P = 0.656) (Table 5).

Inconsistency between mNGS and conventional methods for fungal detection: Among the 27 confirmed CSF specimens, 10 of them were tested negative by mNGS and 15 were tested negative by conventional methods. Moreover, mNGS confirmed the fungal infections in 10 specimens that were tested negative by conventional methods. Among these specimens that tested negative by mNGS, only 5
Table 5 Performance of metagenomic next-generation sequencing and the conventional methods in the diagnosis of central nervous system fungal infections

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Accuracy</th>
<th>Positive predictive value</th>
<th>Negative predictive value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional methods</td>
<td>44.4% (26.0%, 64.4%)</td>
<td>83.3% (36.5%, 99.1%)</td>
<td>51.5% (33.9%, 68.8%)</td>
<td>92.3% (62.1%, 99.6%)</td>
<td>25.0% (9.6%, 49.4%)</td>
</tr>
<tr>
<td>mNGS</td>
<td>63.0% (42.5%, 79.9%)</td>
<td>100.0% (51.7%, 100.0%)</td>
<td>69.7% (51.1%, 83.8%)</td>
<td>100.0% (77.1%, 100.0%)</td>
<td>37.5% (16.3%, 64.1%)</td>
</tr>
<tr>
<td><strong>P value</strong></td>
<td>0.172</td>
<td>1.000</td>
<td>0.131</td>
<td>0.433</td>
<td>0.656</td>
</tr>
</tbody>
</table>

Figure 1 Consistency between metagenomic next-generation sequencing and conventional methods. A: In diagnosing central nervous system (CNS) virus infections; B: In diagnosing CNS fungal infections; C: In diagnosing CNS bacterial infections. mNGS: Metagenomic next-generation sequencing.

cases were confirmed by conventional methods (Table 6).

**Consistency between mNGS and conventional methods for fungal detection:** Seven of 27 (25.93%) cases were tested both positive by mNGS and conventional methods and 5 of 27 (18.52%) cases were tested both negative by these two methods respectively. Moreover, 10 cases (37.04%) were tested positive only by mNGS and 5 (18.52%) were tested positive only by conventional methods (Figure 1C).

**Comparison of pathogenic detection between mNGS and conventional methods:** The mNGS positive detection rate of mNGS in CNS fungal infections was 17/27 (62.96%) and the top 3 pathogens with the highest detection rate were Cryptococcus, Aspergillus, and Candida. The positive detection rate of conventional methods was 12/27 (44.44%), and the top 3 pathogens with the highest detection rate were Cryptococcus, Aspergillus, and Candida. A total of 5 pathogenic fungi were detected by mNGS, and 3 detected by conventional methods (Figure 2C). Among the negative specimens detected by mNGS, only 5 of them were confirmed by conventional methods.

**Overall diagnostic performance of mNGS**

Of the 262 CSF samples, 49.23% (129/262) of the samples were positively detected by conventional methods, while 26.34% (69/262) of the samples were positively detected by mNGS.

The sensitivity and specificity of mNGS were 65.6% (95%CI: 58.2%-72.3%) and 89.6% (95%CI: 79.1%-95.3%), respectively. The PPV of mNGS was 94.5% (95%CI: 88.6%-97.6%), and the NPV was 48.8% (95%CI: 39.7%-57.9%). The pathogen detective sensitivity and accuracy of mNGS were higher than those of conventional methods (sensitivity: 65.6% vs 37.2%; P < 0.001; accuracy: 72.0% vs 50%, P < 0.001). The results showed that compared with conventional methods, mNGS technology was a more sensitive method for the diagnosis of CNS infection after empirical treatment (Table 7).

**DISCUSSION**

The accurate and rapid pathogen detection is essential for the diagnosis of CNS infections[9]. Despite previous studies have already reported the use of mNGS in the diagnosis of CNS infection[10], few studies have comprehensively evaluated the overall diagnostic performance of it in those patients already receiving the empiric treatment before. This cross-sectional study evaluated the diagnostic rate and additional diagnostic value of mNGS in patients with CNS infection after empirical treatment.
Table 6 Inconsistency between metagenomic next-generation sequencing and Conventional methods in diagnosing central nervous system fungal infections

<table>
<thead>
<tr>
<th>mNGS</th>
<th>Conventional test (+, -)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>7, 10</td>
<td>17</td>
</tr>
<tr>
<td>-</td>
<td>5, 5</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td>12, 15</td>
<td>27</td>
</tr>
</tbody>
</table>

mNGS: Metagenomic next-generation sequencing; +: Positive; −: Negative.

Table 7 The results of meningitis in all patients were compared between the two methods

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Accuracy</th>
<th>Positive predictive value</th>
<th>Negative predictive value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional methods</td>
<td>37.2% (30.2%, 44.6%)</td>
<td>85.1% (73.8%, 92.2%)</td>
<td>50.0% (43.7%, 56.3%)</td>
<td>87.2% (77.2%, 83.3%)</td>
<td>33.1% (26.3%, 40.8%)</td>
</tr>
<tr>
<td>mNGS</td>
<td>65.6% (58.2%, 72.3%)</td>
<td>89.6% (79.1%, 95.3%)</td>
<td>72.0% (65.9%, 77.4%)</td>
<td>94.5% (88.6%, 97.6%)</td>
<td>48.8% (39.7%, 57.9%)</td>
</tr>
<tr>
<td>P value</td>
<td>&lt; 0.001</td>
<td>0.436</td>
<td>&lt; 0.001</td>
<td>0.065</td>
<td>0.007</td>
</tr>
</tbody>
</table>

mNGS: Metagenomic next-generation sequencing.

The aim of this study was to apply mNGS directly to clinical specimens in order to evaluate its diagnostic efficacy on CNS infections. We employed the result of clinical diagnosis rather than that of conventional methods as a reference standard. All CSF samples were collected after medical therapy, which would reduce the diagnostic efficacy of the conventional method. In addition, the advantages of other testing methods will not be revealed if the conventional methods are used as the reference standard. Although the clinical diagnosis lacks evidence of pathological findings, a follow-up period longer than 1 mo could greatly reduce the possibility of misdiagnosis. Therefore, we considered that using clinical diagnosis as the reference standard could be an appropriate choice when comparing the two diagnostic methods.

In this study, a systematic comparison of CSF tested by mNGS and conventional methods was performed, and the results showed several advantages of mNGS. First, mNGS is faster, costing an average of 2 d from sample collection to report. In contrast, the conventional methods cost at least 2-5 d. The mNGS is characterized by a short detection time and unbiased detection, which could facilitate the detection of clinical specimens without prior suspicion of certain pathogens. Second, the overall positive detection rate of mNGS (91.1%) was significantly higher than that of the conventional methods (62.2%). The results suggest that the detective sensitivity of mNGS is superior to that of conventional methods, especially in bacterial and fungal infections. In this study, 6 rare pathogens causing CNS infections and 3 mixed infections of CNS were identified, which means that the mNGS has the potential in detecting mixed infections, rare and unanticipated pathogens.

Virus infection is one of the most common types of CNS infections. At present, the cause of more than half of the CNS infections can not be confirmed. The pathogen detection methods of viral encephalitis/meningitis mainly include CSF staining, antigen antibody detection and PCR technology. These methods are often characterized by low sensitivity and time-consuming, resulting in delayed treatments. A significant merit of mNGS compared with traditional viral etiology test is that it can detect thousands of viruses at the same time within one test. It is no need to rely on clinical prediction, which means the detection range is wide, especially when extracting the CSF is difficult with limited resources\[11,12\].

The results showed that the detective sensitivity of mNGS and conventional methods for the diagnosis of CNS virus infection was 66.3% and 53.5% respectively, while the detective specificity of mNGS and conventional methods was 88.6% and 85.7% respectively. Compared with conventional methods, mNGS had high sensitivity and similar specificity in identifying the pathogens which cause the virus infection in CNS. The mNGS detected 9 additional pathogenic viruses compared with conventional methods. Eight of these viruses were rare pathogens, suggesting the latent capacity of mNGS in detecting rare and unanticipated viruses\[13\]. Most of the viruses detected by mNGS in patients with viral encephalitis or meningitis in this study were DNA viruses, with the most common viruses as the herpes simplex virus type 1, 2 type 5, varicella-zoster virus, and cytomegalovirus. RNA viruses were detected in 3 cases including the case 22 with influenza virus, the case 68 with enterovirus, and the case 139 with rhinovirus, which gave a fact that the DNA viruses were more common in CSF in patients with acute or subacute encephalitis or meningitis. And the mNGS was helpful in their detection and diagnosis.
Bacterial meningitis is a serious disease that can be fatal to both children and adults. The incidence rate and mortality rate of bacterial meningitis vary from different pathogen types[13]. In order to effectively treat bacterial meningitis, it is necessary to determine the microorganisms and their antibiotic sensitivity patterns as soon as possible. At present, CSF culture is the gold standard for the diagnosis of bacterial meningitis. However, the lower bacterial proliferation rates could lead to results with higher false negative. Therefore, new test methods are urgently needed. The mGNS is a rapid and high-throughput pathogen detection method, which has been applied to CSF samples in many studies. Miao et al[8] had systematically compared mGNS and CSF culture, and found that the mGNS had advantages in several aspects. The mGNS is highly sensitive to pathogen identification and is less affected by the previous application of antibiotics[14,15].

In this study, we used CSF samples to compare the differences between conventional methods and mGNS in the diagnosis of patients with bacterial meningitis. The sensitivity and accuracy of mNGS in detecting and diagnosing bacterial infections in CNS were 65.7% and 71.9% respectively, significantly higher than those of conventional methods as 14.3% and 33.3%. All patients received antibiotics before the extraction of CSF. This study suggests that mNGS could have a diagnostic advantage over conventional methods in patients who received empiric antimicrobial therapy before sample collection. The use of empirical antibiotic can reduce the detection rate of conventional methods by approximately 20% without affecting the detection rate of mNGS[16], as the microbial culture is susceptible to antimicrobial therapy. The mNGS only requires the DNA fragments of microorganisms for identification, which may explain its relatively high detection rate after treatment[17]. In our study, mNGS identified a total of 37 culture-negative pathogens. Among these pathogens, the non-mycobacterium may require a relative long incubation time, and some other pathogens can’t be cultured under standard conditions, such as Streptococcus haemolyticus. While the mNGS has a short TAT and is non-targeted, enabling rapid detection of these pathogens[18]. Considering these merits, mNGS could be an important complement to conventional culture which can improve the pathogen detection rate and the disease management in
patients with complex infectious diseases. Similar conclusions have been reached in previous studies. When used as a complement of conventional methods, mNGS could improve the diagnosis of focal and CNS infections.

In recent years, with the increasing use of immunosuppressants, the prevalence of CNS mycosis has increased significantly. The main pathogens causing fungal infection in human CNS are opportunistic fungi, such as aspergillus, cryptococcus, pneumocystis girovii and endemic fungi. The conventional methods for the diagnosis of CNS fungal infection mainly include culture, histopathology, antigen detection, serology, imaging and molecular diagnosis. The culture method is often regarded as the gold standard of fungal infection, but most fungi should be cultured a relative long time, some of them even need a culture time as long as one month. The histopathological diagnosis is an invasive examination, whose sensitivity and specificity largely depend on the experience of pathologists, and there often exists a certain misdiagnosis rate[19,20]. This study showed that the positive rate of the fungal CNS infection detected by mNGS was 17/27(62.96%), while that of the conventional methods was only 12/17(44.4%). The diagnostic value of mNGS in fungal infection of CNS is worth more concern from the researchers and physicians. However, the mNGS has no obvious diagnostic advantage in cryptococcal infection in the CNS. In 5 cases of cryptococcal infection, capsular polysaccharide antigen was positive. For cryptococcal infection of CNS, it is recommended to detect the capsular polysaccharide antigen. If the patient's medical history, clinical manifestations and imaging findings are highly suspected of cryptococcal infection, mNGS is not recommended. The reason may be that the thick cryptococcus capsule is difficult to fully destroyed and the DNA used for mNGS can hardly released, which would reduce the diagnostic efficiency of mNGS. Although the positive detection rate of fungal culture is low, the combination of culture, GM test and mNGS is of great significance for the diagnosis of fungal CNS infections to avoid the omissions.

Fungal infections usually occur in immunocompromised individuals. However, in our study, a large proportion 15/27 (55.6%) of patients with CNS fungal infections had normal immune function[21]. There are increasing reports of immunocompetent patients with fungal infections, possibly due to the exposures to environmental genetic factors. We found that mNGS has a higher diagnostic value for CNS fungal infections than traditional methods (ink blot staining, culture, and antigen-antibody testing). mNGS is suitable for the detection of pathogens that cannot be identified by other available detection technologies and in situations when patients fail to respond to standardized drug therapy. For rare and slow-proliferating pathogens, mNGS shows considerable advantages in reducing the time required to diagnose and confirm the type of pathogens, and further facilitating the targeted drug therapy, and improving patient prognosis.

We performed multiple mNGS tests in 11 patients to observe the dynamic changes of mNGS in CNS infections. In all cases, the positive detection rate of mNGS decreased within weeks when the patients received effective drug therapy. mNGS not only has a confirmatory value but also evaluates the efficiency of treatment to some extent.

The mNGS findings in 15 patients led to a change in treatment strategy. mNGS diagnosed rare pathogen infections in 6 cases, as the case 4 with porcine streptococcal meningitis, the case 6 with feline rickettsial meningitis, the case 12 with porcine cisticercosis, the case 82 with porcine pseudorabies infection, the case 111 with Listeria monocytogenes infection, and the case 124 with Mycoplasma pneumoniae encephalitis. While the conventional methods identified only 1 case, which is the case 111 with Listeria monocytogenes infection, and the mNGS positively identified this case earlier than the conventional methods, leading to a rapid change in anti-infective therapies. However, mNGS findings must be combined with epidemiological and clinical features to identify the pathogens.

Limitations
As a revolutionary diagnostic tool, mNGS can detect all pathogens simultaneously. However, there are some inherent defects of mNGS. For example, microbial contaminants may interfere the interpretation of mNGS results, leading to unnecessary testing and inappropriate processing. One hindrance is the genome background of the human host with high abundance, which may limit the extraction of pathogenic sequences and lead to an insufficient sensitivity of mNGS. Other hindrances such as different registration cohorts and reference standards, as well as different types of infectious diseases still exist. Furthermore, we used the results of clinical diagnosis as a reference standard rather than that of conventional methods, which may be incorrect in some cases. These results need to be further explored with studies of more samples.

CONCLUSION
The mNGS method is a useful complement to conventional methods. It has higher positive rate, higher sensitivity and wider pathogen spectrum, especially for rare pathogens and pathogens that are difficult to culture. mNGS showed a good diagnostic efficiency on CNS infection after empirical treatment, which is superior to conventional methods, and can be used to detect special pathogens and mixed infections. All in all, the mNGS technology has great potential in the diagnosis of CNS infection.
ARTICLE HIGHLIGHTS

Research background
The value of metagenomic next-generation sequencing (mNGS) in central nervous system infectious diseases after empirical treatment has not been reported.

Research motivation
The authors evaluated the value of mNGS in cerebrospinal fluid in the diagnosis of empirically treated central nervous system (CNS) infectious diseases.

Research objectives
This study evaluated the value of mNGS in central nervous system infection and whether mNGS can be used to diagnose the pathogen of central nervous system infection.

Research methods
A total of 262 empirically treated central nervous system-infected samples were analyzed by mNGS. Confirmed pathogen. Using the final clinical diagnosis as the gold standard (the final patients were divided into CNS infection and non-CNS infection groups. Differences in continuous variables between groups were calculated using tests and $\chi^2$ tests.

Research results
mNGS is potentially advantageous in terms of speed and sensitivity. mNGS detected six rare pathogens.

Research conclusions
mNGS has a better diagnosis of CNS infection after empirical treatment, and the overall detection rate is better than that of conventional assays.

Research perspectives
mNGS has a better diagnosis of CNS infection after empirical treatment, and the overall detection rate is better than that of conventional assays. mNGS has diagnostic advantages.

FOOTNOTES

Author contributions: Guo Y and Xue XH contributed equally to this work; Guo Y collected data, analysis and drafted the initial manuscript; and reviewed and revised the manuscript; Chen YY and Xue XH performed data analysis, drafted, and revised the manuscript; and All authors read and approved the final manuscript.

Institutional review board statement: The protocol has been reviewed by the Human Research Ethics Committee of the Institutional Review Board of Liaocheng people's Hospital Medical College Hospital.

Informed consent statement: The patient has signed an informed consent form.

Conflict-of-interest statement: The authors declare that they have no competing interests.

Data sharing statement: The original contributions presented in the study are publicly available.

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P-Editor: Ma YJ
REFERENCES


21 McHugh KE, Gersey M, Rhoads DD, Procop GW, Zhang Y, Booth CN, Sturgis CD. Sensitivity of Cerebrospinal Fluid
Prognostic role of multiple abnormal genes in non-small-cell lung cancer

Lu-Da Yan, Liu Yang, Na Li, Meng Wang, Yan-Hua Zhang, Wen Zhou, Zhi-Qiong Yu, Xiao-Chun Peng, Jun Cai

BACKGROUND
Non-small-cell lung cancer (NSCLC) has the highest morbidity and mortality rates among all malignant tumor types. Although therapies targeting the mutated genes such as KRAS have been used in the clinic for many years, the prognosis remains poor. Therefore, it is necessary to further study the aberrant expression or mutation of non-target genes affecting the survival and prognosis.

AIM
To explore the impact of simultaneous abnormalities of multiple genes on the prognosis and survival of patients.

METHODS
We used R packages to analyze gene expression data and clinical data downloaded from The Cancer Genome Atlas (TCGA) database. We also collected samples from 85 NSCLC patients from the First People’s Hospital of Jingzhou City and retrospectively followed the patients. Multivariate Cox regression analysis and survival analysis were performed.

RESULTS
Analysis of gene expression data from TCGA revealed that the overexpression of the following single genes affected overall survival: TP53 ($P = 0.79$), PTEN ($P = 0.94$), RB1 ($P = 0.49$), CTNNB1 ($P = 0.24$), STK11 ($P = 0.32$), and PIK3CA ($P = 0.013$). However, the probability of multiple genes (TP53, PTEN, RB1, and STK11) affecting survival was 0.025. Retrospective analysis of clinical data revealed that sex (hazard ratio [HR] = 1.29; [95%CI: 0.64-2.62]), age (HR = 1.05; [95%CI: 1.02-1.07]), smoking status (HR = 2.26; [95%CI: 1.16-4.39]), tumor histology (HR = 0.58;
The prognosis of lung cancer is poor, and the associated mortality rate is among the highest due to the tumor’s highly invasive and metastatic nature. Non-small-cell lung cancer (NSCLC) accounts for 85% of lung malignancy cases. Despite advances in gene-targeted therapy and immunotherapy, the long-term survival benefits of NSCLC patients are still limited. Cancer patients receiving molecularly targeted therapies have clinically different survival prognoses mainly because currently used targeted therapies primarily target single-gene mutations, while tumor tissues are highly heterogeneous. Moreover, the complex tumor microenvironment plays a crucial role in the survival, ability to evade immune surveillance, and drug resistance of cancer cells.

Single-gene-targeted therapy has provided a survival benefit to patients over conventional chemotherapy. For example, patients with advanced epidermal growth factor receptor (EGFR) mutation-positive lung cancer can be treated with tyrosine kinase inhibitors (TKIs) such as gefitinib or erlotinib, and those with anaplastic lymphoma kinase-positive lung cancer can be treated with crizotinib. Third-generation TKIs including osimertinib further improve the survival of patients with EGFR mutation-positive lung cancer that is also characterized by T790M mutation, in which cases first-generation TKIs are not effective. However, not all patients with EGFR mutation-positive lung cancer respond well to TKIs, and some even develop drug resistance, which will lead to disease progression.

Next-generation sequencing analyses have revealed significant differences in gene mutation sites among patients, with the differences also being apparent between early and late stages of cancer and in the mutation frequency of each site. The differences in gene mutations may also be responsible for differences in the risk of drug resistance and differences in individual treatment responses.

The co-occurrence of TP53 and EGFR mutations is often associated with a worse prognosis and accelerated proliferation and invasion of cancer cells. In this study, we collected clinical data from The Cancer Genome Atlas (TCGA) and analyzed the impact of common mutations in NSCLC patients on targeted therapy and survival prognosis.
MATERIALS AND METHODS

Data collection and analysis
First, we downloaded the clinical and original gene expression data (counts) of lung adenocarcinoma (LUAD) patients from the TCGA public database. Next, we screened 21 target genes detected by second-generation sequencing during clinical treatment and observed the effect of multiple gene expression on the survival and prognosis of patients using the pheatmap package of R software to plot a heat map for visual analysis.

Then, we used the patient mutation information provided in the database and divided all patient samples into EGFR and KRAS mutation groups to study the gene expression differences and explore the correlation between mutations at other loci and these two most common mutations.

Finally, we analyzed the overall survival (OS) of patients whose samples showed different gene expression profiles. The significance of single-gene analysis was improved by considering an expression Z score of more than 1 as high expression and an expression Z score less than -1 as low expression. Then, considering 0 as the critical value, we analyzed the co-expression of multiple genes.

Collection of clinical data from patients
We collected the next-generation sequencing results of more than 300 NSCLC patients from the First People’s Hospital of Jingzhou City from 2017 to 2020. After follow-up, clear OS and detailed data of 85 patients were obtained. If some patients were examined many times during the treatment, we took the first detection results as the basis for analysis.

We collected the medical history and general clinical data of the subjects through the hospital information system and telephone return visit in the hospital's oncology department. We collected the patient’s sex, age, smoking history, pathological type, cancer stage, next-generation sequencing results, treatment with TKIs, OS, and other results and divided the patient population based on the gene mutation status for multivariate Cox regression analysis. Finally, the patients were divided into two groups based on whether they received targeted TKI therapy or chemotherapy to explore the effect of co-occurrence of gene mutations on the OS of patients. All clinical data were collected after being submitted to the ethics committee of Jingzhou First People’s Hospital for approval. All patients provided informed consent before the next-generation sequencing analysis.

Statistical analysis
All patients were followed until December 31, 2020. We screened patients with complete basic information and definite OS data. The results of all patients were obtained using the same high-throughput sequencing equipment. All statistical analyses were performed using several R packages such as edgeR, DESeq, TCGAbiolinks, and ggplot2. We used the Kaplan-Meier method to analyze the differences in OS and compared the effects of gene mutations using the log-rank test. We also investigated the influence of various factors on the total survival of patients using multivariate Cox regression analysis. The Fisher exact test was used for comparing different groups. All P values are based on a two-tail hypothesis with statistical significance defined as P < 0.05.

RESULTS

Differential gene expression
The volcano map (Figure 1) of gene expression data of 533 cancer tissues and 53 normal tissues from TCGA reveals a large number of upregulated (red) and downregulated (green) genes[13]. Differences in gene expression were also seen among different subtypes of cancer tissues. In this study, 21 genes detected by next-generation sequencing were selected to explore the effect of gene mutation and overexpression on OS. A two-dimensional heat map of various parameters was plotted to intuitively observe patients’ basic indicators and gene expression (Figure 2), which shows apparent differences in the expression of different genes, but it is necessary to clarify which indicators impact the OS of patients.

Clinical data regarding the EGFR and KRAS mutation status were also analyzed and compared with data on mutations of other genes[14,15]. The National Comprehensive Cancer Network guidelines have pointed out that KRAS mutation can reduce sensitivity toward EGFR inhibitors. Clinically, the probability of simultaneous occurrence of KRAS mutation and EGFR mutation is very low, and a mutually exclusive relationship between them is also reported[16]. After grouping the samples based on the EGFR and KRAS mutation status with more than 20 samples in each group, the prepared bubble chart and box chart (Figure 3) show that RET, KIT, and TERT exhibited significantly different expression levels between the two groups. These three genes were upregulated in patients with KRAS mutation, while EGFR and BRAF were downregulated (Figure 3).

In the analysis of the survival of patients with single-gene mutations, to amplify the single-gene effect, we considered genes with a Z score greater than 1 to be highly expressed and those with a Z score less than -1 to have a low expression level. After calculating the P value, it was found that except for...
Figure 1 Volcano map of gene expression data of 533 cancer tissues and 53 normal tissues from The Cancer Genome Atlas database reveals a large number of upregulated (red) and downregulated (green) genes. LUAD: Lung adenocarcinoma.

Figure 2 Two-dimensional heat map of various parameters plotted to intuitively observe patients’ basic indicators and gene expression. OS: Overall survival.

*PIK3CA* (*P* < 0.05), there was no statistical significance in the high expression of other single genes: *TP53* (*P* = 0.79), *PTEN* (*P* = 0.94), *RB1* (0.49), *CTNNB1* (*P* = 0.24), and *STK11* (*P* = 0.32) (Figure 4). We speculated that significant *PIK3CA* overexpression indicates a poor prognosis and OS[17-19]. Given that the expression of other single genes did not seem to affect prognosis significantly, we suspected that the
simultaneous overexpression of multiple genes, especially the four tumor suppressor genes (TP53, PTEN, RB1, and STK11), would have some clinical implication. Therefore, we used the Z score of 0 as the critical value and divided the four genes into two groups in which all had a high expression or a low expression level at the same time (Figure 5). A P value of 0.025 showed that when TP53, PTEN, RB1, and STK11 were highly expressed simultaneously, the OS was significantly different from that when these genes showed a low expression level. Moreover, the high expression group had a significantly shorter OS.

Differences in co-occurrence of gene mutations between patients receiving chemotherapy and TKI therapy

We visualized data regarding gene mutations and basic clinical information collected from patients by plotting a heat map (Figure 6). First, we divided the patients based on whether they received chemotherapy or TKI therapy and then carried out Fisher’s exact test (Table 1). We found that sex ($P = 0.0021$), smoking history ($P = 0.0302$), and OS ($P = 0.0022$) differed significantly based on the treatment. To understand the impact of various factors on patients, we separately analyzed the impact of basic indicators and gene mutations by multivariate Cox regression (Figure 7), which demonstrated that sex (hazard ratio [HR] = 1.29; [95%CI: 0.64-2.62]; $P = 0.475$), age (HR = 1.05; [95%CI: 1.02-1.07]; $P < 0.001$), smoking history (HR = 2.26; [95%CI: 1.16-4.39]; $P = 0.017$), tumor histology (HR = 0.58; [95%CI: 0.30-1.11]; $P = 0.098$), cancer stage (HR = 16.63; [95%CI: 4.8-57.63]; $P < 0.001$), EGFR mutation (HR = 1.82; [95%CI: 1.05-3.16]; $P = 0.034$), abundance (HR = 4.95; [95%CI: 0.78-31.36]; $P = 0.09$), and TKI treatment (HR = 0.58; [95%CI: 0.43-0.78]; $P < 0.001$) affected patient survival.

Cox regression analysis (Figure 8) revealed a significant effect of all gene mutations except for BRAF ($P = 0.02$), which indicates that the OS of patients is under the combined influence of multiple-locus genes. The HR values of some gene mutations were positive, such as MAP2K1 (HR = 0.0014), CTNNB1 (HR = 0.1629), and RET (HR = 0.1089), indicating that mutations of these genes may benefit the patients, but further confirmation using more samples is necessary. We selected TP53, PTEN, RB1, and STK11, whose mutation frequency is high in NSCLC patients, to study if the co-occurrence of mutations of these genes
Figure 4 Analysis of survival of patients with single-gene mutations. To amplify the single-gene effect, we considered genes with a Z score greater than 1 to be highly expressed and those with a Z score less than -1 to have a low expression level.

genes has a similar superposition effect\(^\text{[20-22]}\). Patients with mutations in these tumor suppressor genes have a worse survival prognosis\(^\text{[23,24]}\). These co-occurring mutations can allow cancer cells to escape immune surveillance, proliferate aberrantly to malignancy, and develop resistance to targeted therapy. After identifying the effect of TP53 (HR = 1.2602), PTEN (HR = 1.4428), Rb1 (HR = 2.2605), and STK11 (HR = 3.5352), we sought to determine whether either of them could be used individually as an indicator of survival and prognosis of patients. However, the effect of age \((P < 0.001)\) was significant even if its HR value was only 1.05 (Figure 7).

The patients were divided into two groups based on whether they received chemotherapy \((n = 41)\) or TKI treatment \((n = 44)\). According to the number of mutations in the four tumor suppressor genes (TP53, PTEN, Rb1, and STK11), we classified those with more than one mutation into the greater than (GT) 1 group (Figure 9). The number of mutations of these tumor suppressor genes in the chemotherapy group did not bear significance between the GT1 and non-GT1 groups \((P = 0.96)\). Still, it was significant in the TKI treatment group \((P = 0.045)\). Co-occurrence of mutations in these genes worsened the prognosis similarly in both groups. We found that some patients discontinued targeted therapy not because of disease progression but because of economic reasons; this could have affected the results. The complexity of the tumor genome determines that cancer treatment cannot target a single gene. Co-mutation is likely to completely change the biological characteristics of the original tumor through
### Table 1 Variables between patients who received chemotherapy or TKI therapy

<table>
<thead>
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<th>Therapy type</th>
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<th>TKI therapy</th>
<th>P value</th>
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<td>26 (30.6)</td>
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<td>10 (11.8)</td>
<td>11 (12.9)</td>
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<tr>
<td>Ever</td>
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<tr>
<td>Never</td>
<td>17 (20.0)</td>
<td>26 (30.6)</td>
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<td>4 (4.7)</td>
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<tr>
<td>≥ 12 mo</td>
<td>16 (18.8)</td>
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TKI: Tyrosine kinase inhibitor; LUAD: Lung adenocarcinoma; OS: Overall survival.

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**DISCUSSION**

In this study, we focused on the effect of the co-occurrence of gene mutations using TCGA database and clinical patient data. Our analyses revealed significant differences in the gene expression profiles between adenocarcinoma and normal tissues in NSCLC. The upregulated and downregulated genes also differed in different patients and between LUAD patients with EGFR and KRAS mutations. Most tumor-derived TP53 mutations occur in the region encoding the DNA binding domain of p53. The TP53

synergy, endow the tumor with new biological characteristics, and make the tumor tolerant to targeted therapy. This co-mutation may occur gradually in the process of targeted therapy.
mutation significantly impacts the progression of various types of cancer\cite{25,26}. While the overexpression of some genes was significantly associated with good OS and prognosis, such as \textit{PIK3CA}, the single expression of most genes did not have a significant effect. The simultaneous overexpression of multiple tumor suppressor genes (\textit{TP53}, \textit{PTEN}, \textit{RB1}, and \textit{STK11}) was associated with a poor OS. Cox multivariate regression analysis revealed that for NSCLC patients, the most critical factor affecting OS was not the type of treatment or gene mutation but the disease stage, which underscores the importance of early diagnosis of solid tumors. The effects of recognized risk factors such as smoking history were also confirmed in the analysis. Finally, after grouping based on treatment, we found that in patients receiving traditional chemotherapy, mutations of \textit{TP53}, \textit{PTEN}, \textit{RB1}, and \textit{STK11} had no significant influence on the OS; however, these mutations had a significant effect in patients receiving TKIs. Simultaneous mutations in multiple tumor suppressor genes resulted in a risk superposition effect\cite{24}.

These genes have been studied in the context of non-target therapy. While the frequency of mutations in these genes is high in NSCLC patients, the problem of tumor heterogeneity and the possibility of personalized medicine need to be further explored. The influence of these gene mutations on the OS and prognosis of patients receiving immunotherapy has also received attention\cite{27-29}. In the future, the development of new molecular targeted drugs will help deal with the heterogeneity of different mutant subtypes.

\section*{CONCLUSION}

In conclusion, this study summarizes the impact of the co-occurrence of mutations or overexpression of
Figure 7  Multivariate Cox regression analysis of impact of basic indicators and gene mutations.

Figure 8  Cox regression analysis revealed a significant effect of all gene mutations except for BRAF ($P = 0.02$).
Figure 9 According to the number of mutations in the four tumor suppressor genes (TP53, PTEN, Rb1, and STK11), we classified those with more than one mutation into the greater than 1 group. gt1: Greater than 1; TKI: Tyrosine kinase inhibitor; OS: Overall survival.

multiple genes on the OS and prognosis of NSCLC patients. The results indicate that the co-occurrence of mutations results in a risk superposition effect, and such genes must be studied further when predicting patients’ disease progression.

ARTICLE HIGHLIGHTS

Research background
Among all malignant tumor types, non-small cell lung cancer (NSCLC) has the highest incidence rate and mortality.

Research motivation
To investigate the effect of simultaneous polygenic abnormalities on the prognosis and survival of NSCLC patients.

Research objectives
To study the effect of polygene mutation and abnormal expression on the prognosis and survival of patients with non-small cell lung cancer.

Research methods
We used R packages to analyze gene expression data and clinical data downloaded from The Cancer Genome Atlas (TCGA) database. We also collected samples from 85 NSCLC patients from the First People’s Hospital of Jingzhou City and retrospectively followed the patients. Multivariate Cox regression analysis and survival analysis were performed.

Research results
The probability of multiple genes (TP53, PTEN, RB1, and STK11) affecting survival was 0.025. Retrospective analysis of clinical data revealed that sex (hazard ratio [HR] = 1.29), age (HR = 1.05), smoking status (HR = 2.26), tumor histology (HR = 0.58), cancer stage (HR = 16.63), epidermal growth factor receptor (EGFR) mutation (HR = 1.82), abundance (HR = 4.95), and treatment with tyrosine kinase inhibitors (TKIs) (HR = 0.58) affected patient survival. Co-occurring mutation of TP53, PTEN, RB1, and
STK11 did not significantly affect the overall survival of patients receiving chemotherapy (P = 0.96) but significantly affected the overall survival of patients receiving TKIs (P = 0.045).

**Research conclusions**

Co-mutation or overexpression of different genes has different effects on the overall survival and prognosis of NSCLC patients. Combined with TKI treatment, the co-mutations of some genes may have a synergistic effect on the survival and prognosis of NSCLC patients.

**Research perspectives**

In the future, the development of new molecular targeted drugs will help deal with the heterogeneity of different mutant subtypes.

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**FOOTNOTES**

**Author contributions:** Yan LD, Peng XC, and Cai J designed the research; Yan LD, Yang L, Na Li, Peng XC, and Cai J performed the research; Wang M, Zhang YH, Zhou W, and Yu ZQ contributed new reagents/analytic tools; Yan LD, Peng XC, and Cai J analyzed the data; Yan LD and Cai J wrote the paper.

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**Informed consent statement:** The requirement to obtain informed consent was waived by Yangtze University Ethics Board.

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**Data sharing statement:** No additional data are available.

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**P-Editor:** Qi WW

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El-Arabiyy AH, Abdalla M, Abd-Allah AR. SnapShot: TP53 status and macrophages infiltration in TCGA-analyzed


Prospective single-center feasible study of innovative autorelease bile duct supporter to delay adverse events after endoscopic papillectomy

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Abstract

BACKGROUND

Conventional endoscopic papillectomy (EP) is safe and effective for the treatment of small papilla adenoma to even large laterally spreading tumors of duodenum lesions. As reported by some existing studies, temporarily placing a prophylactic stent in the pancreatic and bile duct can lower the risk of this perioperative complication.

AIM

To evaluate the usefulness, convenience, safety, and short-term results of a novel autorelease bile duct supporter after EP procedure, especially the effectiveness in preventing EP.

METHODS

A single-center comparison study was conducted to verify the feasibility of the novel method. After EP, a metallic endoclip and human fibrin sealant kit were applied for protection. The autorelease bile duct supporter fell into the duct segment and the intestinal segment. Specifically, the intestinal segment was extended by nearly 5 cm as a bent coil. The bile was isolated from the pancreatic juice using an autorelease bile duct supporter, which protected the wound surface. The autorelease bile duct supporter fell off naturally and arrived in colon nearly 10 d after the operation.

RESULTS

En bloc endoscopic resection was performed in 6/8 patients (75%), and piecemeal resection was performed in 2/8 of patients (25%). None of the above patients were
positive for neoplastic lymph nodes or distant metastasis. No cases of mortality, hemorrhage, delayed perforation, pancreatitis, cholangitis or duct stenosis with the conventional medical treatment were reported. The autorelease bile duct supporter in 7 of 8 patients fell off naturally and arrived in colon 10 d after the operation. One autorelease bile duct supporter was successfully removed using forceps or snare under endoscopy. No recurrence was identified during the 8-mo (ranging from 6-9 mo) follow-up period.

CONCLUSION
In brief, it was found that the autorelease bile duct supporter could decrease the frequency of procedure-associated complications without second endoscopic retraction. Secure closure of the resection wound with clips and fibrin glue were indicated to be promising and important for the use of autorelease bile duct supporters. Well-designed larger-scale comparative studies are required to confirm the findings of this study.

Key Words: Endoscopic papillectomy; Duodenal papilla; Bile duct stent; Adverse events; Endoscopic retrograde cholangiopancreatography

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Core Tip: In this study, a novel autorelease bile duct supporter was successfully inserted through a guide wire using endoscopic retrograde cholangiopancreatography in all patients after endoscopic papillectomy, during which an experienced operator was required for the insertion of the guide wire. The novel autorelease bile supporter entered the colon nearly 10 d after the endoscopic procedure with automatic shedding characteristics and decreased the frequency of procedure-related complications without a second endoscopic retraction.

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DOI: https://dx.doi.org/10.12998/wjcc.v10.i22.7785

INTRODUCTION
Endoscopic sphincterotomy was first reported in 1981 as an endoscopic operative strategy for the treatment of ampullary tumors[1]. Conventional endoscopic papillectomy (EP) has been indicated to be safe and effective for small papilla adenoma (PA) to even large laterally spreading tumor (LST) of duodenum lesions[2]. The above lesions potentially undergoing the adenoma-carcinoma sequence are expected to be removed by endoscopy resection for curative therapy[3,4]. Compared with surgical management by either pancreaticoduodenectomy or duodenostomy, EP using a snare has less morbidity, less mortality, and shorter hospital stay, and it has been accepted as an effective first-line therapy for resecting ampullary tumors[5].

Before proceeding with attempted endoscopic resection, biopsy specimens from suspicious ampullary lesions are recommended and should be obtained to confirm the diagnosis and exclude carcinoid tumors or gangliocytic parangangiomas[6]. EP has been found to be effective and safe for experienced hands with success rates of nearly 80% for lesions benign ampullary adenoma, HGIN, and noninvasive cancer without intraductal tumor growth[7,8]. Ductography by endoscopic retrograde cholangiopancreatography (ERCP) with bile and pancreatic duct plays a vital role in the evaluation of any ampullary adenomas ductal extension. En bloc resection should be performed by endoscopic snare, because of its advantages of short procedure time, less cautery and complete tissue sample for pathology evaluation. EP is correlated with an increased risk of procedure-related acute pancreatitis.

As reported by several studies, temporarily placing a prophylactic stent in the pancreatic and bile duct can lower the risk of this perioperative complication[9,10]. To date, no clear consensus relating to the parameter of pancreatic and bile duct stents has been reached.

This study assessed the usefulness, convenience, safety, and short-term results of a novel autorelease bile duct supporter after EP procedure, especially the effectiveness in preventing EP-related adverse events.
MATERIALS AND METHODS

Patients
In general, 8 patients were diagnosed histopathologically with PA and duodenum LST between March 2021 and September 2021 in the gastroenterology endoscopy center of Chinese PLA General Hospital (Beijing, China). All patients received abdominal computed tomography (CT) and pathological biopsy in before EP to evaluate the invasion depth. Exclusion criteria included suggestion of malignancy by pathological biopsy and suspicion of invasion into the pancreatobiliary duct. Patients were sedated with a balanced propofol and maintained sedation with initial intravenous administration of midazolam. Carbon dioxide insufflation was conducted, and prophylactic antibiotics were permitted.

EP and stent drainage
The procedure of EP in combination with this novel autorelease bile duct supporter is described in Figure 1. A submucosal injection with 1:10,000 diluted epinephrine into the submucosa at 3 to 4 locations around the ampulla was performed to evaluate the lesion. Electrosurgical snare (SD-7P-1/SD-221L-25; Olympus, Tokyo, Japan) passed over the working channel of the duodenoscope. The snare was carefully deployed around the ampullary lesion, and it grasped all abnormal-appearing mucosal tissues. En bloc or piecemeal resection of the lesion was performed based on the “Forced Coag” mode and “Endocut” mode (VIO 300D; Erbe Elektromedizin GmbH, Tübingen, Germany), and any suspicious residual lesion after resection was ignited through argon plasma coagulation. Electric coagulation forceps were employed for hemostasis when required. The resected specimen was retrieved with either the snare or a grasper. A guidewire was inserted though the catheter into the bile duct. The wound was closed with endoscopic hemoclips. The autorelease bile duct supporter involved the duct segment and the intestinal segment, in which the intestinal segment was extended by nearly 5 cm as a bent coil. The novel autorelease bile duct supporter was inserted through a guide wire using ERCP (Figure 2) to ensure adequate pancreatobiliary drainage. The gravity of the curved coil of autorelease bile stent could ensure the automatic shedding characteristics of this novel bile duct supporter. Fibrin glue (S10959931; Human Fibrinogen, Shanghai, China) was sprayed on the wound. The resected specimen was sent immediately for histopathologic analysis through serial sectioning. The autorelease bile duct supporter fell off naturally and arrived in colon nearly 10 d after the operation.

Stent placement were rechecked under X-radiography. Fasting water, acid-inhibitory drugs, enzyme inhibitors (somatostatin), and total parenteral nutrition were given through intravenous infusion nearly 10 d after the operation. The autorelease bile duct supporter fell off naturally and arrived in colon about 10 d after the operation based on X-ray image examination.

Definitions
Early complications (e.g., bleeding, perforation and acute pancreatitis) after the procedure were controlled by hot-biopsy forceps (Coagrasper; Olympus) hemoclips and somatostatin. Post-EP pancreatitis was set as a 3-fold increase in pancreatic enzymes with abdominal pain[7].

Perforation was recognized as a transmural defect by emergency gastroscopy or radiographic evidence of free retroperitoneal or intraperitoneal air by CT scan. Endoscopic success was defined as complete resection of the lesion without any residual tumor tissue, as well as when no recurrence was detected at the 3-mo and 6-mo follow-up after EP. The resection rate of the tumor, discharge of the autorelease stent, operative time, early complications, late complications and tumor recurrence were predicted.

RESULTS
Table 1 lists the clinicopathological data and outcomes of 2 women and 6 men. The mean age was 55.5 ± 4.9 years. The size of adenomas ranged from 20-43 mm with mean (standard deviation) 28.1 mm. Preoperative pathological diagnosis was tubular adenoma in 3, tubulovillous adenoma with low-grade dysplasia in 1, as well as tubulovillous adenoma with high-grade dysplasia (HGD), HGD/inflammation, and neuroendocrine tumor in 2, 1, in 1, respectively (Table 1).

The median tumor area of the tumors was measured as 7.57 mm² (ranging from 4.7-11.6 mm²). All PA with positive lifting sign after submucous injection was considered a criterion of lower superficial invasion. The resection was histopathologically performed in all patients. En bloc endoscopic resection was performed in 6/8 patients (75%), and piecemeal resection was performed in 2/8 of patients (25%). After EP, the autorelease bile duct supporter was placed. The average operation time was recorded as 47.1 ± 6.7 min. Tumor was confined to the mucosal layer in 5 cases and invaded the submucosa in 2 cases. In 1 case, tumor invaded the muscularis mucosa. None of the above patients were reported to be positive for neoplastic lymph nodes or distant metastasis.

There was only 1 case with positive lateral margin lesion after EP, and no treatment was added, except for endoscopic follow-up. The final histopathological diagnoses of the endoscopic specimens consisted of 3 cases of tubular adenoma, 3 cases of tubulovillous adenoma, 1 case of hamartomatous...
polyp, 1 case of adenocarcinoma, and 1 case of atypical juvenile polyposis with tubulovillous adenoma (Table 2). Among the 3 cases of tubular adenomas, 2 were correlated with HGD, in which the depth of invasion was limited to the mucosa. In the 3 cases of tubulovillous adenoma, HGD was found with submucosa invasion. The case of neuroendocrine tumor was confirmed to be G2 stage based on pathologically immunohistochemical staining. 1 patient had postoperative abdominal pain, which was resolved with antibiotic and somatostatin.

All cases were reported without any mortality, hemorrhage, delayed perforation, pancreatitis, cholangitis or duct stenosis with conventional medical treatment. The autorelease bile duct supporter in 7 of 8 patients fell off naturally and arrived in colon 10 d after the operation. One of this autorelease bile duct supporter was successfully removed with forceps or snare under endoscopy.

This neuroendocrine patient was referred for surgery and received pylorus-preserving pancreaticoduodenectomy after multidisciplinary diagnosis and treatment. No recurrence was identified during the 8-mo (ranging from 6-9 mo) follow-up.

### DISCUSSION

With a thin, highly vascular wall, the major papilla refers to the site of the confluence of the pancreatic and bile duct orifices, which can increase the risk of bleeding, pancreatitis, perforation and other complications after EP[11]. In this study, 8 patients with ampullary adenoma were treated with an autorelease bile duct supporter to investigate the parameters that might define this novel stent without second endoscopic retraction as an effective method. Adenoma of the major duodenal papilla is recognized as a type of benign lesion that requires complete resection for the potential premalignant in patients with reasonable life expectancy[12]. Compared with traditionally surgical segmental or whipple resection, EP exhibits significant advantages in reducing complications (e.g., acute pancreatitis, bleeding and perforation), attendant cost, morbidity, as well as potential mortality risk[2,13]. The overall reported incidence of complication rate changed from 0.4% to 7.9% for bleeding, perforation, cholangitis and pancreatitis[14].

Some closing and covering methods were employed to avoid the exposure of digestive juices for the mitigation of the delayed complications (e.g., clips and stents). Proper closure of the mucosal with clips and fibrin glue could mitigate the complication and improve the EP outcomes[15,16]. Poor operability of clips under duodenoscope after papilla resection might be technically challenging to extend the lesion fully and perform appropriate suturing, whereas we still strongly recommend adopting endoscopic clips to suture the duodenal mucosal wound. Accidental closure of the pancreatic or bile duct might result in pancreatitis or jaundice during the above process with clips.

Implantation of pancreatic duct stent has been generally the preferred route for the palliative drainage with fewer pancreatitis after EP[7,12,17,18]. Endoscopic bile drainage tube can also effectively prevent delayed complications for shunting bile and pancreatic juice to avoid erosion exposure of the duodenal ulcer[19-21]. As mentioned in our previous study, the mixture of bile and pancreatic juice could activate the trypsinogen to achieve a high digestive capacity. Active trypsin in the pancreatic duct would induce pancreatitis and erode the duodenal wound[22,23].

Kim et al[12] used wire-guide EP, requiring the insertion of a guide wire to the pancreatic duct before the papillotomy, to increase the success rate of pancreatic duct stenting.

However, a guide wire could also impede the expansion and angle of the snare, while making it difficult to resect larger adenomas[12]. Zolotarevsky et al[24] performed an RCT targeting pancreatic duct stents, and the spontaneous removal rates in 2 wk were obtained as 68.4% and 75.0% for 3-Fr (n =
Table 2 Endoscopic resection results at baseline and follow-up

<table>
<thead>
<tr>
<th>No.</th>
<th>Tumor size in mm²</th>
<th>Lifting sign</th>
<th>Operation time in min</th>
<th>En bloc or piecemeal</th>
<th>Autorelease at 2 wk</th>
<th>Complications</th>
<th>R0 resection</th>
<th>Depth of invasion</th>
<th>Lesion pathology</th>
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<tbody>
<tr>
<td>1</td>
<td>5.495</td>
<td>(+)</td>
<td>11</td>
<td>En bloc (+)</td>
<td>(-)</td>
<td>(-)</td>
<td>(+)</td>
<td>Mucoса</td>
<td>Tubulovillous adenoma/HGD</td>
</tr>
<tr>
<td>2</td>
<td>8.635</td>
<td>(+)</td>
<td>27</td>
<td>En bloc (-)</td>
<td>(-)</td>
<td>(-)</td>
<td>(-)</td>
<td>Submucosa</td>
<td>Tubulovillous adenoma/HGD</td>
</tr>
<tr>
<td>3</td>
<td>9.734</td>
<td>(+)</td>
<td>21</td>
<td>En bloc (+)</td>
<td>(-)</td>
<td>(+)</td>
<td>Mucoса</td>
<td>Tubular adenoma</td>
<td>Adenomatoid hyperplasia/LGD</td>
</tr>
<tr>
<td>4</td>
<td>6.28</td>
<td>(+)</td>
<td>8</td>
<td>En bloc (+)</td>
<td>(-)</td>
<td>(-)</td>
<td>(+)</td>
<td>Mucosa</td>
<td>Tubular adenoma</td>
</tr>
<tr>
<td>5</td>
<td>4.71</td>
<td>(+)</td>
<td>16</td>
<td>En bloc (+)</td>
<td>(-)</td>
<td>(-)</td>
<td>(+)</td>
<td>Muscularis mucosa</td>
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</tr>
<tr>
<td>6</td>
<td>9.42</td>
<td>(+)</td>
<td>25</td>
<td>Piecemeal (+)</td>
<td>(-)</td>
<td>(+)</td>
<td>Mucoса</td>
<td>Submucosa</td>
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</tr>
<tr>
<td>7</td>
<td>11.618</td>
<td>(+)</td>
<td>16</td>
<td>Piecemeal (+)</td>
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<td>(+)</td>
<td>Submucosa</td>
<td>Tubular adenoma/LGD</td>
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<tr>
<td>8</td>
<td>4.71</td>
<td>(+)</td>
<td>13</td>
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<td>(-)</td>
<td>(+)</td>
<td>Mucoса</td>
<td>Tubular adenoma/LGD</td>
<td></td>
</tr>
</tbody>
</table>

LGD: Low-grade dysplasia; HGD: High-grade dysplasia.

40) and 5-Fr (n = 38) after EP, respectively. In this study, the novel autorelease bile duct supporter was successfully inserted in all patients through a guide wire using ERCP after EP, during which an experienced operator was required for the insertion of the guide wire. The gravity of the curved coil ensured the automatic shedding characteristics of this novel bile stent in 2 wk. No severe or fatal bleeding occur in the above 8 patients. The literature on ampullary papillectomy was examined, and it was found that the insertion of duct stent has been widely recommended by numerous endoscopists to reduce the risk of pancreatitis[25-27]. The autorelease bile duct supporter in 7 of 8 patients fell off naturally and arrived in colon nearly 10 d after the operation.

Acid-inhibitory drugs, enzyme inhibitors (somatostatin) and total parenteral nutrition were given through intravenous infusion till 7 d after EP. With the recovery of diet and bile secretion after 7 d, we presume that autorelease bile duct supporter start to liberate from bile duct and then arrived in colon nearly 10 d after EP. With the separation effect of bile stent shunting bile and pancreatic juice and secure closure by fibrin glue, no pancreatitis was detected in the postoperative period in this small-sample study with this autorelease bile duct.

Accordingly, novel autorelease bile duct supporter might be a safe method to prevent severe or fatal pancreatitis without removal by endoscopy. However, patients should be carefully monitored for pancreatitis after EP with giant tumor or greater manipulation around the orifice of the pancreatic duct for the effect arising from the pancreatic opening and pancreatic juice outflow.

The main limitations of this study were the small sample size (EP with a novel autorelease bile duct supporter conducted at a single center by an experienced endoscopist) and the relatively short follow-up time. Well-designed comparative studies are required to assess the findings of this study. For instance, one autorelease bile duct supporter did not come off successfully by itself, whereas it was removed by endoscopy, which could be attributed to the deep plastic wing opening and the improving friction. However, this has been the first study reporting the endoscopic pancreaticobiliary drainage with autorelease bile duct supporter to prevent delayed complications after EP.

CONCLUSION

In brief, it was confirmed that autorelease bile duct supporter could decrease the frequency of procedure-associated complications without second endoscopic retraction. Secure closure of the resection wound with clips and fibrin glue was indicated to be promising and important for the use of autorelease bile duct supporter. Well-designed larger-scale comparative studies are required to assess the finding of this study.
Figure 1 Endoscopic views of endoscopic papillectomy and autorelease biliary supporter placement in a patient with a laterally spreading tumors of the major duodenal papilla. A: Duodenal papilla tumor was examined by duodenoscopy with indigo carmine staining; B: Submucosal injection was performed to lift the lesion; C: Muscularis propria wound after piecemeal submucosal resection with duodenal papilla; D: The wound was closed with
endoscopic hemoclips, and the novel autorelease bile stent was inserted via a guide wire by endoscopic retrograde cholangiopancreatography; E: Fibrin glue was sprayed to cover the wound; F: Specimen of piecemeal papilla polypectomy; G: X-ray image showed autorelease biliary stents were successfully placed; H: The autorelease biliary supporter fell off naturally and arrived in colon about 10 d after this operation.

Figure 2 The novel autorelease bile supporter was inserted through a guide wire using endoscopic retrograde cholangiopancreatography.

**ARTICLE HIGHLIGHTS**

**Research background**
Conventional endoscopic papillectomy (EP) has been indicated to papilla adenoma of duodenum lesions. Temporarily placing a prophylactic stent in the pancreatic and bile duct can lower the risk of this perioperative complication.

**Research motivation**
A new bile duct stent may help with the complication after EP and streamline the procedure.

**Research objectives**
We evaluated the usefulness, convenient, safety, and short-term results of a novel autorelease bile duct supporter after EP procedure.

**Research methods**
After EP, metallic endoclip and human fibrin sealant kit were applied for protection. The autorelease bile duct supporter fell into the duct segment and the intestinal segment. The bile was isolated from the pancreatic juice using an autorelease bile duct supporter, which protected the wound surface.

**Research results**
The autorelease bile duct supporter in 7 of 8 patients fell off naturally and arrived in colon 10 d after the operation. One of this autorelease bile duct supporter successfully removed using forceps or snare under endoscopy. No recurrence was identified during the 8-mo (ranging from 6-9 mo) follow-up.

**Research conclusions**
Autorelease bile duct supporter could decrease the frequency of procedure-associated complications without second endoscopic retraction.

**Research perspectives**
Well-designed larger-scale comparative studies are required to assess the finding of this study.
FOOTNOTES

Author contributions: Liu SZ and Chai NL contributed equally to this work; Liu SZ, Chai NL, Li HK, and Linghu EQ designed the study; Liu SZ, Gao F, Feng XX, and Wang SS performed the research; Gao Y and Wang NJ contributed new reagents and analytic tools; Liu SZ and Chai NL analyzed the data and wrote the manuscript; All authors have read and approved the final manuscript.

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Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

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REFERENCES


Performance of Dexcom G5 and FreeStyle Libre sensors tested simultaneously in people with type 1 or 2 diabetes and advanced chronic kidney disease

Arndís Finna Ólafsdóttir, Mervi Andelin, Aso Saeed, Sheyda Sofizadeh, Hussein Hamoodi, Per-Anders Jansson, Marcus Lind

Abstract

BACKGROUND

Advanced chronic kidney disease (CKD) is a common complication for people with type 1 and 2 diabetes and can often lead to glucose instability. Continuous glucose monitoring (CGM) helps users monitor and stabilize their glucose levels. To date, CGM and intermittent scanning CGM are only approved for people with diabetes but not for those with advanced CKD.

AIM

To compare the performance of Dexcom G5 and FreeStyle Libre sensors in adults with type 1 or 2 diabetes and advanced CKD.

METHODS

This was a non-randomized clinical trial that took place in two outpatient clinics in western Sweden. All patients with type 1 or 2 diabetes and an estimated glomerular filtration rate (eGFR) of < 30 mL/min per 1.73 m² were invited to participate. Forty patients (full analysis set = 33) carried the Dexcom G5 sensor for 7 d and FreeStyle Libre sensor for 14 d simultaneously. For referencing capillary
blood glucose (SMBG) was measured with a high accuracy glucose meter (HemoCue®) during the study period. At the end of the study, all patients were asked to answer a questionnaire on their experience using the sensors.

RESULTS
The mean age was 64.1 (range 41-77) years, hemoglobin A1c was 7.0% [standard deviation (SD) 3.2], and diabetes duration was 28.5 (SD 14.7) years. A total of 27.5% of the study population was on hemodialysis and 22.5% on peritoneal dialysis. The mean absolute relative difference for Dexcom G5 vs SMBG was significantly lower than that for FreeStyle Libre vs SMBG [15.2% (SD 12.2) vs 20.9% (SD 8.6)], with a mean difference of 5.72 [95% confidence interval (CI): 2.11-9.32; \( P = 0.0036 \)]. The mean absolute difference was also significantly lower for Dexcom G5 than for FreeStyle Libre, 1.21 mmol/L (SD 0.78) and 1.76 mmol/L (SD 0.78), with a mean difference of 0.55 (95%CI: 0.27-0.83; \( P = 0.0004 \)). The mean difference (MD) was -0.107 mmol/L and -1.10 mmol/L (\( P = 0.0002 \)), respectively. In all, 66% of FreeStyle Libre values were in the no risk zone on the surveillance error grid compared to 82% of Dexcom G5 values.

CONCLUSION
Dexcom G5 produces more accurate sensor values than FreeStyle Libre in people with diabetes and advanced CKD and is likely safe to be used by those with advanced CKD.

Key Words: Type 1 diabetes; Type 2 diabetes; Chronic kidney disease; Continuous glucose monitoring; Accuracy; Mean absolute relative difference

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Core Tip: This study bridges a needed gap within the diabetes device area for people with diabetes and advanced chronic kidney disease and was done in a home setting for analyses as close to real life as possible. The study found that Dexcom G5 showed greater accuracy both in relation to the mean absolute relative difference and on a surveillance error grid, but participants rated their user experience for FreeStyle Libre higher but rated no difference in feeling safe.

INTRODUCTION
For people with diabetes, good glycemic control is essential to avoid problems due to diabetes complications[1]. To reach recommended glucose levels, it is important to monitor glucose levels and for several years, self-measurement of blood glucose (SMBG) with capillary measurements has been the best way to do this[1,2]. Over the last decades, continuous glucose monitoring (CGM) and intermittent glucose monitoring (isCGM) has become more common within diabetes management and for many, has replaced the multiple capillary tests. Both systems are made up of a small sensor that is inserted under the skin where it measures glucose levels in the interstitial fluid. CGM measures glucose levels continuously and every 5 min sends a glucose value to a handheld receiver or mobile telephone. It sends alarms for high and low glucose levels. The isCGM collects data, and when the user scans the sensor with a handheld receiver or a mobile phone, it sends the glucose levels to the receiver[3,4].

Within the diabetes field, there are many discussions regarding who should be given CGM and isCGM. To date, CGM and isCGM are only approved for people with diabetes but not with chronic kidney disease (CKD)[3,4] and mainly recommended for those with type 1 diabetes and who have problems with recurrent hypoglycemia[1].

Advanced CKD is a common complication in people with type 1 and 2 diabetes. It is estimated that 20%-40% of people with diabetes will develop diabetic kidney disease, and it is the leading cause of end-stage renal failure[5,6]. A recent study showed that up to 5.1% of people with type 1 diabetes in Germany and Austria had an estimated glomerular filtration rate (eGFR) below 30 mL/min, and for Sweden and United States, the corresponding figures were 1.5% and 2.1%[7]. Advanced CKD increases the risk of hypoglycemia and great glycemic variation, and therefore it can be helpful to monitor blood
glucose with a CGM or isCGM[8,9]. There are very few studies available on the accuracy of CGMs or isCGMs for people with advanced CKD[10]. Two of the most common systems are Dexcom and FreeStyle Libre. Neither of these systems are approved for people in dialysis[3,4].

The aim of this study was to compare the performance of Dexcom G5 and FreeStyle Libre in adults with type 1 or 2 diabetes with CKD and an eGFR < 30 mL/min/1.73 m², including patients on maintenance dialysis.

**MATERIALS AND METHODS**

This study took place at NU Hospital Group and Sahlgrenska University Hospital, Sweden. It was a non-randomized, non-blinded clinical study over a 14 d period to compare the performance of FreeStyle Libre 1 and Dexcom G5 for people with diabetes and advanced CKD in an at-home situation. The protocol was approved by the regional ethics review board of Gothenburg, Sweden.

**Study procedures**

All participants provided written informed consent before the study began. The inclusion criteria were: type 1 or type 2 diabetes, between 18-years-old and 80-years-old, and eGFR < 30 mL/min per 1.73 m² for people undergoing or not undergoing dialysis. The exclusion criteria were pregnancy, patients with severe cognitive dysfunction or other diseases that makes glucose monitoring difficult, continuous use of paracetamol, history of allergic reaction to chlorhexidine or alcohol antiseptic solution, abnormal skin at the anticipated glucose sensor attachment sites, and eGFR ≥ 30 mL/min per 1.73 m².

After obtaining written and informed consent, a diabetes nurse inserted two different sensors in accordance with instructions from the manufacturer. Dexcom G5 was inserted in the abdomen and FreeStyle Libre on the upper arm. Participants were instructed on how they should use each monitor and instructed how to calibrate the Dexcom G5. Calibrations were done using the HemoCue® DM RD 201 (Aneholm, Sweden). All HemoCue meters were calibrated before being assigned to participants using the absolute isotope dilution gas chromatography/mass spectrometry measurement system[11]. The total measurement error/reproducibility imprecision of HemoCue is less than 6.5%[12]. Earlier studies using HemoCue showed a strong correlation between capillary and venous HemoCue concentrations, and capillary concentrations were considered to be a suitable reference[13]. All participants were instructed by a diabetes nurse on how to use the HemoCue meter. Participants were instructed to simultaneously document their blood glucose measured by HemoCue and the value of the FreeStyle Libre and Dexcom G5 in a diary a minimum of three times per day. Participants were instructed to calibrate their Dexcom G5 twice daily in accordance with the manufacturer’s instructions and to do so after recording its value in the diary. Participants on maintenance dialysis (peritoneal dialysis or hemodialysis) were also asked to register the start and finish of each session in their diary. After 7 d, Dexcom G5 was removed by the participants but they continued to record results from the FreeStyle Libre and HemoCue. After the 14 d period, participants returned the meters to the site. The study personnel downloaded data from the meters using the Glooko-Diasend system. HemoCue measurements were manually validated by personnel going through each value and comparing to the diary. When each sensor was finished, participants rated their experience on a 10-item visual analogue scale. Similar questionnaires have been used in earlier studies[14,15].

**Predefined endpoints**

All endpoints were predefined and registered on ClinicalTrials.gov. The primary endpoint was the difference of mean absolute relative difference (MARD) between Dexcom G5 and FreeStyle Libre using HemoCue (capillary glucose meter) as a reference. Secondary endpoints were the difference in mean absolute difference (MAD) between the Dexcom G5 and FreeStyle Libre sensors, the difference in mean difference (MD) between the Dexcom G5 and FreeStyle Libre sensors, and the correlation between the different systems. Predefined subgroup analyses for glucose ranges below 3.9 mmol/L, between 3.9 and 10 mmol/L, and above 10 mmol/L as well as for those without dialysis and undergoing dialysis.

**Independence of the study**

The manufacturers of FreeStyle Libre and Dexcom G5 were not involved in the design, performance, data analysis, or publication of the article. No support was received from the manufacturers.

**Statistical analysis**

After sample size analysis, 40 patients were included in the study (see supplement). All main analyses between Dexcom G5 and FreeStyle Libre were performed with paired analyses. All statistical analyses were predefined in the statistical analysis plan before database lock. All participants having at least 10 matched time points, with evaluable blood glucose values from both sensors and HemoCue (reference capillary value) during the whole study period, were included in the Full Analysis Set (FAS). All matching time points were used. For paired analysis regarding continuous variables, Fisher’s non-parametric permutation test for paired observations was used and for dichotomous and ordered
categorical variables sign test was used. For comparison between dialysis subjects and subjects not in
dialysis, Fisher’s non-parametric permutation test was used for continuous variables.

The primary variable was MARD, which is the mean absolute relative difference between the
estimated sensor glucose value of FreeStyle Libre or Dexcom G5 and blood glucose measured with
HemoCue. For each individual mean of following differences from each time point was evaluated for
both sensors: \(|(\text{sensor}_i - \text{HemoCue}_i)|/\text{HemoCue}_i\), where \(i\) = time-point during the analyzed days in the study.

MAD is the mean absolute difference between estimated sensor glucose value of FreeStyle Libre or
Dexcom G5 and blood glucose measured with HemoCue. For each individual mean of following
differences from each time point was evaluated for both sensors: \(|\text{sensor}_i - \text{HemoCue}_i|\). MAD is the mean
difference between estimated sensor glucose value of FreeStyle Libre or Dexcom G5 and blood glucose
measured with HemoCue. For each individual mean of following differences from each time point was evaluated:
\(|(\text{sensor}_i - \text{HemoCue}_i)|\). MD is the mean difference between each of the sensor and HemoCue was also given together with Intraclass correlation
coefficient (ICC), Bland-Altman plots, and scatterplots.

Agreement between each of the devices and HemoCue were analyzed with Bland-Altman’ methods.

The main result was the limit of agreement. If one got a value measured with one of the sensors, you can
calculate an interval where 95% of the HemoCue values would have been. The distributions of the
difference between each of the sensor and HemoCue was also given together with Intraclass correlation
coefficient (ICC), Bland-Altman plots, and scatterplots.

All significance tests were two-sided and conducted at the 5% significance level. All statistical
analyses were performed with SAS System Version 9.4 (Cary, NC, United States).

Post-hoc analyses
The surveillance error grid graph for Dexcom G5/FreeStyle Libre vs HemoCue was calculated by using
https://www.diabetestechnology.org/seg/. The proportion of sensor values within 15%, 20%, and 30%
of reference values HemoCue for blood glucose > 100 mg/dL (5.6 mmol/L) or within 15, 20, and 30
mg/dL (0.8, 1.1, 1.7 mmol/L) of reference values for blood glucose ≤ 100 mg/dL (5.6 mmol/L),
respectively, was calculated (%15/15, %20/20, %30/30). MARD FreeStyle Libre
vs HemoCue the first
week was compared with the second week with the same requirements as main study with Fisher’s
non-parametric permutation test one sample test.

To study the covariation between Dexcom G5/FreeStyle Libre and HemoCue Pearson correlation
coefficient between each of the devices and HemoCue was calculated for each subject. These correlations
were also analyzed both for Dexcom G5 and FreeStyle Libre with Fisher’s non-parametric
permutation test one sample test.

Agreement between each of the devices and HemoCue were analyzed with Bland-Altman’ methods.

The main result was the limit of agreement. If one got a value measured with one of the sensors, you can
calculate an interval where 95% of the HemoCue values would have been. The distributions of the
difference between each of the sensor and HemoCue was also given together with Intraclass correlation
coefficient (ICC), Bland-Altman plots, and scatterplots.

All significance tests were two-sided and conducted at the 5% significance level. All statistical
analyses were performed with SAS System Version 9.4 (Cary, NC, United States).

RESULTS
The study included 40 participants with type 1 and 2 diabetes and advanced CKD; 33 (FAS) met the
criteria for data analysis and at least 10 time points with evaluable values from both systems and the
HemoCue within 5 min during the whole study period (June 2016-March 2019). Of the 7 patients who
were not included in FAS, 2 chose not to participate after starting the study and 5 did not meet the
criteria for data analysis described above; that is, they did not have 10 matched time points for both
sensors. Mean hemoglobin A1c (HbA1c) was 7.0%, 25.6% were women, mean age was 64.1 (range 41-
77), and 50% were on dialysis. Additional baseline characteristics are shown in Table 1.

Accuracy evaluations
The MARD analyzed for all participants for Dexcom G5 was significantly lower than that for FreeStyle
Libre vs SMBG (15.2% [SD 12.2] vs 20.9% [SD 8.6]), respectively, with mean difference of 5.72 (95%CI:
2.11-9.32; \(P = 0.0036\)). The MAD was also significantly lower for Dexcom G5 than for FreeStyle Libre,
1.21 mmol/L (SD 0.78) and 1.76 mmol/L (SD 0.78), with a mean difference of 0.55 (95%CI: 0.27-0.83; \(P =
0.0004\)). There was also a significant difference between the MD of the systems. There was a systematic
MD between FreeStyle Libre and HemoCue of -1.10 mmol/L (95%CI: -1.55 to -0.66 mmol/L; \(P < 0.0001\))
but no systematic MD between Dexcom G5 and HemoCue -0.107 (95%CI: -0.439 to 0.225; \(P = 0.052\))
(Table 2).

We found that for glucose values that were in range (3.9-10.0 mmol/L) and above range (> 10
mmol/L), there was a significantly lower MARD, MAD, and MD for Dexcom G5 than for FreeStyle
Libre (Table 2). For glucose values in range, the MARD was 14.8% (SD 10.6) for Dexcom G5 and 22.6%
(SD 8.9) for the FreeStyle Libre, with a mean difference of 7.83 (95%CI: 4.32-11.33; \(P < 0.0001\)). The
MARD for hyperglycemic values were 12.3% (SD 11.6) and 16.6% (SD 11.1), respectively, with a mean
difference of 4.22 (95%CI: 1.06-7.39; \(P = 0.010\)). There were few values below range (< 3.9 mmol/L), 14
values from 9 individuals (Table 2).
Table 1 Baseline characteristics

<table>
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<th>Variable</th>
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<td>66 (41; 77)</td>
<td>65.5 (41; 77)</td>
</tr>
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<td></td>
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<td>n = 32</td>
</tr>
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<td>53.9 (11.5)</td>
</tr>
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<td>HbA1c %</td>
<td>7 (3.2)</td>
<td>7.1 (3.2)</td>
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<td>53 (5; 9)</td>
<td>7.1 (5; 9)</td>
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<tr>
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<td>Dialysis</td>
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<tr>
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<td>17 (51.5%)</td>
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<tr>
<td>Hemodialysis</td>
<td>11 (27.5%)</td>
<td>7 (21.2%)</td>
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<tr>
<td>Peritoneal dialysis</td>
<td>9 (22.5%)</td>
<td>9 (27.3%)</td>
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<tr>
<td>Diabetes duration</td>
<td>28.5 (14.7)</td>
<td>29.2 (15.4)</td>
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<tr>
<td></td>
<td>27.5 (5.3; 64.5)</td>
<td>28.5 (5.3; 64.5)</td>
</tr>
<tr>
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<td>n = 26</td>
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<tr>
<td>Sex</td>
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<tr>
<td>Man</td>
<td>29 (74.4%)</td>
<td>22 (68.8%)</td>
</tr>
<tr>
<td>Woman</td>
<td>10 (25.6%)</td>
<td>10 (31.3%)</td>
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<tr>
<td>Smoking</td>
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<tr>
<td>No</td>
<td>25 (71.4%)</td>
<td>19 (67.9%)</td>
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<tr>
<td>Yes</td>
<td>3 (8.6%)</td>
<td>3 (10.7%)</td>
</tr>
<tr>
<td>Do not know</td>
<td>7 (20.0%)</td>
<td>6 (21.4%)</td>
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<tr>
<td>Systolic blood pressure in mmHg</td>
<td>145.6 (24.2)</td>
<td>146.5 (24.7)</td>
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<td>145 (95; 213)</td>
<td>142.5 (95; 213)</td>
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<td>n = 30</td>
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<tr>
<td>Diastolic blood pressure in mmHg</td>
<td>77.4 (13.7)</td>
<td>78.6 (13.8)</td>
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<td>80 (52; 103)</td>
<td>80 (52; 103)</td>
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<td>Insulin delivery</td>
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<tr>
<td>Basal insulin only</td>
<td>12 (32.4%)</td>
<td>10 (33.3%)</td>
</tr>
<tr>
<td>Mix insulin</td>
<td>2 (5.4%)</td>
<td>2 (6.7%)</td>
</tr>
<tr>
<td>MDI</td>
<td>24 (64.9%)</td>
<td>20 (66.7%)</td>
</tr>
<tr>
<td>Other glucose lowering treatment</td>
<td>5 (13.5%)</td>
<td>3 (10.0%)</td>
</tr>
<tr>
<td>Total insulin dose per day</td>
<td>73.0 (60.3)</td>
<td>65.7 (63.8)</td>
</tr>
<tr>
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<td>45 (8; 277)</td>
<td>41 (8; 277)</td>
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<td>n = 20</td>
</tr>
<tr>
<td>Type of diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 1</td>
<td>11 (30.6%)</td>
<td>10 (33.3%)</td>
</tr>
<tr>
<td>Type 2</td>
<td>25 (69.4%)</td>
<td>20 (66.7%)</td>
</tr>
</tbody>
</table>
Subgroup analysis: People needing and not needing dialysis
Subgroup analyses for MARD, MAD, and MD were done for people requiring and not requiring dialysis. The MARD for FreeStyle Libre for people in dialysis was 19.3% (SD 7.4) compared to 22.5% (SD 9.5) for those not in dialysis (P = 0.29). The corresponding values for Dexcom G5 were 15.5% (SD 14.8) and 15.0% (SD 9.6), respectively (P = 0.91). For people not in dialysis, there was a significant difference between the sensors MARD and MAD (P = 0.0033 and P = 0.0057, respectively). For people in dialysis, there was a significant difference between the systems MAD (P = 0.035), whereas a numerical difference was found between the sensors MARD, although not statistically significant (Table 2). Further subgroup analysis with people on peritoneal dialyses showed numerically lower MARD and MAD for Dexcom G5 compared to FreeStyle Libre as in the total population, and there was a significant systematic difference between FreeStyle Libre and HemoCue -1.58 (P = 0.01). There were 7 people on hemodialysis and Dexcom G5 showed a numerically lower MARD and MAD compared to FreeStyle Libre in this subgroup, but the differences were less (Table 2).

Correlation between the systems
Analyses were done to see how well the systems correlated with the capillary reference system. Values obtained by Dexcom G5 and FreeStyle Libre significantly correlated with those obtained by the HemoCue capillary reference system [r = 0.784, (SD 0.29) P < 0.0001, and 0.777, (SD 0.34) P < 0.0001, respectively]. Interclass correlation coefficient (ICC) was 0.68 for FreeStyle Libre and 0.88 for Dexcom G5 and limits of agreement (-3.54 - 1.34) for FreeStyle Libre and (-1.94 - 1.73) for Dexcom G5 (Supplementary Table 1). This could clearly be seen on the Bland-Altman plot in Figure 1 and Supplementary Figures 1 and 2.

Patient experience
After using the systems, participants evaluated their experience (Table 3). Participants were significantly more positive towards FreeStyle Libre than Dexcom G5 in all factors except feeling safe, for which there was no significance between the two systems. FreeStyle Libre scored 7.94 of 10 and Dexcom G5 scored 7.19 of 10 (P = 0.32; Table 3).

Post hoc analysis
For Dexcom G5, %20/20 = 79.6, which indicates that 79.6% of the values above 5.6 mmol/L were within 20% of the reference instrument and within 1.11 mmol/L (20 mg/dL) for values below 5.6 mmol/L. The corresponding figure for FreeStyle Libre was 61.3%. For %15/15 the values were 70.3% for Dexcom G5 and 43.9% for FreeStyle Libre. For %30/30 the corresponding figures were 89.1% and 84.6% respectively. The surveillance error grid (Figure 2) showed that 82% of the values for Dexcom G5 were within the no risk zone (green color) compared to 66.3% of the values for FreeStyle Libre. Data from the second week of Libre showed that there was a greater MARD during this week, 24.8% (95%CI: 20.4-29.2 mmol/L) compared to the first week when it was 19.4%, P = 0.0042. MARD for participants with type 1 diabetes was 11.8% (SD 10.0) for Dexcom G5 and 17.4% (SD 5.7) for FreeStyle Libre with a mean difference of 5.6 (95%CI: -0.4-11.8, P = 0.068). Corresponding results for participants with type 2 diabetes were 16.2% (SD 12.7) for Dexcom G5 and 21.6% (SD 8.6) for FreeStyle Libre with a mean difference of 5.4 (95%CI: 0.25-10.49, P = 0.042).

DISCUSSION
Dexcom G5 showed greater overall accuracy than FreeStyle Libre. Dexcom G5 also showed greater accuracy for glucose values within range (3.9-10 mmol/L) and above range (> 10 mmol/L). Furthermore, in a subgroup analysis, Dexcom G5 showed greater accuracy for people not in dialysis. However, for people in dialysis, Dexcom G5 had a numerically lower MARD and a significantly lower MAD compared with FreeStyle Libre. On the surveillance error grid, Dexcom G5 had 82% of values within the no risk zone compared to 66% for FreeStyle Libre. Glucose values from both sensors correlated well with the reference instrument, HemoCue. FreeStyle Libre showed a greater systematic deviation than Dexcom G5. Participants rated their user experience of FreeStyle Libre higher after a 2 wk period than Dexcom G5 but did not experience a difference in safety.

Earlier studies with similar methodology and the same reference instrument showed that the FreeStyle Libre had a MARD of 13.2% and an earlier Dexcom sensor (Dexcom 4G) had a MARD of 13.8% when tested in people with type 1 diabetes[14,15]. A recent study analyzed how well FreeStyle Libre correlates with capillary measurements (Medisafe® Fit) during hemodialysis in people with type 2 diabetes.
<table>
<thead>
<tr>
<th>Variable</th>
<th>FreeStyle Libre (isCGM)</th>
<th>Dexcom G5 CGM</th>
<th>Difference (isCGM-CGM)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean MARD</td>
<td>20.9 (8.6)</td>
<td>15.2 (12.2)</td>
<td>5.72 (10.17)</td>
<td>0.0036</td>
</tr>
<tr>
<td></td>
<td>19.8 (8.5; 43.1)</td>
<td>11.9 (2.2; 60.5)</td>
<td>6.5 (-26.75; 24.68)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n = 33</td>
<td>n = 33</td>
<td>(2.11; 9.32)</td>
<td></td>
</tr>
<tr>
<td>Mean MAD</td>
<td>1.76 (0.78)</td>
<td>1.21 (0.78)</td>
<td>0.548 (0.795)</td>
<td>0.0004</td>
</tr>
<tr>
<td></td>
<td>1.65 (0.48; 4.48)</td>
<td>0.95 (0.23; 3.12)</td>
<td>0.679 (-1.662; 2.11)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n = 33</td>
<td>n = 33</td>
<td>(0.267; 0.830)</td>
<td></td>
</tr>
<tr>
<td>Mean MD</td>
<td>-1.10 (1.24)</td>
<td>-0.107 (0.937)</td>
<td>0.548 (0.795)</td>
<td>0.0004</td>
</tr>
<tr>
<td></td>
<td>-1.46 (-4.48; 1.63)</td>
<td>-0.229 (-2.47; 3.007)</td>
<td>-1.1 (-3.586; 2.431)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n = 33</td>
<td>n = 33</td>
<td>(-1.451; -0.545)</td>
<td></td>
</tr>
</tbody>
</table>

Persons in dialysis

Mean MARD | 19.3 (7.4) | 15.5 (14.8) | 3.80 (11.09) | 0.19 |
|          | 17.7 (8.5; 33.7) | 8.6 (4.1; 60.5) | 6.51 (-26.75; 15.75) |         |
|          | n = 16       | n = 16       | (-2.11; 9.71) |         |
| Mean MAD | 1.74 (0.91) | 1.26 (0.85) | 0.489 (0.828) | 0.035 |
|          | 1.65 (0.77; 4.48) | 0.99 (0.43; 3.12) | 0.611 (-1.236; 1.65) |         |
|          | n = 16       | n = 16       | (0.048; 0.931) |         |
| Mean MD  | -1.29 (1.29) | -0.056 (1.232) | -1.34 (1.30) | 0.0019 |
|          | -1.32 (-4.48; 0.96) | -0.252 (-2.47; 3.007) | -1.46 (-3.59; 1.07) |         |
|          | n = 16       | n = 16       | (-2.03; -0.65) |         |

People not in dialysis

Mean MARD | 22.5 (9.5) | 15.0 (9.6) | 7.53 (9.19) | 0.0033 |
|          | 19.8 (8.8; 43.1) | 12.5 (2.2; 38.5) | 6 (-15.59; 24.68) |         |
|          | n = 17       | n = 17       | (2.80; 12.25) |         |
| Mean MAD | 1.77 (0.65) | 1.16 (0.72) | 0.604 (0.784) | 0.0057 |
|          | 1.67 (0.48; 3.22) | 0.95 (0.23; 2.77) | 0.679 (-1.662; 2.11) |         |
|          | n = 17       | n = 17       | (0.201; 1.007) |         |
| Mean MD  | -0.934 (1.211) | -0.260 (0.529) | -0.673 (1.209) | 0.037 |
|          | -1.482 (-2.586; 1.632) | -0.223 (-1.323; 0.932) | -0.855 (-2.348; 2.431) |         |
|          | n = 17       | n = 17       | (-1.295; -0.052) |         |

Glucose values < 3.9 mmol/L.

Mean MARD | 53.0 (37.1) | 89.8 (66.8) | -36.9 (42.0) | 0.027 |
<p>|          | 35.3 (12.8; 115.2) | 66.7 (7.7; 197.4) | -44.7 (-127.2; 7.1) |         |</p>
<table>
<thead>
<tr>
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<tr>
<td>Mean MAD</td>
<td>1.81 (1.33)</td>
<td>3.10 (2.47)</td>
<td>-1.29 (1.52)</td>
</tr>
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<td>1.2 (0.47; 3.9)</td>
<td>1.8 (0.27; 7.2)</td>
<td>-1.3 (-4.65; 0.2)</td>
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<td></td>
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<td>n = 9</td>
</tr>
<tr>
<td>Mean MD</td>
<td>1.18 (1.96)</td>
<td>3.03 (2.54)</td>
<td>-1.85 (1.42)</td>
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<tr>
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<td>1.2 (-1.2; 3.9)</td>
<td>1.8 (0.27; 7.2)</td>
<td>-1.8 (-4.65; 0.2)</td>
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Glucose values 3.9-10.0 mmol/L

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<tr>
<td>Mean MARD</td>
<td>22.6 (8.9)</td>
<td>14.8 (10.6)</td>
<td>7.83 (9.88)</td>
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<td>21 (8.7; 44.1)</td>
<td>11.9 (1.5; 40.5)</td>
<td>8.05 (-13.18; 28.95)</td>
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<tr>
<td>Mean MAD</td>
<td>1.60 (0.62)</td>
<td>1.03 (0.71)</td>
<td>0.568 (0.689)</td>
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<td>1.45 (0.5; 2.98)</td>
<td>0.82 (0.13; 2.59)</td>
<td>0.633 (-0.918; 2.045)</td>
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<tr>
<td>Mean MD</td>
<td>-0.868 (1.183)</td>
<td>0.136 (0.859)</td>
<td>-1.00 (1.19)</td>
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<td>-1.067 (-2.9; 2.508)</td>
<td>-0.017 (-2.1; 2.445)</td>
<td>-1.07 (-3.57; 1.36)</td>
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Glucose values > 10.0 mmol/L

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<tr>
<td>Mean MARD</td>
<td>16.6 (11.1)</td>
<td>12.3 (11.6)</td>
<td>4.22 (8.63)</td>
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<td>15.3 (1.9; 59)</td>
<td>7.9 (1.9; 50.4)</td>
<td>4.69 (-25.08; 16.94)</td>
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</tr>
<tr>
<td>Mean MAD</td>
<td>2.06 (1.29)</td>
<td>1.54 (1.31)</td>
<td>0.520 (1.139)</td>
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<td>1.9 (0.2; 6.45)</td>
<td>1.04 (0.2; 5.5)</td>
<td>0.533 (-3.4; 2.18)</td>
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<tr>
<td>Mean MD</td>
<td>-1.82 (1.56)</td>
<td>-0.944 (1.633)</td>
<td>-0.875 (1.777)</td>
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<td>-1.89 (-6.45; 1.16)</td>
<td>-0.563 (-5.5; 2.7)</td>
<td>-0.95 (-4.1; 5.72)</td>
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Hemodialysis

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<tr>
<td>Mean MARD</td>
<td>21.4 (9.1)</td>
<td>20.3 (18.9)</td>
<td>1.13 (14.27)</td>
</tr>
<tr>
<td></td>
<td>20.7 (8.5; 33.7)</td>
<td>17 (5.6; 60.5)</td>
<td>2.88 (-26.75; 15.75)</td>
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<td>n = 7</td>
<td>n = 7</td>
</tr>
<tr>
<td>Mean MAD</td>
<td>1.79 (0.69)</td>
<td>1.44 (0.87)</td>
<td>0.354 (1.012)</td>
</tr>
<tr>
<td></td>
<td>1.89 (0.77; 2.73)</td>
<td>1.28 (0.56; 3.12)</td>
<td>0.211 (-1.236; 1.614)</td>
</tr>
</tbody>
</table>
For comparison between FreeStyle Libre and Dexcom G5 the Fisher’s Non-Parametric Permutation test for matched pairs was used. For continuous variables, distribution of differences is given by mean (SD)/median (min; max)/(95% confidence interval for mean)/n = is presented and the distribution of values within the two sensors is given by mean (SD)/median (min; max)/n = is presented. CGM: Continuous glucose monitoring; MAD: Mean absolute difference; MARD: Mean absolute relative difference; MD: Mean difference; isCGM: Intermittent glucose monitoring.

For comparison between FreeStyle Libre and Dexcom G5 the Fisher’s Non-Parametric Permutation test for matched pairs was used. For continuous variables, distribution of differences is given by mean (SD)/median (min; max)/(95% confidence interval for mean)/n = is presented and the distribution of values within the two sensors is given by mean (SD)/median (min; max)/n = is presented. CGM: Continuous glucose monitoring; MAD: Mean absolute difference; MARD: Mean absolute relative difference; MD: Mean difference; isCGM: Intermittent glucose monitoring.

Diabetes, and showed that the FreeStyle Libre had a MARD between 13% and 22% depending on the glycemic range and that it showed a 18.4 mg/dL (1.0 mmol/L) lower value than the capillary reference instrument. The same study found that the Medtronic iPro Enlite sensor had a MARD between 5% and 30% depending on the glycemic value and showed a 4.7 mg/dL (0.3 mmol/L) lower value than the reference instrument[10]. It was previously shown that the FreeStyle Libre deviates systematically by -
### Table 3 Patient experience of FreeStyle Libre and Dexcom G5 measured on a visual analogue scale

<table>
<thead>
<tr>
<th>Variable</th>
<th>FreeStyle Libre isCGM, n = 31</th>
<th>Dexcom G5 CGM, n = 31</th>
<th>Change from FreeStyle Libre isCGM to Dexcom G5 CGM</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>My experience of the system was very positive</td>
<td>8.35 (2.03)</td>
<td>6.84 (2.70)</td>
<td>-1.52 (3.41)</td>
<td>0.023</td>
</tr>
<tr>
<td></td>
<td>9.00 (3.00; 10.00)</td>
<td>8.00 (2.00; 10.00)</td>
<td>-2.00 (-7.00; 7.00)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(7.61; 9.10)</td>
<td>(5.85; 7.83)</td>
<td>(-2.77; -0.26)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n = 31</td>
<td>n = 31</td>
<td>n = 31</td>
<td></td>
</tr>
<tr>
<td>The insertion of the sensor was easy</td>
<td>9.03 (1.71)</td>
<td>8.27 (2.29)</td>
<td>-0.767 (1.455)</td>
<td>0.0084</td>
</tr>
<tr>
<td></td>
<td>10.00 (2.00; 10.00)</td>
<td>9.00 (1.00; 10.00)</td>
<td>0.000 (-5.000; 2.000)</td>
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</tr>
<tr>
<td></td>
<td>(8.39; 9.67)</td>
<td>(7.41; 9.12)</td>
<td>(-1.310; -0.223)</td>
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</tr>
<tr>
<td></td>
<td>n = 30</td>
<td>n = 30</td>
<td>n = 30</td>
<td></td>
</tr>
<tr>
<td>I felt safe during my time using the system</td>
<td>7.94 (2.67)</td>
<td>7.19 (2.46)</td>
<td>-0.742 (3.916)</td>
<td>0.32</td>
</tr>
<tr>
<td></td>
<td>9.00 (0.00; 10.00)</td>
<td>8.00 (3.00; 10.00)</td>
<td>-1.00 (-7.00; 9.000)</td>
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<tr>
<td></td>
<td>(6.96; 8.91)</td>
<td>(6.29; 8.09)</td>
<td>(-2.178; 0.694)</td>
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<td>n = 31</td>
<td>n = 31</td>
<td>n = 31</td>
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</tr>
<tr>
<td>It was easy to use the system</td>
<td>9.52 (0.96)</td>
<td>7.60 (2.62)</td>
<td>-1.93 (2.21)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td></td>
<td>10.00 (6.00; 10.00)</td>
<td>9.00 (2.00; 10.00)</td>
<td>-1.00 (-7.00; 0.00)</td>
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</tr>
<tr>
<td></td>
<td>(9.16; 9.87)</td>
<td>(6.62; 8.58)</td>
<td>(-2.76; -1.11)</td>
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<td>n = 30</td>
<td>n = 30</td>
<td>n = 30</td>
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<tr>
<td>It was easy to interpret the information on the receiver screen</td>
<td>9.42 (0.99)</td>
<td>7.97 (2.46)</td>
<td>-1.45 (1.98)</td>
<td>&lt; 0.0001</td>
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<tr>
<td></td>
<td>10.00 (7.00; 10.00)</td>
<td>9.00 (1.00; 10.00)</td>
<td>-1.00 (-7.00; 1.00)</td>
<td></td>
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<tr>
<td></td>
<td>(9.06; 9.78)</td>
<td>(7.07; 8.87)</td>
<td>(-2.18; -0.73)</td>
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<td></td>
<td>n = 31</td>
<td>n = 31</td>
<td>n = 31</td>
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<tr>
<td>I was not in pain or had discomfort in connection to my use of the system</td>
<td>9.74 (0.73)</td>
<td>8.48 (2.78)</td>
<td>-1.26 (2.68)</td>
<td>0.0078</td>
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<td></td>
<td>10.00 (7.00; 10.00)</td>
<td>10.00 (0.00; 10.00)</td>
<td>0.00 (-10.00; 0.00)</td>
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<td></td>
<td>(9.47; 10.01)</td>
<td>(7.46; 9.50)</td>
<td>(-2.24; -0.27)</td>
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<td></td>
<td>n = 31</td>
<td>n = 31</td>
<td>n = 31</td>
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<tr>
<td>I experienced no problem scanning/contact with the system</td>
<td>9.55 (0.93)</td>
<td>7.19 (3.29)</td>
<td>-2.35 (3.23)</td>
<td>&lt; 0.0001</td>
</tr>
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<td></td>
<td>10.00 (7.00; 10.00)</td>
<td>9.00 (0.00; 10.00)</td>
<td>-1.00 (-10.00; 2.00)</td>
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<tr>
<td></td>
<td>(9.21; 9.89)</td>
<td>(5.99; 8.40)</td>
<td>(-3.54; -1.17)</td>
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<td>n = 31</td>
<td>n = 31</td>
<td>n = 31</td>
<td></td>
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<tr>
<td>The sensor was comfortable to have on my body in my daily life</td>
<td>9.20 (1.40)</td>
<td>7.23 (2.69)</td>
<td>-1.90 (2.34)</td>
<td>&lt; 0.0001</td>
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<td>-1.00 (-8.00; 1.00)</td>
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<td>(-2.77; -1.05)</td>
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<td>n = 30</td>
<td>n = 31</td>
<td>n = 31</td>
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<tr>
<td>The system did not disturb my daily life</td>
<td>9.33 (1.09)</td>
<td>7.74 (2.62)</td>
<td>-1.50 (2.43)</td>
<td>0.0024</td>
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<td>0.00 (-7.00; 4.00)</td>
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<td></td>
<td>(8.93; 9.74)</td>
<td>(6.78; 8.70)</td>
<td>(-2.41; -0.59)</td>
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<td></td>
<td>n = 30</td>
<td>n = 31</td>
<td>n = 31</td>
<td></td>
</tr>
<tr>
<td>I would like to use the system in my daily life</td>
<td>8.45 (2.86)</td>
<td>5.42 (3.49)</td>
<td>-2.66 (4.98)</td>
<td>0.0096</td>
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<td>-3.00 (-10.00; 9.00)</td>
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<tr>
<td></td>
<td>(7.36; 9.54)</td>
<td>(4.14; 6.70)</td>
<td>(-4.55; -0.76)</td>
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</table>
It was easy to calibrate the Dexcom G5

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<tr>
<td></td>
<td>8.40 (2.21)</td>
<td>10.00 (3.00; 10.00)</td>
<td>(7.58; 9.22)</td>
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<tr>
<td>The alarms did not disturb my daily life</td>
<td>7.97 (2.74)</td>
<td>9.00 (0.00; 10.00)</td>
<td>(6.95; 8.99)</td>
</tr>
</tbody>
</table>

For categorical variables n (%) is presented. For continuous variables mean (SD)/median (min; max)/(95% confidence interval for mean)/n = is presented.

For comparison over time, Fisher’s non-parametric permutation test for paired observations was used for continuous variables. The evaluation of questions of the flash glucose monitoring/continuous glucose monitoring were expressed on a visual analogue scale with lowest value (0) meaning Not true at all and highest value (10) meaning completely true.

Figure 2 Surveillance error grid. A: FreeStyle Libre vs HemoCue -66.3% of values fall within the dark green area; B: Dexcom G5 vs HemoCue -82% of values fall within the dark green area.

0.5 mmol/L in people with type 1 diabetes using HemoCue capillary measurements as a reference[15]. The Dexcom G5 was found to have a MARD of 7.1%-15.7% when tested in people with type 1 diabetes and using a Yellow Spring Instrument as a reference[16].

People with advanced CKD more frequently experience glycemic excursions[15]. During hemodialysis, there is an increased risk for hypoglycemia, whereas patients with peritoneal dialysis have an increased hyperglycemia risk[17,18]. It is therefore important that this group of patients receives all possible help to monitor their glucose levels and to increase their possibility of better glycemic control. It is possible to speculate if these increased glucose excursions can possibly be the cause to the lower accuracy of these sensors for people with advanced CKD. This study found that the accuracy of FreeStyle Libre and Dexcom G5 while being used by people with advanced CKD is similar to the accuracy of earlier sensors which were used as glucose indicators and not for insulin dosing decisions[14,15]. An earlier study has found that when people on dialysis used CGM it led to more frequent treatment changes and better glycemic control[19].

This study showed that even people undergoing peritoneal dialysis, which can have high glucose fluctuations, had a MARD which is similar to previous systems. The peritoneal dialysis fluids did not seem to affect the MARD.

FreeStyle Libre had a higher MARD and MAD than Dexcom G5 and there was a greater percentage of values within the safe zone for Dexcom G5. This can partly be explained by the fact that the FreeStyle Libre showed a systematic deviation of -1.1 mmol/L. It is important that users of the system are aware of the systems tendency of reporting lower glucose values. This systematic deviation is not only evident when the sensor is used by people with advanced CKD although it seems to be greater for this patient group[15]. The surveillance error grid showed that only 66% of FreeStyle Libre values were in the no risk zone whilst 82% of Dexcom G5 values were within the no risk zone.
Participants rated the user experience of the FreeStyle Libre significantly higher than for the Dexcom G5. They found the system easier to use and easier to interpret the data on the receiver. The sensor was more comfortable, and it was less painful to insert. There was a greater interest to use the system in their daily life. This might be different with Dexcom's latest sensors which do not require calibration by the user. It is important to note that the users did not experience any difference of safety when using the system.

The strength of this study is that it was done independently from the manufacturers of this study. The study was done in a real-life environment as patients used the sensors in their daily life. All analyses were predefined. The limitations of this study were the short duration the participants used the sensors, and the evaluation of the user experience might change if the users become more comfortable and confident in the use of the sensors, and the questionnaire used is not validated. For certain subgroup analysis the number of participants or values obtained was low, therefore these analyses have to be interpreted with caution. It should be noted that Dexcom G5 was calibrated with the same capillary method as the reference system, and it cannot be excluded that more novel generations of Dexcom sensors which do not need calibrations may have a greater systematic deviation from HemoCue. Neither Dexcom G5 nor FreeStyle Libre are approved to be used by people with advanced chronic kidney disease. Another limitation is that the most novel sensors often used today were not evaluated. However, these data must be viewed in the light that CGM accuracy data are overall lacking in people with Diabetes and advanced CKD and data are therefore urgently needed.

CONCLUSION
In conclusion, this study supports that Dexcom G5 has a similar accuracy in people with diabetes and advanced CKD as in people with diabetes without advanced CKD. The FreeStyle Libre system showed similar correlations between sensor value and blood glucose values as Dexcom, but a lower number of values in the no risk zone indicating that greater caution should be taken to use it in the current population. The FreeStyle Libre showed a systematic deviation at least partly explaining the lower accuracy.

ARTICLE HIGHLIGHTS

Research background
People with diabetes and advanced chronic kidney disease (CKD) often have fluctuating blood glucose levels and today no blood glucose sensors are approved to be used in this patient group.

Research motivation
It is of great importance to give the best possible care to all people with diabetes. This is a patient group with difficult complications due to their diabetes and need all the help they can get.

Research objectives
The objective of this study was to see if the sensors FreeStyle Libre and Dexcom G5 were accurate when used by people with advanced CKD.

Research methods
This was a non-randomized clinical study. The results were evaluated by using mean absolute relative difference as a main analysis. Mean absolute difference and mean difference was also calculated. A surveillance error grid was even used for accuracy evaluations.

Research results
The main analysis found that the Dexcom G5 had a mean absolute relative difference of 15.2% while it was 20.9% for the FreeStyle Libre. There was no significant difference if the patients were on maintenance dialysis or not. There was no significant difference between those with type 1 or 2 diabetes. The surveillance error grid showed that Dexcom G5 had 82% of its values within the safe zone while FreeStyle Libre had 66% within the safe zone.

Research conclusions
The study concludes that the Dexcom G5 produces more accurate values than the FreeStyle Libre.

Research perspectives
This study is a great start for evaluating how we can use glucose sensors for this patient group, but further studies have to be done with more novel glucose sensors.
ACKNOWLEDGEMENTS

We would like to thank Lena Heijdenberg, Mary Dana, and Anders Bergdahl for their involvement in the study and examining participants. We would also like to thank Nils-Gunnar Pehrsson for his assistance in the data analyses and interpretation.

FOOTNOTES

**Author contributions:** Ólafsdóttir AF, Andelin M, and Lind M contributed to the design of this study; Ólafsdóttir AF drafted the manuscript; All authors contributed to the analysis and interpretation of the data, revised the manuscript, and gave final approval of the version to be published.

**Institutional review board statement:** The protocol was approved by the regional ethical review board of Gothenburg.

**Clinical trial registration statement:** The trial is registered on clinicaltrial.gov NCT, No. 03378271.

**Conflict-of-interest statement:** AFO has done consultancy work for Nordic Infucare. SS has done consultancy work for Novo Nordisk, Bayer, Sanofí, and Boehringer Ingelheim ML has received research grants from Ely Lilly and Novonordisk outside the submitted work and personal fees from Astra Zeneca, Boehringer Ingelheim, DexCom, Eli Lilly, MSD and Novonordisk, all outside the current work. AM, AS, HH, and PAJ have no conflict of interest to report.

**Data sharing statement:** All data are available from the corresponding author (AFO) upon a reasonable request.

**CONSORT 2010 statement:** The authors have read the CONSORT 2010 statement, and the manuscript was prepared and revised according to the CONSORT 2010 statement.

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6. Njureregister S. Svenskt Njuregister Årsrapport 20202020. 2021.05.27


Complications of chronic pancreatitis prior to and following surgical treatment: A proposal for classification

Marko Murruste, Ülle Kirsimägi, Karri Kase, Tatjana Veršinina, Peep Talving, Urmas Lepner

Abstract

BACKGROUND
Chronic pancreatitis (CP) is a long-lasting disease frequently associated with complications for which there is no comprehensive pathophysiological classification.

AIM
The aims of this study were to: Propose a pathophysiological classification of the complications of CP; evaluate their prevalence in a surgical cohort prior to, and following surgical management; and assess the impact of the surgical treatment on the occurrence of new complications of CP during follow-up. We hypothesized that optimal surgical treatment can resolve existing complications and reduce the risk of new complications, with the exclusion of pancreatic insufficiency. The primary outcomes were prevalence of complications of CP at baseline (prior to surgical treatment) and occurrence of new complications during follow-up.

METHODS
After institutional review board approval, a prospective observational cohort study with long-term follow-up (up to 20.4 years) was conducted. All consecutive single-center adult patients (≥ 18 years of age) with CP according to the criteria of the American Pancreas Association subjected to surgical management between 1997 and 2021, were included. The prevalence of CP complications evaluated, according to the proposed classification, in a surgical cohort of 166 patients. Development of the pathophysiological classification was based on a literature review on the clinical presentation, course, and complications of CP, as well a review of previous classification systems of CP.

RESULTS
We distinguished four groups of complications: Pancreatic duct complications,
peripancreatic complications, pancreatic hemorrhages, and pancreatic insufficiency (exocrine and endocrine). Their baseline prevalence was 20.5%, 23.5%, 10.2%, 31.3%, and 27.1%, respectively. Surgical treatment was highly effective in avoiding new complications in the first and third groups. In the group of peripancreatic complications, the 15-year Kaplan-Meier prevalence of new complications was 12.1%. The prevalence of pancreatic exocrine and endocrine insufficiency increased during follow-up, being 66.4% and 47.1%, respectively, at 15 years following surgery. Pancreatoduodenal resection resulted optimal results in avoiding new peripancreatic complications, but was associated with the highest rate of pancreatic exocrine insufficiency.

CONCLUSION
The proposed complication classification improves the understanding of CP. It could be beneficial for clinical decision making, as it provides an opportunity for more comprehensive judgement on patient’s needs on the one hand, and on the pros and cons of the treatment under consideration, on the other. The presence of complications of CP and the risk of development of new ones should be among the main determinants of surgical choice.

Key Words: Chronic pancreatitis; Complications; Classification; Pathophysiology; Surgical treatment

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Core Tip: Chronic pancreatitis is frequently associated with complications for which there exists no classification. This study proposes a pathophysiological classification of the complications of chronic pancreatitis (CP) and reports their prevalence in a surgical cohort. We distinguished four groups of complications: Pancreatic duct complications, peripancreatic complications, pancreatic hemorrhages, and pancreatic insufficiency. We believe the proposed classification improves the understanding of CP and could be beneficial for clinical decision making, as it provides an opportunity for more comprehensive judgement on patient’s needs on the one hand, and on the pros and cons of the treatment under consideration, on the other.

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DOI: https://dx.doi.org/10.12998/wjcc.v10.i22.7808

INTRODUCTION
Chronic pancreatitis (CP) is a benign chronic inflammatory damage of the pancreatic gland, with common morphologic features including the triad of fibrosis, loss of the acinar tissue, and ductal changes with highly heterogeneous clinical presentations[1]. The disease may present either with a single, most frequent symptom of CP, i.e. chronic abdominal pain, or as a combination of symptoms encompassing pain, symptoms of loss of pancreatic function and symptoms of local complications of peripancreatic organs[2,3]. Behind the myriad of symptoms, there can be distinct morphological changes of the pancreatic gland and surrounding structures[4]. During the course of the disease, most of the patients suffer from some, or even many, of the complications of CP. Although surgical treatment is usually indicated in the case of intractable abdominal pain, in up to one-third of cases, surgery is indicated mainly due to local complications of CP[5]. Previous systematic reviews have noted that surgery is the best option for the treatment of chronic pancreatic pain, and is effective in the treatment of most complications of CP[6,7]. However, the impact of surgical treatment on occurrence of new complications of CP is not sufficiently evaluated. Furthermore, it would be important to assess which pathophysiological pathways of the complications of CP are most effectively treated surgically and which surgical methods are most effective. A prerequisite for this kind analysis is a pathophysiological classification of the complications of CP. Although the surgical literature offers high-quality descriptions of all known complications of CP and lists of them[8], there are yet no pathophysiological classifications of complications available.

In this study, we proposed this classification comprising the major clinical problems seen in patients with CP. We reported data about the prevalence of the complications in a surgically treated cohort of 166 patients as well as data about the occurrence of new complications of CP during the postoperative period.
MATERIALS AND METHODS

Patients
After institutional review board approval, a prospective observational cohort study with long-term follow-up (up to 20.4 years) was conducted. All consecutive single-center adult patients (≥ 18 years of age) with CP according to the criteria of the American Pancreas Association subjected to surgical management between 1997 and 2021, were included. All patients gave their informed consent.

Aims and outcome
The aims of this study were to: Propose a classification of complications of CP based on the predominant pathophysiological mechanism and clinical presentation, evaluate the prevalence of complications of CP in a surgical cohort; and assess the impact of surgical treatment on the occurrence of new complications of CP during follow-up. We hypothesized that optimal surgical treatment can resolve existing complications and reduce the risk for new complications, with the exclusion of pancreatic insufficiency. The primary outcomes were prevalence of complications of CP at baseline (prior to surgical treatment) and occurrence of new complications during follow-up.

Baseline and follow-up data
Data about the patients’ demographics, indications for surgical treatment, and operative characteristics, as well as about local changes in the pancreatic gland were recorded prospectively after surgical treatment; additional data were retrieved from surgical case files and computed tomography (CT) scan descriptions. CT scan was routinely used in all cases. CP-associated data comprised duration and etiology of CP, data on pancreatic function, and local changes in the pancreatic gland. All data about complications of CP occurring before surgical treatment and during follow-up were collected. The patients were followed up from surgical treatment until the end of the study (August 31, 2021) or until death. No patients were lost during follow-up. Additional health-related data were obtained from hospital case files, from the National Electronic Health Database (E-health), and from general practitioners’ reports.

Statistics
Collected data were entered in a computerized database (Microsoft Access 2016, Microsoft Inc., Redmond, WA, United States). The main characteristics are presented as the mean ± SD or the median with interquartile range as appropriate. The prevalence of the complications of CP was assessed according to the proposed pathophysiological classification. Complication-free survival was characterized using the Kaplan-Meier method. The impact of surgical treatment on the occurrence of new complications during the postoperative period was assessed using the Kaplan-Meier method. The log-rank test was deployed to assess differences between the Kaplan-Meier curves. The software package Statistica version 13.3 (TIBCO Software, Palo Alto, CA, United States) was utilized for statistical calculations.

Classification of complications of CP
All pathological changes of CP were divided into three groups: Cardinal histological features of CP (microscopic changes), common anatomical changes seen in pancreatic imaging (macroscopic changes), and complications of CP.

Histological features of CP–microscopic changes: The main microscopic features, or so-called ‘triad of CP’, were defined by Klöppel and Kleeff et al. as progressive irreversible loss of acinar tissue (atrophy), its replacement by fibrotic tissue, and changes of the pancreatic duct (PD, atrophic epithelium, protein plugs, distortions). However, clinical decision making usually has to be done without histological confirmation of CP. Given the potential for complications, pancreatic biopsy is not indicated for proving the diagnosis of CP. Thus, diagnosis is usually based on a typical history of CP and radiological finding. The only indication for pancreatic biopsy is in suspected malignancy or autoimmune pancreatitis.

Common anatomical changes in pancreatic imaging–macroscopic changes: The second group of pathological changes was defined as macroscopic abnormalities of the pancreatic gland and ducts that are commonly seen in pancreatic imaging. Four distinguished findings of CP were noted: Pancreatic calcifications, pancreatic ductal changes (dilatations and strictures of PD; dilated PD was defined as PD with a diameter ≥ 3.5 mm); pancreatic head enlargement (chronic inflammatory mass or pancreatic pseudotumor, defined as antero-posterior diameter of the pancreatic head > 35 mm), and pancreatic atrophy (defined as a thickness of the pancreas ≤ 20 mm in the left vertebral margin). Although the magnitude of these changes may significantly vary, none of them (if asymptomatic) is an indication for any type of treatment, as there is currently no known therapy to reverse or stop the progression of chronic inflammation in the pancreatic gland. Clinical management primarily consists of screening for and treating complications.
Complications of CP—changes with clinical relevance: The third group of pathological changes of CP was titled ‘complications of CP’ due to association with more or less severe clinical signs and symptoms. According to predominant pathophysiology and associated clinical presentation, we distinguished four groups of complications: PD complications, peripancreatic complications, pancreatic hemorrhages, and pancreatic insufficiency (Figure 1). Figure 2 shows a schematic illustration of the main complications of CP.

Group I: PD complications

Main pathophysiology: This particular group consists of complications caused by obstruction of PD by calcifications, protein plugs and/or periductal fibrosis, followed by intraductal hypertension and disruption of the main PD or its branches[15,16]. PD disruption results in the development of pancreatic pseudocysts (PPC) or leakage of pancreatic secretions, and hence to the development of various types of pancreatic fistulas (PF)[17]. The source of PF can be leakage directly from a rupture of the PD, or more frequently, leakage from a ruptured PPC. In the case of pancreatic ascites, pancreatic secretions leak into the abdominal cavity. In the case of pancreaticopleural fistula, pancreatic secretion flows through the retroperitoneum via the area of least resistance into the pleural cavity, usually through the esophageal hiatus. The tract of fistula directly through the diaphragm has also been described[18].

Prevalence and main clinical problems: PPC are common complications of CP, with a reported prevalence as high as 10%-40%[19,20]. Most of the small PPC are asymptomatic and do not need any treatment. Clinical presentation tends to occur if some of the secondary complications of PPC, such as bleeding, rupture or infection, evolve[21]. Additionally, large PPC can alone, through compression or in conjunction with underlying CP, lead to obstruction of the lumen of adjacent organs (biliary tract, gastric outlet, and peripancreatic veins)[22]. All secondary complications of PPC can occur throughout the clinical course, and if present, usually do need active treatment[20]. Although the complications of PPC and related clinical presentation can be diverse and dependent on the localization and size of PPC, patients most frequently present with abdominal pain[23].

Despite the fact that PF are relatively rare, the gross prevalence of various types of PF is reportedly as high as 3.5%[24,25]. Pancreatocorporitoneal fistulas with a prevalence of 2% (leading to pancreatic ascites) and pancreatopleural fistulas with a prevalence of 1% (leading to pancreatic pleural effusions) are more common[26,27]. Both of them need PD decompression; in most cases endoscopic stenting of PD is sufficient[19]. Pancreatocogastric or intestinal fistulas, which may appear as symptomless findings in endoscopic evaluation, are rarer. Pancreatocutaneous fistulas are usually the consequence of previous percutaneous drainages of PPC or pancreatic fluid collections, and may lead to significant loss of pancreatic juice and local skin problems. Pancreatocopericardial fistulas (leading to pancreatic pericardial effusion) and pancreaticocutaneous fistulas (leading usually to portal thrombosis with following consequences) are casuistic[28,29].

Group II: Peripancreatic complications

Main pathophysiology: The second group of complications comprises obstructive complications of organs adjacent to the pancreas (biliary tract, duodenum and major peripancreatic veins). Although the particulars of the process of the development of these obstructions are slightly different, it is hypothesized that obstructive complications occur mainly as a consequence of recurrent episodes of acute pancreatitis, which may ultimately result in fibrosis and scarring within and around the pancreatic gland[30,31]. An additional contributing factor to obstruction can be PPC, especially in the region of the pancreatic head[32]. Duodenal obstruction usually occurs in the second or third part of the duodenum[33]. It has been suggested that an underlying mechanism in its evolution is duodenal ischemia caused by arterial narrowing and thrombosis in the region of inflammatory mass in the pancreatic head[34]. An uncommon form of CP is groove pancreatitis or paraduodenal pancreatitis characterized by inflammation in the ‘groove’ between the duodenal wall and the pancreatic head[35]. The pathophysiology of this particular condition remains unclear, despite many suggested theories[36]. Among the various pathological findings of groove pancreatitis, fibroinflammatory process in the pancreatiduodenal groove has been described as the only consistent finding in this disease[37]. Groove pancreatitis is more common in middle-aged men and is strongly associated with history of alcohol consumption and tobacco smoking[38].

Prevalence and main clinical problems: Biliary strictures in patients with CP are relatively common with a prevalence of 3% to 23% and a mean of 6%[39]. Some patients with biliary obstruction may be asymptomatic and have only modestly deranged liver function tests[40]. However, common bile duct obstruction may lead to jaundice, persistent cholestasis, acute cholangitis, and secondary biliary cirrhosis[41]. Timely treatment of symptomatic strictures is required to prevent these secondary complications[40].

Duodenal obstruction is much rarer, with a prevalence of 0.5% to 13% and a mean of 1.2%[39]. Patients usually present with symptoms of gastric outlet obstruction such as vomiting, fluid and electrolyte imbalance, and weight loss.
Figure 1 Pathophysiological classification of complications of chronic pancreatitis. [1]References to the rates of prevalence. PEI: Pancreatic exocrine insufficiency; T3cDM: Type 3c diabetes mellitus.

The prevalence of major peripancreatic vein thrombosis varies from 10.9% to 22.0% with a pooled prevalence of 11.6% [42,43]. Splenic vein is mainly involved (up to 80.6%), followed by portal vein. Splenic vein thrombosis leads to left-side portal hypertension; these patients are at risk of development of gastric varices, splenomegaly, and severe variceal bleeding, which reportedly occurs in 4%-17% of all cases [44]. Several other splenic complications such as spontaneous splenic rupture, intrasplenic PPC, and splenic infraction have also been reported, but their prevalence remains well below 1% [45].

**Group III: Pancreatic hemorrhages**

Main pathophysiology: The third group of complications comprises all pancreatic hemorrhages due to the erosion of major intra and peripancreatic vessels, mainly arteries. Local inflammation, possibly combined with local release of pancreatic enzymes, pressure necrosis from ductal calcifications, and PPC may result in either pseudoaneurysm (PA) formation or bleeding into pre-existing PPC, which transforms PPC into PA [46,47].

Prevalence and main clinical problems: Although pancreatic bleeding in patients with CP is considered uncommon, the prevalence among in-patient cohorts is reportedly 4.6% to 7.7% [48,49]. Splenic artery is the most commonly involved vessel, followed by gastroduodenal and pancreaticoduodenal arteries [31,50]. As severity of blood loss and patients’ hemodynamical status depend on the rupture of PA, it is important from the clinical point of view distinguish between non-ruptured (contained PA) and ruptured PA. Patients with non-ruptured PA have the best prognosis, as blood loss is relatively small and the effect of self-tamponade can provide spontaneous hemostasis [51]. Usually, these patients present with abdominal pain combined with symptoms of moderate blood loss, or sometimes even without the latter. Radiological imaging is essential to establish the diagnosis. Diagnosis of PA is usually made on the basis of abdominal contrast-enhanced CT (CECT) scan done for evaluation of the etiology of abdominal pain [42].

Almost two-thirds of patients with PA have ruptured PA that is associated with much more severe hemorrhage and often with shock [48]. The most common site of rupture is the gastrointestinal tract (GIT), presenting as acute upper GIT bleeding with hematemesis and/or melena [52]. Rarely, PA can rupture into the PD and further into GIT through the papilla of Vater, leading to hemosuccus pancreaticus [53]. In most cases, this condition is associated with diagnostic difficulties because of the concealed source of bleeding. Correct diagnosis is commonly made only after many episodes of bleedings and
Main complications of chronic pancreatitis. (1) Pancreatic duct complications: 1-A: Pancreatic pseudocyst; 1-B: Pancreatic ascites; 1-C: Pancreatic pleural effusion; (2) Peripancreatic complications: 2-A: Common bile duct stenosis; 2-B: Duodenal stenosis; 2-C: Venous thrombosis (spleenic vein); 2-D: Left-side portal hypertension due to splenic vein thrombosis; (3) Pancreatic hemmorhages: 3-A: Peripancreatic pseudoaneurysm; 3-B: Ruptured pseudoaneurysm (into pancreatic duct–hemosuccus pancreaticus); and (4) Pancreatic exocrine and endocrine insufficiency due to extensive loss of functional pancreatic parenchyma (acinar atrophy, fibrosis, inflammatory infiltrates).

numerous endoscopic evaluations and CECT scans. High index of suspicion should arise if the triad of symptoms i.e. GIT bleeding, abdominal pain and hyperamylasemia, is present[47]. The two other possible sites of PA rupture are the abdominal cavity, presenting as massive intrabdominal hemorrhage, and the retroperitoneum, presenting as retroperitoneal hematoma[54,55]. Acute GIT hemorrhages in patients with CP, which are not directly associated with CP (e.g., variceal bleeding, peptic ulcer bleeding, Mallory-Weiss syndrome), are not included in this group of complications.

Group IV: Pancreatic insufficiency
Main pathophysiology: The fourth group represents complications due to extensive loss of the functioning pancreatic parenchyma, leading to pancreatic exocrine and endocrine insufficiency.

Prevalence and main clinical problems: As damage to the pancreatic tissue is a continuous process throughout the course of the disease, the prevalence of pancreatic exocrine insufficiency (PEI) in patients with CP increases steadily with times, being from 20% in early CP to 94% in the late phase of the disease[56,57]. Long duration of CP (> 30 years) is associated with > 80% prevalence of PEI[58]. Patients’ main complaints are steatorrhea, weight loss, flatulence, and abdominal discomfort. If untreated, the deficit of fat-soluble vitamins may lead to secondary complications (osteoporosis, fractures, immunodeficiency, and infections)[59].

Diabetes mellitus (DM) secondary to pancreatic diseases or pancreatic surgery is classified as pancreatogenic diabetes or type 3c DM (T3cDM) according to the current classification of DM[60]. The prevalence of DM in CP is between 25% and 80%[61,62]. Similar to PEI, T3cDM shows a clear correlation with duration of CP. In CP patients with associated T3cDM, blood glucose control may be complicated due to the loss of glucagon response to hypoglycemia, food malabsorption, and irregular eating patterns because of debilitating pain and/or continuous alcohol abuse[63].

The proposed classification does not include infectious complications of CP. The authors of the classification believe that infectious complications are mainly caused by exacerbations of pancreatitis: ‘Acute’ or ‘acute on chronic’ pancreatitis. Secondary complications are also excluded. Although it is well known that all complications of CP can lead to secondary complications (e.g., biliary obstruction to cholangitis or biliary cirrhosis; duodenal obstruction to fluid and electrolytes imbalance; portal hypertension to bleeding from esophageal varices; PEI to osteopathy; diabetes to possible decompensation of etc), they
remain beyond the scope of this classification.

RESULTS

Patients and surgical treatment

All surgically treated CP patients, operated on at a single referral hospital between 1997 and 2021, were prospectively enrolled. A total of 166 patients were subjected to surgical management due to chronic pain or local complications of CP. The average rate of surgical treatment of CP was 18.1% from all patients admitted due to CP. The mean age of the patients was 49.8 ± 9.9 years; there were 140 males (84.3%) and 26 females (Table 1). In 148 patients (89.2%), CP was alcohol-induced; in the remaining cases, the etiology was idiopathic or rare causes. The median duration of symptomatic CP before surgical treatment was 18 mo.

Similar to a previous study[64], the most common indication for surgical treatment was chronic abdominal pain, being the predominant indication in 112 cases (67.5%). Local complications of CP were the predominant indication for surgical treatment in 54 cases (32.5%). However, almost half of the patients (81 patients, 48.8%) had had at least one local complication of CP before surgical treatment. The clinical relevance of these was highly variable (from asymptomatic PPC to ruptured PA). Ten patients (6.0%) had more than one local complication. Besides local anatomical complications, 52 patients (31.3%) had PEI and 45 patients (27.1%) had T3cDM prior to surgical treatment. Surgical treatment was pancreatic resection in 60 cases (36.2%), pancreatic drainage operation in 93 cases (56.0%), and extrapancreatic palliative procedure in 13 cases (7.8%; Table 2). There was no perioperative mortality. Cumulative Kaplan-Meier 10-year survival and median survival were 70.4% and 13.9 years, respectively. Median follow-up was 7.2 years. During follow-up 12 patients required secondary surgery, mostly due to emerged new local complications of CP (predominantly biliary stenosis).

Prevalence of complications of CP prior to, and following surgical treatment

The impact of surgical treatment on the occurrence of the de novo complications of CP during postoperative years was assessed according to the above proposed pathophysiological classification of complications of CP (Figure 1). The prevalence of PD complications was at baseline (before surgical treatment of CP) 20.5% (Figure 3); 10.8% of the patients had PPC, and 9.6% had various types of PF (Table 3). Endoscopic PD stenting precedes to surgical therapy in two out of 16 patients (12.5%) with PF. Further surgical treatment was undertaken due to continuous PD leakage. Surgical treatment demonstrated high effectiveness in decompressing PD, with very low risk of new ‘PD complications’ during follow-up (only one new PPC developed).

Peripancreatic complications showed a baseline prevalence of 23.5% (39 patients); 3 patients had concurrent biliary tract and duodenal or venous obstruction. The most common complication was biliary tract obstruction with 29 cases (17.5%), 8 patients had duodenal obstruction (4.8%) and venous occlusion was seen in 5 patients (3.0%). Endoscopic common bile stenting precedes to surgical therapy in 18 of 29 cases (62.1%) of patients with common bile duct stenosis. Further surgical treatment was indicated because of unsuccessful endoscopic treatment (defined as inconsistent effect of endoscopic stenting. During follow-up 13 new complications were documented in 11 patients, which resulted in a 15-year Kaplan-Meier prevalence of 12.1% of new peripancreatic complications. The total 15-year prevalence of peripancreatic complications was 35.6%. The most common among them was biliary tract obstruction (8 patients), followed by venous thrombosis (4 patients) and duodenal obstruction in 1 case. Five patients with biliary stenosis were managed via endoscopic stenting, and the remaining 3 patients needed secondary surgery.

As the occurrence of new complications requiring retreatment is a major drawback, we re-evaluated the distribution of these complications by the surgical subgroups depending on the type of surgical procedure applied. Analysis was performed for three subgroups: Pancreatic drainage operations, pancreatic resections (excluding Whipple’s procedure), and Whipple’s pancreaticoduodenal resection as the only procedure incorporating new biliary and gastric bypasses (Table 4).

The analysis revealed differences in the occurrence of new peripancreatic complications. No new complications appeared in the group of Whipple’s procedure (11 patients); among the other types of pancreatic resections (49 patients), five complications occurred and in the group of pancreatic drainage operations (93 patients), there were eight complications. The 15-year Kaplan-Meier prevalence of peripancreatic complications following surgical treatment of CP was 0%, 11.4%, and 16.5%, respectively (Figure 4A).

The baseline prevalence of pancreatic hemorrhages was 10.2% (17 patients). There were 10 cases (58.8%) of ruptured pancreatic PA and 7 cases of contained PA. Ruptured PA presented as an acute life-threatening intraabdominal hemorrhage in 2 cases and as an acute recurrent gastrointestinal hemorrhage in 8 cases: Fistulation into GIT occurred in 6 cases and into PD, in 2 cases (hemosuccus pancreaties). All patients with ruptured PA were treated via pancreatic resection. All but 1 patient with contained PA underwent intra-aneurysmatic hemostasis and a pancreatic drainage procedure. In 1 case, the affected part of pancreas was resected. Surgical treatment of pancreatic hemorrhages was highly...
Table 1 Characteristics of the surgically treated patients with chronic pancreatitis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients, n = 166</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in yr</td>
<td>49.8 ± 9.9</td>
</tr>
<tr>
<td>Duration of CP before surgery, median (IQR)</td>
<td>1.5 (0.5–3.0)</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>140 (84.3)</td>
</tr>
<tr>
<td>Etiology of CP, n (%)</td>
<td></td>
</tr>
<tr>
<td>Alcoholic</td>
<td>148 (89.2)</td>
</tr>
<tr>
<td>Other</td>
<td>18 (10.8)</td>
</tr>
<tr>
<td>Predominant indication for surgery, n (%)</td>
<td></td>
</tr>
<tr>
<td>Chronic pain</td>
<td>112 (67.5)</td>
</tr>
<tr>
<td>Complications of CP 1</td>
<td>54 (32.5)</td>
</tr>
<tr>
<td>Follow-up (yr), median (IQR)</td>
<td>7.2 (3.8–10.8)</td>
</tr>
<tr>
<td>Long-term survival (Kaplan-Meier), (95% CI)</td>
<td></td>
</tr>
<tr>
<td>1 yr</td>
<td>100</td>
</tr>
<tr>
<td>5 yr</td>
<td>88.2 (83.0–93.5)</td>
</tr>
<tr>
<td>10 yr</td>
<td>70.4 (61.7–79.1)</td>
</tr>
<tr>
<td>15 yr</td>
<td>41.2 (27.4–55.1)</td>
</tr>
<tr>
<td>Median survival in yr</td>
<td>13.9</td>
</tr>
</tbody>
</table>

1In many cases, patients had also more or less intense abdominal pain.

Data are presented as mean ± SD, unless otherwise specified. CI: Confidence interval; CP: Chronic pancreatitis; IQR: Interquartile range; SD: Standard deviation.

Table 2 Surgical treatment of 166 patients with chronic pancreatitis

<table>
<thead>
<tr>
<th>Type of surgery</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatic resection</td>
<td>60 (36.2)</td>
</tr>
<tr>
<td>Pancreatoduodenal resection (Whipple procedure)</td>
<td>11</td>
</tr>
<tr>
<td>DPPHR (Beger or Berne or Frey procedure)</td>
<td>34</td>
</tr>
<tr>
<td>Pancreatic distal resection</td>
<td>15</td>
</tr>
<tr>
<td>Pancreatic drainage operation</td>
<td>93 (56.0)</td>
</tr>
<tr>
<td>Pancreatecojejunostomy (Partington-Rochelle)</td>
<td>93</td>
</tr>
<tr>
<td>Palliative procedures</td>
<td>13 (7.8)</td>
</tr>
<tr>
<td>Biliointestinal anastomosis</td>
<td>11</td>
</tr>
<tr>
<td>Gastrointestinal anastomosis</td>
<td>2</td>
</tr>
</tbody>
</table>

DPPHR: Duodenum-preserving pancreatic head resection.

effective: There were no recurring hemorrhages among patients with PA, nor were there new hemorrhages among the entire surgically treated cohort, regardless of the indication for surgical treatment of CP.

Pancreatic insufficiency was evaluated for two subgroups: PEI and T3cDM. Prior to surgical treatment, 73 patients (44.0%) had one of these or both. The prevalence of PEI was 31.3% (52 patients) and the prevalence of T3cDM was 27.1% (45 patients). During follow-up, a steady and almost synchronous increase in both complications was evident, resulting in a 15-year Kaplan-Meier prevalence of 66.4% and 47.1%, respectively. The 15-year Kaplan-Meier prevalence of either exocrine or endocrine insufficiency was 74.5%.

Re-evaluation of the development of pancreatic insufficiency was performed for the surgical subgroups depending on the type of surgical procedure. The highest rate of new cases of PEI was seen
Table 3 Baseline and 15-yr Kaplan-Meier prevalence of complications of chronic pancreatitis in a surgically treated cohort of 166 patients

<table>
<thead>
<tr>
<th>Complications</th>
<th>Baseline, n (%)</th>
<th>15-yr, Kaplan-Meier, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatic duct complications</td>
<td>34</td>
<td>20.5</td>
</tr>
<tr>
<td>Pancreatic pseudocysts</td>
<td>18</td>
<td>10.8</td>
</tr>
<tr>
<td>Pancreatic fistulas</td>
<td>16</td>
<td>9.6</td>
</tr>
<tr>
<td>Pancreaticocutaneous (pancreatic anc)</td>
<td>4</td>
<td>2.4</td>
</tr>
<tr>
<td>Pancreaticopleural (pancreatic pleural effusion)</td>
<td>5</td>
<td>3.0</td>
</tr>
<tr>
<td>Other (mostly pancreaticocutaneous)</td>
<td>6</td>
<td>4.2</td>
</tr>
<tr>
<td>Peripancreatic complications</td>
<td>39¹</td>
<td>23.5</td>
</tr>
<tr>
<td>Bile duct obstruction</td>
<td>29</td>
<td>17.5</td>
</tr>
<tr>
<td>Duodenal obstruction</td>
<td>8</td>
<td>4.8</td>
</tr>
<tr>
<td>Venous thrombosis (spleenic or portal vein)</td>
<td>5</td>
<td>3.0</td>
</tr>
<tr>
<td>Pancreatic hemorrhages</td>
<td>17</td>
<td>10.2</td>
</tr>
<tr>
<td>Contained pseudoaneurysms</td>
<td>7</td>
<td>4.2</td>
</tr>
<tr>
<td>Ruptured pseudoaneurysms into</td>
<td>10</td>
<td>6.0</td>
</tr>
<tr>
<td>Abdominal cavity</td>
<td>2</td>
<td>1.2</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>6</td>
<td>3.6</td>
</tr>
<tr>
<td>Pancreatic duct</td>
<td>2</td>
<td>1.2</td>
</tr>
<tr>
<td>Pancreatic exocrine insufficiency–PEI</td>
<td>52</td>
<td>31.3</td>
</tr>
<tr>
<td>Pancreatic endocrine insufficiency–T3cDM</td>
<td>45</td>
<td>27.1</td>
</tr>
</tbody>
</table>

¹Three patients had two concurrent complications at baseline. PEI: Pancreatic exocrine insufficiency; T3cDM: Type 3c diabetes mellitus.

DISCUSSION

This study proposed a new pathophysiological classification of complications of CP, reported their prevalence in a surgically treated cohort, and assessed the impact of surgical treatment on occurrence of new complications during the further course of the disease. As there is currently no treatment to reverse or delay disease progression in CP, clinical management consists primarily of screening for and treating of complications[3]. The most effective treatment of complications is pathophysiological treatment. The proposed classification allows the easy determination of the predominant pathophysiologic mechanism. This could be beneficial for clinical decision making, as it provides an opportunity for more comprehensive judgement on patient’s needs on the one hand, and on the pros and cons of the treatment under consideration, on the other. Moreover, this classification could be used as an instrument for quality improvement in the treatment of CP. We strongly believe that the potential of any treatment to avoid further complications of CP would serve, besides known indicators of quality of treatment (e.g., pain relief, quality of life), as an additional relevant indicator.

The goal of the surgical treatment of CP is usually to decompress PD or to resect the nidus of chronic inflammation, and to eliminate local complications of CP. In our study, the clinical impact of surgical treatment on different complications of CP was highly variable and clearly dependent on the underlying predominant pathophysiological mechanism. The first group of complications (PD complications) were effectively treated by pancreatic drainage operations, as well as by pancreaticojejunostomies created during pancreatic resection. The achieved effect was long lasting over time: Only 1 PPC developed during follow-up vs 34 preoperative complications. Unfortunately, we failed to find previous data about
Table 4 Distribution of complications of chronic pancreatitis according to the used type of surgical procedure prior to surgical
treatment, and appearance of new complications during follow-up, in 166 surgically treated patients

<table>
<thead>
<tr>
<th>Classification</th>
<th>Type of surgical procedure, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PD resection, n = 11</td>
</tr>
<tr>
<td>Complications, n (%)</td>
<td></td>
</tr>
<tr>
<td><strong>Pancreatic duct complications</strong></td>
<td></td>
</tr>
<tr>
<td>Preoperative cases</td>
<td>1 (9.1)</td>
</tr>
<tr>
<td>New cases, FU</td>
<td>-</td>
</tr>
<tr>
<td><strong>Peripancreatic complications</strong></td>
<td>6 (54.5)</td>
</tr>
<tr>
<td>Preoperative cases</td>
<td>6</td>
</tr>
<tr>
<td>New cases, FU</td>
<td>-</td>
</tr>
<tr>
<td><strong>Pancreatic hemorrhages</strong></td>
<td>1 (9.1)</td>
</tr>
<tr>
<td>Preoperative cases</td>
<td>1</td>
</tr>
<tr>
<td>New cases, FU</td>
<td>-</td>
</tr>
<tr>
<td><strong>PEI</strong></td>
<td>8 (72.7)</td>
</tr>
<tr>
<td>Preoperative cases</td>
<td>1</td>
</tr>
<tr>
<td>New cases, FU</td>
<td>7</td>
</tr>
<tr>
<td><strong>T3cDM</strong></td>
<td>3 (27.3)</td>
</tr>
<tr>
<td>Preoperative cases</td>
<td>1</td>
</tr>
<tr>
<td>New cases, FU</td>
<td>2</td>
</tr>
</tbody>
</table>

1Three patients had simultaneously two peripancreatic complications. DPPHR: Duodenum-preserving pancreatic head resection; FU: Follow up; PD: Pancreatoduodenal resection; P: Pancreatic; PEI: Pancreatic exocrine insufficiency; T3cDM: Type 3c diabetes mellitus.

The recurrence rate of PPC or PF after PD drainage for comparison. Less radical treatment modalities, e.g., anastomoses with PPC and endoscopic drainage, have shown relatively high rate of recurrence. According to Ye et al [65], the recurrence rate of PPC was 11.2% after pseudocystojejunostomy and 7.5% after pseudocystogastrostomy, with an average follow-up of 42.7 mo [65]. However, the authors did not provide data about the etiology of the PPC (acute or chronic pancreatitis). Endoscopic treatment seems to be associated with a higher recurrence rate: Rückert et al [66] reported a recurrence rate of 23.3% after endoscopic drainage during 42.2 mo of follow-up and underlined the high recurrence risk of CP-associated PPC [66]. Farias et al [67] compared endoscopic and surgical drainage (mainly via pseudocystogastrostomy) of PPC in a meta-analysis and found no significant difference in their recurrence rates [67]. Our data support surgical decompression of PD in the case of CP-provoked PPC and PF. High effectiveness of surgical decompression is attributable to the most radical relief of main pathology (PD obstruction and intraductal hypertention).

The impact of surgical treatment on peripancreatic complications revealed significant dependency on the surgical method used. During follow-up, there were no new complications in the Whipple’s procedure group, which can be explained by the nature of this procedure (creation of new bilioenteric and gastroenteric anastomoses). After the other surgical procedures (pancreatic drainage operations and non-Whipple’s pancreatic resections, mostly Beger or Berne modifications of pancreatic head resection, and pancreatic tail resection, new peripancreatic complications developed, which necessitated readmissions and reoperations. In most cases, there were biliary strictures (8 patients) and venous thrombosis of SV or PV (4 patients); 1 patient developed duodenal obstruction. The causes of new peripancreatic complications in the postoperative period can be variable. It seems that among the predominant causes are further development of the fibrotic tissue and the process of scarring within and around the pancreas. This theory is indirectly supported by the results of endoscopic stenting of CP-associated biliary strictures. Several studies have found that long-lasting stenting (10-12 mo) is more effective than short-term therapy (3-6 mo), indicating persistent fibrosis and scarring [68,69]. The present study showed that biliary strictures can occur even many years after surgical treatment of CP. In these cases, exacerbations of CP, whether clinical or subclinical, might be responsible, as they are associated with additional extrinsic compression due to edema or development of PPC in the region of the
pancreatic head[70]. The ability to avoid new peripancreatic complications is one of the obvious advantages of Whipple’s procedure in the treatment of CP, as reported earlier by Diener et al[71] in the ChroPac trial and by Müller et al[72]. Whether this advantage of the Whipple’s procedure is sufficient to prefer this operation to other surgical options remains a subject of discussion. In fact, Whipple’s operation also has disadvantages, such as longer operating time, and according to most studies, higher perioperative morbidity and mortality, and higher rate of postoperative PEI.

The third group of complications (pancreatic hemorrhage) is associated with the poorest prognosis. Even with prompt diagnosis and immediate therapy, the mortality rate reported in earlier studies is 15% to 50%[73]. In the past two decades, due to the enormous improvement in radiological techniques and instrumentation, angiographic treatment as the first-line therapy has been widely employed to stop bleeding from visceral PA in hemodynamically stable patients. In a recent meta-analysis Sagar et al[74] reported a technical success rate of 88%, a clinical success rate of 86%, a rebleeding rate of 16.3%, and a mortality rate of 8% for endovascular therapy[74]. Surgical treatment is reserved for patients in whom vascular interventional therapy has failed or is not accessible, as well as in those with unstable vital signs; during the study period we had 17 such patients. Our surgical approach was relatively radical. In cases of recurrent GIT bleeding from the fistulation of PA and ineffective endovascular therapy, or in cases of ongoing bleeding in an unstable patient, surgical treatment always consisted in resection of the affected area of the pancreas.

In most such cases, pancreatic tail resection was performed (8 cases), as hemorrhages emerged from the splenic artery, but in 2 cases pancreatic head resection was necessary. In cases of contained PA, the treatment of choice was intra-aneurysmatic hemostasis followed by pancreatic drainage operation. This approach resulted in a highly effective treatment result; there were no recurrent pancreatic hemorrhages in our cohort during follow-up (median 7.2 years). As re-bleedings occurred after surgery in our cohort and we managed to achieve zero perioperative mortality, we are convinced that surgical therapy remains an important highly effective treatment modality for patients with pancreatic hemorrhage. In unstable patients, surgery should be the first-line therapy; in hemodynamically stable patients, surgery should be indicated in cases of unsuccessful endovascular therapy, as the next step of treatment.

Besides effective treatment of pancreatic hemorrhages, surgical therapy demonstrated the potential to avoid pancreatic hemorrhages; there were no episodes of pancreatic hemorrhage during follow-up in the entire surgically treated cohort. One explanation of this might be the beneficial effect of PD decompression: Previous studies have revealed PPC as the most important risk factor for development of PA and pancreatic hemorrhage[42]. Regarding occurrence of chronic PPC, which usually precedes PD obstruction and intraductal hypertension[75], surgical PD decompression has a preventive effect on development of PPC, as well as on its transformation into PA.
Figure 4 Kaplan-Meier curves of complication-free survival characterizing the impact of the type of surgery on occurrence of the new complications of chronic pancreatitis. The log-rank test was used to assess differences between the curves. A: Peripancreatic complications (Whipple’s pancreatoduodenal resection–red line, other pancreatic resections–blue line, pancreatic drainage operations–green line); B: Pancreatic exocrine insufficiency (Whipple’s pancreatoduodenal resection–red line, other pancreatic resections–blue line, pancreatic drainage operations–green line); C: Pancreatic endocrine insufficiency (pancreatic distal resection–orange line, other pancreatic resections–blue line, pancreatic drainage operations–green line).

The fourth group of complications (pancreatic insufficiency) showed continuous steady deterioration of pancreatic function. A similar result, i.e. impairment of pancreatic function over time, has been repeatedly demonstrated earlier, most recently by Kempeneers et al[76], on the basis of data from the Dutch Chronic Pancreatitis Registry[272]. Comparison of the surgical options revealed higher rate of PEI after Whipple’s pancreatoduodenal resection (compared to the other types of surgery) and slightly higher rate of T3cDM in the group of pancreatic tail resection.

Several studies have found that early surgery could be beneficial in terms of slowing impairment of pancreatic function[77,78]. The data of the present study are insufficient to provide any additional information regarding this effect, as our patients were clearly not ‘early cases’ of CP. An important contribution to the understanding of complications of CP was made by a study of Olesen et al[79]’s. The cluster analysis used by these authors distinguished between inflammatory, fibrotic and functional complications and they assessed association between clusters and etiological risks. The present pathophysiological classification is aimed at facilitating clinical decision-making; e.g., should one eliminate PD problems vs peripancreatic problems vs pancreatic hemorrhage vs treat pancreatic insufficiency?

Based on pathophysiological grouping, our analysis shows that there exist no ideal surgical options suitable for all cases of CP. Nevertheless, despite the lack of evidence supporting the universal superiority of any available surgical procedure, it is obvious that each of them has its own specific advantages. Thus, the choice of the surgical procedure should proceed from at least four aspects; predominant indication for surgery; anatomical changes of the pancreatic gland; presence and entity of local complications of CP; and procedure-specific risks of surgery (immediate and long-term). This is consistent with the conclusion by Frola et al[80] according to which a tailored approach to CP patients is mandatory[80].

Limitations
Our center is a tertiary care referral center and hence the prevalence of complications of CP may be an overestimation.
CONCLUSION

The proposed complication classification improves the understanding of CP. It could be beneficial for clinical decision making, as it provides an opportunity for more comprehensive judgement on patient’s needs on the one hand, and on the pros and cons of the treatment under consideration, on the other. Existing complications of CP and the risk for development of new complications should be among the main determinants of surgical choice.

ARTICLE HIGHLIGHTS

Research background
Chronic pancreatitis (CP) is a long-lasting disease frequently associated with complications for which there exists so far no comprehensive pathophysiological classification.

Research motivation
The motivation of present study was: To propose a pathophysiological classification of the complications of CP; evaluate their prevalence in a surgical cohort prior to, and following surgical management; and assess the impact of the surgical treatment on the occurrence of new complications of CP during follow-up.

Research objectives
To describe the full diversity of severe complications of CP seen in our cohort during 20 years of study using proposed classification of complications of CP; and to assess the impact of surgical treatment on the development of new complications during follow-up.

Research methods
After institutional review board approval, a prospective observational cohort study with long-term follow-up (up to 20.4 years) was conducted. All consecutive single-center adult patients (≥ 18 years of age) with CP according to the criteria of the American Pancreas Association subjected to surgical management between 1997 and 2021, were included. The prevalence of the complications of CP was evaluated, according to the proposed classification, in a surgical cohort of 166 patients.

Research results
We distinguished four groups of complications: Pancreatic duct complications, peripancreatic complications, pancreatic hemorrhages, and pancreatic insufficiency (exocrine and endocrine). Their baseline prevalence was 20.5%, 23.5%, 10.2%, 31.3% and 27.1%, respectively. Surgical treatment was highly effective in avoiding new complications in the first and third groups. In the group of peripancreatic complications, the 15-year Kaplan-Meier prevalence of new complications was 12.1%. The prevalence of pancreatic exocrine and endocrine insufficiency increased during follow-up, being 66.4% and 47.1%, respectively, 15 years following surgery.

Research conclusions
The proposed complication classification improves the understanding of CP. It could be beneficial for clinical decision making, as it provides an opportunity for more comprehensive judgement on patient’s needs on the one hand, and on the pros and cons of the treatment under consideration, on the other. The presence of the complications of CP and the risk of development of new ones should be among main determinants of surgical choice.

Research perspectives
It would be interesting to compare the effectiveness of the surgical and endoscopic treatment of complications of CP using our proposed classification.

FOOTNOTES

Author contributions: Murruste M, Kirsimägi Ü, Kase K, Veršinina T, Talving P, and Lepner U designed the study; Murruste M, Kirsimägi Ü, Kase K, and Veršinina T performed the study; Murruste M and Kirsimägi Ü produced the statistics and wrote the paper.

Institutional review board statement: The study was reviewed and approved by the University of Tartu (UT REC) Institutional Review Board, No. 291/T-1.
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Effects of comprehensive nursing on postoperative complications, mental status and quality of life in patients with glioma

Heng Dong, Xiao-Li Zhang, Chun-Xiang Deng, Bo Luo

BACKGROUND
The complexity and refractory of brain glioma requires treatment that should involve a multidisciplinary approach to improve quality of care and fulfill patients' needs.

AIM
To explore the effects of comprehensive nursing on postoperative complications, psychological state and quality of life in patients with brain glioma.

METHODS
A total of 106 patients with confirmed brain gliomas admitted to Nanchong Central Hospital between January 2019 and May 2021 were selected by random sampling. They were categorized into an observation group and a control group using a random number table with 53 patients in each group. Patients in the observation group were given comprehensive nursing in addition to conventional nursing and patients in the control group were given conventional nursing. The overall incidence of postoperative complications including limb dysfunction, high fever and epilepsy was compared between the two groups. The mental status was evaluated in the two groups before and after intervention using self-rating anxiety scale (SAS) and self-rating depression scale (SDS). Quality of life was assessed and compared using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire between the two groups before and after the intervention.

RESULTS
After intervention, the overall incidence of postoperative complications was significantly lower in the observation group (7.55%) than that in the control group (20.75%) (P < 0.05). Before intervention, there was no significant difference in SAS and SDS scores between the two groups (P > 0.05). However, after intervention, scores of SAS and SDS decreased in the two groups compared with those before
intervention, and the scores of SAS and SDS were lower in the observation group than in the control group (all \( P < 0.05 \)). There was no significant difference in quality of life between the two groups before the intervention (\( P > 0.05 \)). In contrast, quality of life increased in the two groups compared with those before intervention, and it was higher in the observation group than in the control group (\( P < 0.05 \)).

**CONCLUSION**
Comprehensive nursing can reduce the incidence of postoperative complications, improve the psychological state of anxiety and depression and improve quality of life in patients with brain glioma.

**Key Words:** Brain glioma; Comprehensive nursing; Complications; Mental state; Quality of life

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**Core Tip:** Treatment for brain glioma is always challenging. Surgery associated complications, psychological dysfunction and poor quality of life are some of the more common harms of the disease and should be actively managed. Comprehensive nursing aims to increase patients’ knowledge about their disease and encourages patients to improve their confidence and positive attitude to manage their disease through evaluation and intervention measures. This study explored the effectiveness of comprehensive nursing in relieving anxiety and depression and optimizing quality of life in patients with brain glioma undergoing operation.

**INTRODUCTION**
Brain glioma is a common type of primary brain tumor in patients with intracranial tumors. It grows rapidly with a high incidence of complications, mortality and recurrence rate[1,2]. Surgical resection of the tumor is the most used therapy for the treatment of brain glioma. However, damage to functional areas of the brain may occur due to the special location of brain glioma leading to a high incidence of complications and even death[3-5]. Complications frequently occurring include limb dysfunction, high fever and epilepsy, which seriously influences the mental status and quality of life in patients with brain glioma[6]. Luckily, effective nursing can reduce the incidence of postoperative complications[7]. Comprehensive nursing provides thorough and scientific nursing to patients. Unfortunately, few studies discuss the usage of comprehensive nursing in patients with brain glioma. Therefore, the current study aimed to explore the efficacy of comprehensive nursing in patients who underwent operation for brain glioma and analyze its effects on the incidence of postoperative complications, psychological state and quality of life in patients with brain glioma.

**MATERIALS AND METHODS**

**Participants**
A total of 106 patients with confirmed brain gliomas who received treatment at Nanchong Central Hospital were selected in the study by random sampling between January 2019 and May 2021. Patients who were included were initially diagnosed with gliomas by pathological examination and underwent surgery for the disease with conscious self-awareness and complete medical records. Patients with other comorbid malignant tumors, severe cardiovascular diseases or metastatic brain gliomas, recurrent or multiple malignant gliomas, patients with cognitive dysfunction and patients with critical illnesses were excluded from the study[8]. A random number table was used to categorize these patients into an observation group and a control group with 53 patients in each group. The observation group included 28 male and 25 female patients with an age range of 43 to 64 (57.34 ± 11.57) years. Of them, 29 patients had astrocytoma and 24 patients had medulloblastoma. Twenty-seven underwent complete resection, and 26 patients underwent partial resection. The control group included 27 male and 26 female patients who received standard treatment.
with an age range of 44 to 63 (56.92 ± 12.32) years. Of them, 30 patients had astrocytoma and 23 patients had medulloblastoma. Twenty-nine patients underwent complete resection, and 24 patients underwent partial resection. Sex, age, types of diseases and operations were comparable between the two groups.

**Nursing intervention**
Patients in the control group received conventional nursing care which included four aspects: (1) Guidelines at hospital admission. Clinicians and nurses will collect patient data, monitor vital signs regularly and correctly process physician order; (2) Preoperative guidelines. Preoperative preparations such as preoperative skin and gastroenterological preparations will be completed; (3) Psychological nursing care. Psychological support is provided to patients, and patients and family members are informed of points for postoperative matters needs attention; and (4) Propaganda and education on health. Clinicians and nurses will educate their patients about the knowledge of brain glioma and instruct patients and their family members to increase adherence to care instructions and assist clinicians and nurses to conduct relevant examination.

In addition to the above conventional nursing, the observation group also received comprehensive nursing. It involved: (1) Creating nursing care plans; (2) Improve preoperative guidelines; and (3) Provide postoperative interventions. In terms of creating nursing care plans, a personalized nursing care plan is worked out based on the individual records of patients such as age, education background and personality. With regards to preoperative guidelines, clinicians and nurses will educate their patients with the relative knowledge on the disease and operation, the potential pain and complications that may occur after the operation and how they are managed. Meanwhile, an information request form is required by clinicians and nurses to understand to what extent a patient knows the disease. Moreover, preoperative psychological intervention was offered by nurses who received specialized psychological training. Through communication, reasons hidden behind negative emotions are explored to help patients with emotional disclosure to lessen their psychological burden. For postoperative interventions, nurses will assess and ascertain their patients’ pain every 4 h and provide corresponding management. Furthermore, nurses will report these conditions to clinicians and process physician orders. Music therapy is usually used to lessen postoperative discomfort. In general, clinicians and nurses should focus on mental and emotional changes in patients and provide psychological counseling promptly based on clinical presence of this patient. In addition, clinicians and nurses will introduce previous successful cases to their patients to increase patient confidence to fight against the disease.

**Measures**
The overall incidence of postoperative complications was compared between the two groups including limb dysfunction, high fever and epilepsy. Self-rating anxiety scale (SAS) and self-rating depression scale (SDS) was used to assess changes in mental state in the two groups before and after the intervention. A cutoff value of 50 was fixed for the standard deviation of the SAS score. A standard score of 50 to 59 indicated mild anxiety, a standard score of 60 to 69 indicated moderate anxiety, and a standard score of > 69 indicated severe anxiety. For SDS, a standard score of ≥ 50 indicated depression with higher scores indicating more severe symptoms. The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire was used to assess quality of life in the aspects of physical, cognitive, emotional, role and social function in the two groups before and after the intervention with higher score indicating better quality of life.

**Statistical analysis**
SPSS 19.0 was used as the statistical software for data analysis. Measurement data was expressed using mean ± SD and inter-group difference was compared using Student’s t test. Enumeration data was expressed using n (%) and inter-group difference was compared using χ². P < 0.05 represented a significant difference.

**RESULTS**

**Complications**
Limb dysfunction occurred in 2 patients, high fever occurred in 1 patient, and epilepsy occurred in the observation group. The overall incidence of complications was 7.55%. In the control group, 5 patients had limb dysfunction, 4 patients had high fever, and 2 patients had epilepsy. The overall incidence of complications was 20.75%. By comparison, the overall incidence of complications was lower in the observation group than in the control group (P < 0.05, Table 1).

**Mental state**
Before the intervention, there was no significant difference in scores of SAS and SDS between the two groups (P > 0.05). After the intervention, SAS and SDS scores were lower compared with before the intervention. However, the scores were significantly lower in the observation group than in the control
Table 1 The overall incidence of complications in the two groups, n (%)

<table>
<thead>
<tr>
<th>Groups</th>
<th>Limb dysfunction</th>
<th>High fever</th>
<th>Epilepsy</th>
<th>Overall incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation group (n = 53)</td>
<td>2 (3.77)</td>
<td>1 (1.89)</td>
<td>1 (1.89)</td>
<td>4 (7.55)</td>
</tr>
<tr>
<td>Control group (n = 53)</td>
<td>5 (9.43)</td>
<td>4 (7.55)</td>
<td>2 (3.77)</td>
<td>11 (20.75)</td>
</tr>
<tr>
<td>$\chi^2$ value</td>
<td></td>
<td></td>
<td></td>
<td>5.421</td>
</tr>
<tr>
<td>$P$ value</td>
<td></td>
<td></td>
<td></td>
<td>0.041</td>
</tr>
</tbody>
</table>

Table 2 Mental state in the two groups before and after the intervention (mean ± SD, points)

<table>
<thead>
<tr>
<th>Groups</th>
<th>SAS score Before the intervention</th>
<th>SAS score After the intervention</th>
<th>SDS score Before the intervention</th>
<th>SDS score After the intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation group (n = 53)</td>
<td>56.34 ± 14.21</td>
<td>42.14 ± 10.21</td>
<td>53.21 ± 11.10</td>
<td>43.91 ± 11.07</td>
</tr>
<tr>
<td>Control group (n = 53)</td>
<td>54.12 ± 11.61</td>
<td>48.73 ± 9.12</td>
<td>52.56 ± 10.17</td>
<td>47.04 ± 12.45</td>
</tr>
<tr>
<td>$t$ value</td>
<td>0.982</td>
<td>6.092</td>
<td>1.223</td>
<td>5.011</td>
</tr>
<tr>
<td>$P$ value</td>
<td>0.235</td>
<td>0.036</td>
<td>0.201</td>
<td>0.042</td>
</tr>
</tbody>
</table>

*P < 0.05 vs before the intervention.
SAS: Self-rating anxiety scale; SDS: Self-rating depression scale.

DISCUSSION

Brain glioma can develop rapidly. Surgical tumor removal is the main treatment for this disease. However, the postoperative mental state is poor in these patients because of the high incidence of postoperative complications, which have a strong impact on quality of life[11]. Fortunately, patient-centered comprehensive nursing can pay close attention to patient’s thoughts and psychological change [12-14]. It does realize joint nursing, and it optimizes communication and promotes the relationship between patients and nurses so that the quality of nursing is improved[15,16]. In comprehensive nursing, effective personalized nursing can be provided to patients by using a scientific, systemic and standardized nursing program and nursing plan[17,18].

In the current study, patients with brain glioma were given comprehensive nursing. The results showed that the overall incidence of complications was 7.55% in the observation group, which was higher than the 20.75% incidence of the control group, suggesting comprehensive nursing can reduce the incidence of postoperative complications and accelerate postoperative rehabilitation in this population. This can be explained by the well thought-out nursing care plan, full focus on patients and prompt nurse-patient communication that is typical of comprehensive nursing and reduces the incidence of postoperative complications.

Meanwhile, the results indicated that SAS and SDS scores were lower in the observation group than in the control after the intervention. It manifested that comprehensive nursing could improve postoperative mental states in patients with brain glioma. It guides nurses to try to understand what concerns patients and experience and help patients to relieve stress. In addition, it builds patient trust in clinicians and improves patient mental state. Moreover, quality of life was better in the observation group than in the control group in the present study, which showed that comprehensive nursing can improve quality of life by reducing the incidence of postoperative complications and improving patient mental state.
CONCLUSION

Comprehensive nursing can reduce the incidence of postoperative complications and improve psychological status and quality of life in patients with brain glioma.

ARTICLE HIGHLIGHTS

Research background
Brain glioma is a common type of aggressive disease that is related to a deterioration in mental health and quality of life. The complex condition raises high demand for the optimal treatment approaches and postoperative nursing strategies.

Research motivation
Comprehensive nursing care is cooperative nursing care that is provided by health professionals of different medical domains to fulfill a patient’s practicable physical, mental and psychosocial healthcare requirements. Based on this, this study discussed the effectiveness of comprehensive nursing care in patients with brain glioma.

Research objectives
To determine the effects of comprehensive nursing care on postoperative complications, mental health and quality of life in patients with brain glioma.

Research methods
A total of 106 patients with brain glioma were selected and randomly categorized into an observation group and a control group with 53 patients in each group. The observation group was given comprehensive nursing as well as conventional nursing, and the control group was only given conventional nursing. Postoperative complications, mental status and quality of life were compared between the two groups after the nursing intervention.

Research results
After the nursing intervention, the incidence of complications, including limb dysfunction, high fever and epilepsy, was lower in the observation group than in the control group. Anxiety and depression were relieved in the observation group compared with the control group. Quality of life scores were higher in the observation group than in the control group.

Research conclusions
The findings of this study provide evidence that comprehensive nursing can effectively reduce the incidence of postoperative complications, promote comfort and ease, relieve anxiety and depression and improve quality of life in patients with brain glioma.

Research perspectives
Here we present our experience in providing comprehensive nursing in patients with brain glioma, and it shows that this nursing approach is effective. We need better and detailed evidence to demonstrate...
the significance of this nursing strategy in this population.

FOOTNOTES

Author contributions: Dong H, Zhang XL, Deng CX, and Luo B contributed to the design of the study; Dong H wrote the manuscript; All authors have read and approve the final manuscript.

Institutional review board statement: The study was approved by the Nanchong Central Hospital Institutional Review Board.

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Prospective Study

Predictors of long-term anxiety and depression in discharged COVID-19 patients: A follow-up study

Rabia Kevser Boyraz, Ebru Şahan, Muhammed Emin Boylu, İsmet Kırpınar

**Abstract**

**BACKGROUND**
Patients who were hospitalized for coronavirus disease 2019 (COVID-19) faced an extremely stressful experience that challenged their mental health and the long-term effects are not definitely known yet.

**AIM**
To identify both the course of mental symptoms (anxiety and depressive symptoms) and the related risk factors of recovered patients at the 20-22 mo follow-up.

**METHODS**
One hundred and seventy-two patients were enrolled. The patients were evaluated with a telepsychiatry interview and the Hospital Anxiety and Depression Scale (HADS). Sociodemographic and clinical features were analyzed by regression analysis.

**RESULTS**
The mean HADS-Anxiety (HADS-A) score was 9.08 ± 4.90, and the mean HADS-Depression (HADS-D) score was 8.55 ± 4.39. The mean HADS-A ($P = 0.484$) and HADS-D ($P = 0.011$) scores were increased compared to scores during hospitalization. Being over 50 years old, having lower financial status, and being vaccinated were associated with symptoms of depression (adjusted $R^2 = 0.168$) while being over 50 years old, female sex, being vaccinated, and dyspnea were associated with higher anxiety (adjusted $R^2 = 0.245$).

**CONCLUSION**
To prevent the deterioration of mental health, psychiatrists should play an active role in identifying emerging mental problems as soon as possible, more vulnerable groups should be characterized, and psychological support should be sustained after discharge.

Key Words: Coronavirus; Anxiety disorders; Depressive disorders; Tele medicine; Psychiatry

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Core Tip: Coronavirus disease 2019 causes various psychiatric outcomes like other coronaviruses. This study aimed to observe the anxiety and depressive symptoms and related factors of recovered patients at the 20-22 mo follow-up. The goal of this study was to identify groups at high risk of anxiety and to raise awareness about providing psychiatric support to these groups.

INTRODUCTION

Pandemics may cause major health problems both physically and mentally. Factors such as various biological reasons, difficulties in the treatment process, loss of relatives, quarantine conditions, social isolation, and the uncertainty of the process are among the main factors affecting mental health. Studies on previous infectious epidemics, like severe acute respiratory syndrome, Middle East respiratory syndrome, and Ebola virus disease outbreak, reported that psychological symptoms might persist or arise after the infection with long-term negative outcomes[1].

Neurological and psychiatric outcomes of coronavirus disease 2019 (COVID-19) have been reported in various studies[2,3]. A 6-mo retrospective cohort study of 236379 COVID-19 survivors reported the prevalence and incidence rates of psychiatric and neurologic disorders. A lifetime anxiety disorder rate was 17.39%, a first anxiety disorder rate was 7.11%, while a lifetime and first attack mood disorder rates were 13.6% and 4.22%, respectively. Different from other studies, it was shown that the prevalence of substance use disorders and psychotic episodes increased. The first psychotic episode psychosis diagnosis rate was 0.42% while the first substance use disorder rate was 1.92% and insomnia rate was 2.53%[4].

There have been short-term follow-up studies on how the discharged COVID-19 patients’ mental health manifests along with the disease course, but long-term follow-up studies are very few. One of them is from an Italian cohort with 238 patients 4 mo after discharge. In psychiatric assessment, 32.9% and 29.5% of participants showed anxiety and depressive symptoms, respectively. Changes in appetite and sleep patterns emerged in 15.6% and 31.2% of patients[5].

With the pandemic due to the risk of being infected and the prioritization of COVID-19 patients, patient follow-up has become difficult in psychiatry as in many branches. The spread of the use of telepsychiatry after the pandemic made online psychiatric interviews possible. Thus, studies about the pandemic could be continued, as well.

In this context, we aimed to investigate the long-term psychiatric effects of the pandemic on discharged COVID-19 patients through telepsychiatric interviews.

MATERIALS AND METHODS

This study was conducted in accordance with the Declaration of Helsinki Ethical Principles and was approved by the Ethical Committee of the Bezmialem Vakıf University (2021/414).

Setting, design, and participants

This retrospective cohort study focused on the longitudinal follow-up of psychological sequelae in recovered COVID-19 patients 20-22 mo after hospital discharge. Those 281 patients were hospitalized with COVID-19 according to the guidelines of the Turkish Ministry of Health between March 24, 2020 and May 24, 2020 at Bezmialem Vakıf University Hospital (İstanbul/Turkey). In the first part of this study, patients were evaluated psychiatrically during hospitalization and predictors of anxiety and depression were investigated[6]. This study, as a second step, aimed to explore anxiety and depression...
levels of the same sample and their correlates after a long period (20-22 mo).

Two hundred and eighty-one patients were planned to be included. Twenty-nine patients refused to participate, 29 died, 25 changed their telephone numbers and new information was not available, 22 could not be reached, and 4 could not speak. Thus, 172 patients, who agreed to undergo a comprehensive telepsychiatric assessment, were enrolled (Figure 1).

Detailed socio-demographic data were recollected. Additionally, patients were asked for their vaccination status, if they lost any relatives and had been reinfected, any persistent physical symptoms, or insomnia after COVID-19 infection. To evaluate their anxiety-depressive symptoms, the Hospital Anxiety and Depression Scale (HADS) was administered through a telephonic interview. Those with significant complaints were advised to take psychiatric support.

**Hospital anxiety and depression scale:** As a self-report scale, HADS is composed of 14 items, of which seven (HADS-A) evaluate the anxiety and another seven (HADS-D) evaluate the depression severity of patients with physical illness. The cut-off score is 10 for the anxiety subscale and 7 for the depression subscale in the Turkish version[7]. Scales for anxiety and depression showed a high internal consistency, with Cronbach’s alpha values ranging between 0.83 and 0.85.

### Statistical analysis

All statistical analyses were performed using the IBM Statistical Package for the Social Sciences (SPSS) for Windows version 20.0 (SPSS Inc., Chicago, IL, United States).

In descriptive statistics, categorical variables are reported as numbers and percentages. Continuous data are presented as the mean ± SD. Variables were checked for normal distribution assumption using histogram, skewness, and kurtosis in addition to the Kolmogorov-Smirnov test. HADS scores were analyzed by repeated measures ANOVA for different time points (at baseline and after 20-22 mo). Either Student’s t-test or one way ANOVA (for independent variables in more than two categorical groups) tests were used to explore HADS-A, HADS-D scores, and related factors.

We did not adjust significance for multiple comparisons because the study is exploratory in nature. Two dependent variables (HADS-A and HADS-D) were included in each group comparison, thus the significance level was adjusted to 0.025. In order to test the association between significant predictors (sex, age, day of hospitalization, medical history, etc.) and each of the psychological outcomes above the cut-off scores, univariate logistic regressions were used. Variables that showed statistical significance at a P-value of less than 0.05 in the univariate analysis were included in the multivariate regression. Multivariate regression analysis was performed to identify the contribution of each factor associated with anxiety and depression separately. Post-hoc Tukey and Games-Howell tests were applied when there was a statistically significant difference in the Kruskal-Wallis test to determine which groups form the difference. A P value < 0.05 was considered significant.

### RESULTS

The initial data of the follow-up study were evaluated cross-sectionally and published as a preliminary study.

This study focused on the current status of discharged patients 20-22 mo after discharge and compared the results. The sociodemographic and clinical features of participants are shown in Table 1. Of the 172 patients included in the study, 83 (48.3%) were male, and 89 (51.7%) were female. The mean age was 53.23 ± 13.63 (range, 18–86) years. One hundred (58.1%) patients were over 50 years. Most (79.7%) of the participants were married, 13 (7.6%) were single, 7 (4.1%) were divorced, and 15 (8.7%) were widowed. The majority (91.1%) of the patients had child/children. The mean age of children was 24.39 ± 14.25 years. Regarding employment status, 41.3% of the patients were housewives, 30.2% were employed, 23.3% were unemployed, 23.3% were retired, and 2.9% were in the “other” (students and those whose job status was uncertain) category. Most of the participants were from low and middle-income groups (42.4% and 47.7%, respectively), and only 17 (9.9%) participants had a high income. Eighty-five (49.4%) patients had medical comorbidity, and hypertension, diabetes, and pulmonary diseases were the most common ones. Forty-six (26.7%) participants had psychiatric comorbidity, nearly half (11.6%) of them had depressive disorders, and anxiety disorders were the second most common psychiatric disorder (8.7%). Thirty-four (19.7%) patients reported past psychiatric treatment, and more than half of them (11.6%) used selective serotonin reuptake inhibitors. The vaccination rate was 89%; 2 BioNTech was the most commonly preferred vaccination type. Thirty-two (18.6%) patients had been reinfected by COVID-19; 29.7% had lost at least one relative due to COVID-19. Eighty-three (48.3%) patients had residual symptoms like tiredness, palpitation, insomnia, easy fatigue, and dyspnea. Tiredness was the most common one (39%). The mean days of initial hospitalization were 7.28 ± 5.17. Post-hoc Tukey and Games-Howell tests were applied when there was a statistically significant difference in the Kruskal-Wallis test to determine which groups form the difference. A P value < 0.05 was considered significant.

The initial mean HADS-A score was 8.73 ± 5.422, while the HADS-D score was 7.12 ± 5.508 during hospitalization for COVID-19. At the 20-22 mo follow-up, the mean HADS-A score was 9.08 ± 4.90, and
<table>
<thead>
<tr>
<th>Sociodemographic features</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>89 (51.7)</td>
</tr>
<tr>
<td>Male</td>
<td>83 (48.3)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
</tr>
<tr>
<td>18-50</td>
<td>72 (41.9)</td>
</tr>
<tr>
<td>50-86</td>
<td>100 (58.1)</td>
</tr>
<tr>
<td>Marital status</td>
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<tr>
<td>Married</td>
<td>137 (79.7)</td>
</tr>
<tr>
<td>Single</td>
<td>13 (7.6)</td>
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<tr>
<td>Divorced</td>
<td>7 (4.1)</td>
</tr>
<tr>
<td>Widowed</td>
<td>15 (8.7)</td>
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<tr>
<td>Partner</td>
<td>23 (13.4)</td>
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<td>Alone</td>
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<td>Yes</td>
<td>155 (90.1)</td>
</tr>
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<td>4 (2.3)</td>
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<tr>
<td>Retired</td>
<td>40 (23.3)</td>
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<td>Housewife</td>
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<td>Middle income</td>
<td>82 (47.7)</td>
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<td>17 (9.9)</td>
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<td>Smoking history</td>
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<td>Yes</td>
<td>29 (16.9)</td>
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<tr>
<td>No</td>
<td>143 (83.1)</td>
</tr>
<tr>
<td>Alcohol</td>
<td></td>
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<tr>
<td>Yes</td>
<td>6 (3.5)</td>
</tr>
<tr>
<td>No</td>
<td>166 (96.5)</td>
</tr>
</tbody>
</table>

| Clinical features         |       |
| Chronic disease           |       |
| No comorbidity            | 85 (49.4) |
| Hypertension              | 10 (5.8) |
| Diabetes                  | 8 (4.7) |
| Cardiovascular            | 6 (3.5) |
| Cancer                    | 3 (1.7) |
| Pulmonary                 | 13 (7.6) |
| Neurologic                | 3 (1.7) |
| Gastrointestinal          | 1 (0.6) |
| Thyroid                   | 1 (0.6) |
| Allergic                  | 2 (1.2) |
| Rheumatologic             | 1 (0.6) |
| Endocrinology             | 1 (0.6) |
| Metabolic                 | 1 (0.6) |
| Other infections          | 1 (0.6) |
follow-up of discharged COVID-19 patients

Fibromyalgia 1 (0.6)
2 medical diseases, one from first 5 16 (9.3)
2 medical diseases, two from the first 5 2 (1.2)
2 or more of first 5 17 (9.9)

Psychiatric comorbidity
Yes 46 (26.7)
No 126 (73.3)

Reinfection
Yes 32 (18.6)
No 140 (81.4)

Vaccination
Yes 153 (89)
No 19 (11)

Which vaccine
None 17 (9.9)
2 Sinovac 22 (12.9)
3 Sinovac 33 (19.3)
2 BioNTech 55 (32.2)
2 Sinovac+1 BioNTech 36 (21.1)
2 Sinovac+2 BioNTech 3 (1.8)
1 BioNTech 4 (2.3)
1 Sinovac 1 (0.6)

Death of relatives caused by COVID-19
Yes 51 (29.7)
No 121 (70.3)

Persistent symptoms
Yes 83 (48.3)
No 89 (51.7)

Tiredness 67 (39)
Palpitation 30 (17.4)
Dyspnea 30 (17.4)
Sleep disorders 5 (2.9)
Easy fatigue 5 (2.9)
Other symptoms 9 (5.2)

Figure 1 Flowchart of excluded cases.

the mean HADS-D score was 8.55 ± 4.39. The mean HADS-A (P = 0.484) and HADS-D (P = 0.011) scores were increased when compared to those during hospitalization. Repeated measures ANOVA revealed that changes in HADS-D scores at follow-up were significant (Wilks’ Lambda Sig.: 0.011; Partial Eta Squared: 0.038), while HADS-A score changes were not significant (Wilks’ Lambda Sig.: 0.484; Partial Eta Squared: 0.003).

As shown in Table 2, we evaluated the associations between HADS-A and HADS-D scores at the 20-22 mo follow-up and sociodemographic and clinical features. Female patients had more anxiety symptoms than males. Participants over 50 years had more anxiety and depression symptoms than
**Table 2** Comparison of anxiety and depression scores by different variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>HADS-A score (mean ± SD)</th>
<th>P value</th>
<th>HADS-D score (mean ± SD)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>10.65 ± 5.16</td>
<td>0.0</td>
<td>8.65 ± 4.14</td>
<td>0.76</td>
</tr>
<tr>
<td>Male</td>
<td>7.40 ± 4.01</td>
<td></td>
<td>8.44 ± 4.67</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 50</td>
<td>7.50 ± 4.73</td>
<td>0.000</td>
<td>7.12 ± 4.66</td>
<td>0.0</td>
</tr>
<tr>
<td>&gt; 50</td>
<td>10.23 ± 4.73</td>
<td></td>
<td>9.58 ± 3.90</td>
<td></td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>8.73 ± 4.93</td>
<td>0.003 (between married and widowed)</td>
<td>8.59 ± 4.34</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Single</td>
<td>8.38 ± 4.48</td>
<td></td>
<td>6.61 ± 4.42</td>
<td></td>
</tr>
<tr>
<td>Divorced</td>
<td>10.57 ± 6.57</td>
<td></td>
<td>9.42 ± 6.60</td>
<td></td>
</tr>
<tr>
<td>Widowed</td>
<td>12.2 ± 2.98</td>
<td></td>
<td>9.40 ± 3.54</td>
<td></td>
</tr>
<tr>
<td>Having children</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>8.64 ± 4.22</td>
<td>0.69</td>
<td>6.94 ± 4.13</td>
<td>0.11</td>
</tr>
<tr>
<td>Yes</td>
<td>9.13 ± 4.98</td>
<td></td>
<td>8.72 ± 4.40</td>
<td></td>
</tr>
<tr>
<td>Employment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employed</td>
<td>7.11 ± 4.57</td>
<td>0.000 (between employed and housewife)</td>
<td>7.76 ± 4.80</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Unemployed</td>
<td>5.50 ± 3.51</td>
<td></td>
<td>8.50 ± 8.34</td>
<td></td>
</tr>
<tr>
<td>Retired</td>
<td>9.00 ± 3.96</td>
<td></td>
<td>9.15 ± 3.81</td>
<td></td>
</tr>
<tr>
<td>Housewife</td>
<td>10.80 ± 5.19</td>
<td></td>
<td>9.05 ± 4.13</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>8.80 ± 3.49</td>
<td></td>
<td>4.80 ± 2.28</td>
<td></td>
</tr>
<tr>
<td>Financial status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low income</td>
<td>9.86 ± 4.25</td>
<td>&gt; 0.05</td>
<td>9.16 ± 3.60</td>
<td>0.009 between low income and high income; 0.03 between middle income and high income</td>
</tr>
<tr>
<td>Middle income</td>
<td>8.79 ± 5.26</td>
<td></td>
<td>8.59 ± 4.78</td>
<td></td>
</tr>
<tr>
<td>High income</td>
<td>7.17 ± 5.36</td>
<td></td>
<td>5.70 ± 4.66</td>
<td></td>
</tr>
<tr>
<td>Household</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family</td>
<td>8.68 ± 4.87</td>
<td>&gt; 0.05</td>
<td>8.31 ± 4.52</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Roommate</td>
<td>10.00 ± 5.29</td>
<td></td>
<td>8.66 ± 1.52</td>
<td></td>
</tr>
<tr>
<td>Partner</td>
<td>11.08 ± 4.07</td>
<td></td>
<td>9.73 ± 3.10</td>
<td></td>
</tr>
<tr>
<td>Alone</td>
<td>9.77 ± 6.55</td>
<td></td>
<td>9.11 ± 5.77</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>9.33 ± 5.08</td>
<td>0.14</td>
<td>8.58 ± 4.38</td>
<td>0.81</td>
</tr>
<tr>
<td>Yes</td>
<td>7.86 ± 3.73</td>
<td></td>
<td>8.37 ± 4.53</td>
<td></td>
</tr>
<tr>
<td>Chronic medical disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>9.01 ± 4.48</td>
<td>0.84</td>
<td>8.59 ± 4.25</td>
<td>0.90</td>
</tr>
<tr>
<td>Yes</td>
<td>9.16 ± 5.32</td>
<td></td>
<td>8.51 ± 4.55</td>
<td></td>
</tr>
<tr>
<td>Lifetime psychiatric disorder</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>8.28 ± 4.90</td>
<td>0.00</td>
<td>8.29 ± 4.51</td>
<td>0.20</td>
</tr>
<tr>
<td>Yes</td>
<td>11.28 ± 4.24</td>
<td></td>
<td>9.26 ± 4.02</td>
<td></td>
</tr>
<tr>
<td>Family member death caused by COVID-19</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
patients younger than 50 years. Marital status had a significant association with anxiety symptoms but had no significant association with depressive symptoms. In the post hoc analysis, widowed patients had a higher mean HADS-A score than married patients (Games-Howell test; \( P = 0.003 \)). Employment status was significantly associated with anxiety symptoms as well. In the post hoc analysis, housewives had a significantly higher mean HADS-A score than employed patients (Tukey test; \( P = 0.000 \)). Additionally, financial status had a significant association with depressive symptoms, but no significant association with anxiety symptoms. In the post hoc analysis, patients with a low and middle income showed more depressive symptoms than patients with a high income (Tukey test; \( P = 0.009 \) and \( P = 0.03 \), respectively).

Vaccinated patients had significantly higher mean HADS-A and HADS-D scores compared to unvaccinated ones. There was no significant difference between the vaccination preferences of the individuals. When all the residual symptoms were considered, the mean HADS-A score of those with residual symptoms after COVID-19 was significantly higher. Tiredness caused a significantly higher mean HADS-D score (\( P = 0.01 \)). On the other hand, being reinfected was not associated with higher anxiety and depression scores.

Multiple linear regression analysis showed that being vaccinated, having a low income, and being over 50 years old were associated with increased depressive symptoms (adjusted \( R^2 = 0.170 \)) (Table 3).

Being vaccinated, being over 50 years old, female sex, and dyspnea were significantly associated with increased anxiety symptoms (adjusted \( R^2 = 0.245 \)) (Table 4).

Changes in HADS scores (HADS scores at the 20-22 mo follow-up minus those at the hospitalization/baseline) were analyzed by multivariate regression for associated factors as well. The “tiredness” and HADS-D score changes were associated with increased anxiety symptoms (adjusted \( R^2 = 0.487 \)) (Table 5). Being vaccinated and baseline HADS-D were significantly associated with increased depressive symptoms (adjusted \( R^2 = 0.671 \)) (Table 6).
Table 3 Multivariate regression analysis of factors associated with depressive symptoms

<table>
<thead>
<tr>
<th>Model</th>
<th>Unstandardized coefficients</th>
<th>Standardized coefficients</th>
<th>T</th>
<th>Sig.</th>
<th>95.0% confidence interval for B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>Std. error</td>
<td>Beta</td>
<td></td>
<td>Lower bound</td>
</tr>
<tr>
<td>(Constant)</td>
<td>5.381</td>
<td>1.8439</td>
<td>2.92679</td>
<td>0.004</td>
<td>1.750</td>
</tr>
<tr>
<td>Vaccination</td>
<td>4.172</td>
<td>1.002</td>
<td>0.298</td>
<td>4.162</td>
<td>0.000</td>
</tr>
<tr>
<td>&gt; 50 yr</td>
<td>1.644</td>
<td>0.643</td>
<td>0.185</td>
<td>2.558</td>
<td>0.011</td>
</tr>
<tr>
<td>Financial status</td>
<td>-1.174</td>
<td>0.478</td>
<td>-0.173</td>
<td>-2.455</td>
<td>0.015</td>
</tr>
</tbody>
</table>

Table 4 Multivariate regression analysis of factors associated with anxiety symptoms

<table>
<thead>
<tr>
<th>Model</th>
<th>Unstandardized coefficients</th>
<th>Standardized coefficients</th>
<th>T</th>
<th>Sig.</th>
<th>95.0% confidence interval for B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>Std. error</td>
<td>Beta</td>
<td></td>
<td>Lower bound</td>
</tr>
<tr>
<td>(Constant)</td>
<td>8.678</td>
<td>2.232</td>
<td>3.887</td>
<td>0.000</td>
<td>4.270</td>
</tr>
<tr>
<td>Vaccination</td>
<td>3.355</td>
<td>1.108</td>
<td>0.215</td>
<td>3.028</td>
<td>0.003</td>
</tr>
<tr>
<td>&gt; 50 yr</td>
<td>1.656</td>
<td>0.695</td>
<td>0.167</td>
<td>2.384</td>
<td>0.018</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>1.747</td>
<td>0.874</td>
<td>0.135</td>
<td>2.030</td>
<td>0.047</td>
</tr>
<tr>
<td>Sex</td>
<td>-2.747</td>
<td>0.702</td>
<td>-0.280</td>
<td>-3.914</td>
<td>0.000</td>
</tr>
<tr>
<td>Marital status</td>
<td>0.641</td>
<td>0.364</td>
<td>0.121</td>
<td>1.761</td>
<td>0.080</td>
</tr>
<tr>
<td>Psychiatric comorbidity</td>
<td>-1.348</td>
<td>0.789</td>
<td>-0.122</td>
<td>-1.709</td>
<td>0.089</td>
</tr>
</tbody>
</table>

Table 5 Tiredness and hospital anxiety and depression scale-depression score change are associated with increased anxiety symptoms

<table>
<thead>
<tr>
<th>Model</th>
<th>Unstandardized coefficients</th>
<th>Standardized coefficients</th>
<th>T</th>
<th>Sig.</th>
<th>95.0% confidence interval for B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>Std. error</td>
<td>Beta</td>
<td></td>
<td>Lower bound</td>
</tr>
<tr>
<td>(Constant)</td>
<td>-1.226</td>
<td>1.151</td>
<td>-1.065</td>
<td>0.288</td>
<td>-3.499</td>
</tr>
<tr>
<td>Delta HADS-D</td>
<td>0.634</td>
<td>0.054</td>
<td>0.675</td>
<td>3.028</td>
<td>0.000</td>
</tr>
<tr>
<td>Tiredness</td>
<td>1.793</td>
<td>0.761</td>
<td>0.131</td>
<td>2.384</td>
<td>0.020</td>
</tr>
<tr>
<td>Vaccination</td>
<td>0.002</td>
<td>1.209</td>
<td>0.000</td>
<td>2.000</td>
<td>0.999</td>
</tr>
</tbody>
</table>

Delta-HADS-D: Delta-hospital anxiety and depression scale-depression score.

**DISCUSSION**

It is known that major pandemics negatively affect mental health for many reasons. Going through a severe COVID-19 infection, being hospitalized, and being taken to the intensive care unit can cause great stress in patients and leave them with psychiatric problems. Long-term follow-up studies about the COVID-19 outbreak are newly established, but the difficulty of accessing patients due to the risk of contamination also limits the studies in this area. Although the use of telepsychiatry serves to reduce this limitation, it also raises questions when compared to the detailed and efficient evaluation of face-to-face interviews. There are also studies showing that online interviews and treatments using the telepsychiatry method which has become widespread, especially after the epidemic in Turkey, have similar effectiveness to face-to-face interviews[8].

In our study, we conducted a follow-up interview among patients who underwent psychiatric evaluation while receiving inpatient care for COVID-19 between March-May 2020 20-22 mo later (in January 2022). We updated the initial data for 172 patients to maintain comparisons only with those
who completed the follow-up study. We observed that the mean HADS-A and HADS-D scores were increased in the follow-up compared to the baseline status. Sixty-five (38.5%) patients had over-the-threshold anxiety and 68 (39.5%) had over-the-threshold depression during hospitalization while these figures were 111 (64.5%) for anxiety and 63 (36.6%) for depression at the follow-up.

Despite that we expected a decrease in anxiety after recovery from COVID-19, it increased according to both the mean scores and the cut-off values of HADS-A. Further analysis revealed that being over 50 years old, female gender, marital status (widowed), psychiatric comorbidity, and dyspnea as a residual symptom were factors associated with this increase. Old age is a period of increased physical/mental fragility. Thus, the incapacity to face major life crises may be related to anxiety (also to depression). The fact that the curfew lasted for a long time for people over 65 years in Turkey, isolation from their relatives due to the risk of contamination, and being subjected to travel ban may be among the factors that have increased their anxiety. Besides, being widowed is the loss of closest social support and relationship, and it is more common in the elderly. Residual dyspnea can also increase anxiety by causing health concerns. Female gender and comorbid psychiatric diseases are notable risk factors for anxiety disorders as in the general population[9]. Additionally, the ongoing pandemic process, the persistence of uncertainty, the loss of relatives and friends, the need for repeated vaccinations, and the economic problems experienced after the pandemic can be related to the rise in anxiety symptoms.

When depression is considered, the mean depression score was increased, but there was no significant increase in the percentage of patients who had over-the-threshold depression. Even though the acute phase of the pandemic with no vaccine has passed, we observed an increase in the depression scores while we had expected a decrease. Having a low income, being older than 50 years, and being vaccinated were found to be associated with increased depressive symptoms. Low financial status and being elderly were both expected and understandable risk factors for depression, apart from COVID-19. Moreover, it may be necessary to distinguish between the loss of loved ones, grieving processes, and other negative effects of the pandemic.

In contrast to our results, the current literature shows that vaccinated people reported decreased mental distress levels. As expected, vaccinated people become less worried about getting infected, they may become more active socially, or they may venture into different work opportunities[10]. The correlation between vaccination and HADS-A and HADS-D scores in our study may be related to the tendency of people with anxiety and depression to be vaccinated.

After the first study, the decrease in the rate of medical comorbidity in our sample was due to the death of 29 people with comorbidities. We thought that losing a relative, being reinfected, having a comorbid medical disease, and having residual complaints would be associated with an increase in anxiety and depression, but we could not find a significant difference. This may be due to the small size of our sample and should be replicated in further studies. Lack of a significant increase in anxiety in reinfected patients may be explained by the "habitation with repeated exposure".

In Wuhan, following COVID-19 treatment in the hospital during the general quarantine period, 782 discharged patients were re-evaluated 1 mo later in home isolation. The prevalence rates of insomnia, anxiety, and depressive symptoms among discharged COVID-19 patients during the centralized quarantine period were 44.37%, 31.59%, and 27.62%, respectively. Afterward, the prevalence rates during the home isolation were 27.11%, 17.26%, and 16.11%, respectively[11]. Inconsistent with our results, anxiety and depressive symptoms were decreased. Unlike our study, they observed that mental symptoms decreased significantly when home isolation started but the period after discharge was only 1 mo in this sample. Similar to our study, being women, being elderly, and having previous medical history were associated with anxiety and depressive symptoms. In our study, the mean HADS-A score was higher in patients with medical comorbidity compared to those without, but there was no significant statistical difference. The small size of our sample compared to this study may be the reason why we could not find a difference. Surprisingly, the mean depression score was lower in those with

---

**Table 6 Being vaccinated and baseline HADS-D score are significantly associated with increased depressive symptoms**

<table>
<thead>
<tr>
<th>Coefficients</th>
<th>Unstandardized coefficients</th>
<th>Standardized coefficients</th>
<th>T</th>
<th>Sig.</th>
<th>95.0% confidence interval for B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model</td>
<td>B</td>
<td>Std. error</td>
<td>Beta</td>
<td>Lower bound</td>
<td>Upper bound</td>
</tr>
<tr>
<td>(Constant)</td>
<td>4.592</td>
<td>1.113</td>
<td>4.125</td>
<td>0.000</td>
<td>2.394</td>
</tr>
<tr>
<td>Reinfection</td>
<td>0.600</td>
<td>1.113</td>
<td>0.032</td>
<td>0.723</td>
<td>0.471</td>
</tr>
<tr>
<td>Vaccination</td>
<td>4.680</td>
<td>1.012</td>
<td>0.204</td>
<td>4.626</td>
<td>0.000</td>
</tr>
<tr>
<td>HADS-A</td>
<td>-0.014</td>
<td>0.093</td>
<td>-0.010</td>
<td>-0.149</td>
<td>0.881</td>
</tr>
<tr>
<td>HADS-D</td>
<td>-1.015</td>
<td>0.093</td>
<td>-0.773</td>
<td>0.10951</td>
<td>0.000</td>
</tr>
</tbody>
</table>

HADS-A: Hospital anxiety and depression scale-anxiety score; HADS-D: Hospital anxiety and depression scale-depression score.
chronic illness, although it was not statistically significant. In a study in Wuhan, fewer mental health problems were detected in alcohol and cigarette users. In our study, we also found the mean scores of both anxiety and depression in smokers to be lower, although not significantly. As stated in this study, this is possible because most of the smokers and drinkers were men who had fewer mental health problems than women. On the other hand, the decrease in psychiatric complaints was surprising since smokers may have difficulties in managing stress.

As far as we could see in the literature, the longest follow-up study was a cohort study evaluating patients between 24-60 wk after COVID-19. Similar to our study, symptom scale scores for depression, insomnia, and posttraumatic stress disorder were increased at the long-term follow-up[12]. As far as we can see, our study is both the longest follow-up study in the literature and the first follow-up study in Turkey investigating anxiety and depression symptoms.

The fact that anxiety and depression scores increased especially in women, the elderly, patients with lower financial status, and patients with psychiatric comorbidity compared to the baseline indicates that special support by psychological counseling should be given to these groups. Women may have been affected more than men due to their gender roles (caring for children and sick family members, more responsibility for housework). People over the age of 50 may be at greater risk of anxiety and depression due to their general health concerns and their potential to experience a decrease in general functionality. Psychiatric comorbidity has always been a predictor of new psychiatric problems. Additionally, in the telepsychiatry interview, patients frequently complained about the economic difficulties experienced during the pandemic process which may cause as many adverse psychological effects as the pandemic. For this reason, the economic support strategy seen in many countries is an appropriate and necessary step to be taken.

Limitations: Post-pandemic various issues such as boredom of living with pandemic conditions, the obligation to wear a mask, the obligation to be vaccinated, vaccine hesitancy, and economic difficulties may have an impact on the increase in anxiety and depression in Turkey. National identity and each country’s unique socio-political interventions towards the pandemic process also change the course of the pandemic as a confusing factor[13]. It is a limitation of our study, not to review the impact of such various events separately with a control group. In this way, we have associated everything that affects anxiety and depression in the long follow-up period of about two years with COVID-19. The lack of face-to-face interviews and the limitations of self-report scales are our other shortcomings.

CONCLUSION
The course of long-term psychiatric symptoms related to COVID-19 is still uncertain. Contrary to what we expected in our study, we observed that anxiety and depression scores increased even more in long-term follow-up. As this is the longest follow-up study in the literature, we would like to emphasize the importance of our results in clinical practice. To prevent the deterioration of mental health, psychiatrists should play an active role in identifying emerging mental problems as soon as possible, and psychological support should be offered for discharged patients, especially for more vulnerable groups. For this purpose, we need stronger data with larger samples to properly identify the consequences of the COVID-19 pandemic on mental health and detect patients who might be more in need of further support and care.

ARTICLE HIGHLIGHTS

Research background
The authors designed a prospective study to compare the scores at baseline (hospitalization) of patients diagnosed with coronavirus disease 2019 (COVID-19) on a rating scale measuring anxiety and depression with their scores at the end (after 20-22 mo). This is the longest follow-up study in the literature.

Research motivation
The course of long-term psychiatric symptoms related to COVID-19 is still unknown.

Research objectives
To evaluate how anxiety and depression progress and identify the factors that play a role in this course by long-term follow-up.

Research methods
A large number of patients were reached in a short time using the telepsychiatry method.
Research results
In our study, we observed that anxiety and depression scores increased during the follow-up. The continuation of long-term follow-up studies will contribute to the clarification of the subject.

Research conclusions
The authors found that the mean scores of anxiety and depression increased in the follow-up after recovery in patients who had COVID-19. This confirmed the knowledge that there may be various permanent or temporary mental symptoms related to COVID-19. The authors observed that the symptoms of anxiety and depression secondary to COVID-19 increased while we expected them to decrease in the long follow-up. For this reason, patients with COVID-19 should be examined as soon as possible and necessary treatments should be given.

Research perspectives
More comprehensive follow-up studies for psychiatric symptoms secondary to COVID-19 should be continued and the importance of early intervention should be emphasized.

FOOTNOTES
Author contributions: Boyraz RK contributed to literature search, figure preparation, study design, data analysis and interpretation, and draft writing; Boylu ME contributed to data collection and interpretation, and statistical analysis; Şahan E contributed to literature search, figure preparation, study design, data analysis and interpretation, and revision and supervision of the manuscript; and Kırpınar İ contributed to supervision of the manuscript.

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Yilmaz O, Yogeeswaran K, Ziemer CT, Zwaan RA, Boggio PS. National identity predicts public health support during a
META-ANALYSIS

Same-day single-dose vs large-volume split-dose regimens of polyethylene glycol for bowel preparation: A systematic review and meta-analysis

Hui Pan, Xiao-Ling Zheng, Chao-Ying Fang, Lan-Zai Liu, Jian-Su Chen, Chao Wang, Yu-Dai Chen, Jian-Min Huang, Yu-Shen Zhou, Li-Ping He

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**Abstract**

**BACKGROUND**

Split-dose regimens (SpDs) of 4 L of polyethylene glycol (PEG) have been established as the “gold standard” for bowel preparation; however, its use is limited by the large volumes of fluids required and sleep disturbance associated with night doses. Meanwhile, the same-day single-dose regimens (SSDs) of PEG has been recommended as an alternative; however, its superiority compared to other regimens is a matter of debate.

**AIM**

To compare the efficacy and tolerability between SSDs and large-volume SpDs PEG for bowel preparation.

**METHODS**

We searched MEDLINE/PubMed, the Cochrane Library, RCA, EMBASE and Science Citation Index Expanded for randomized trials comparing (2 L/4 L) SSDs to large-volume (4 L/3 L) SpDs PEG-based regimens, regardless of adjuvant laxative use. The pooled analysis of relative risk ratio and mean difference was calculated for bowel cleanliness, sleep disturbance, willingness to repeat the procedure using the same preparation and adverse effects. A random effects model or fixed-effects model was chosen based on heterogeneity analysis among studies.
RESULTS
A total of 18 studies were included. There was no statistically significant difference of adequate bowel preparation (relative risk = 0.97; 95%CI: 0.92-1.02) (14 trials), right colon Boston Bowel Preparation Scale (mean difference = 0.00; 95%CI: -0.04, 0.03) (9 trials) and right colon Ottawa Bowel Preparation Scale (mean difference = 0.04; 95%CI: -0.27, 0.34) (5 trials) between (2 L/4 L) SSDs and large-volume (4 L/3 L) SpDs, regardless of adjuvant laxative use. The pooled analysis favored the use of SSDs with less sleep disturbance (relative risk = 0.52; 95%CI: 0.40, 0.68) and lower incidence of abdominal pain (relative risk = 0.75; 95%CI: 0.62, 0.90). During subgroup analysis, patients that received low-volume (2 L) SSDs showed more willingness to repeat the procedure using the same preparation than SpDs ($P < 0.05$). No significant difference in adverse effects, including nausea, vomiting and bloating, was found between the two arms ($P > 0.05$).

CONCLUSION
Regardless of adjuvant laxative use, the (2 L/4 L) SSD PEG-based arm was considered equal or better than the large-volume (≥ 3 L) SpDs PEG regimen in terms of bowel cleanliness and tolerability. Patients that received low-volume (2 L) SSDs showed more willingness to repeat the procedure using the same preparation due to the low-volume fluid requirement and less sleep disturbance.

Key Words: Bowel preparation; Colonoscopy; Polyethylene glycol; Same-day single-dose; Split-dose; Meta-analysis

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Core Tip: Same-day single-dose polyethylene glycol-based regimens for bowel preparation seemed to be equal or better than large-volume (≥ 3 L) split-dose polyethylene glycol solution in terms of bowel cleanliness and tolerability as long as the optimal preparation-to-colonoscopy interval and diet instruction for bowel preparation were respected.

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DOI: https://dx.doi.org/10.12998/wjcc.v10.i22.7844

INTRODUCTION
A colonoscopy is an important tool used for colorectal cancer screening and the management of colorectal lesions. However, the success of colonoscopy is strongly dependent on the quality of bowel preparation. Prior studies have reported that poor bowel preparation can increase the risk of missed diagnosis for smaller and/or flat lesions, especially in the right colon, and prolong cecal intubation time [1,2]. Polyethylene glycol (PEG) solutions, as efficient and safe purgative agents, offer the advantage of minimal fluid and electrolyte shifts and are reportedly the most widely used solutions for bowel preparation [1-3]. High volume (4 L) split-dose regimens (SpDs) of PEG have been recommended as the gold-standard regimen for bowel preparation [4], however, the large volume of fluids or poor tolerability associated with SpDs have become a source of patient dissatisfaction. The same-day single-dose (SSD) PEG has been recommended as an alternative for patients scheduled for afternoon colonoscopy [5,6], exhibiting equal cleansing efficacy and fewer sleep disturbances than SpDs. Meanwhile, it was reported to be in favor of reducing the preparation volume and improving patient tolerance by using PEG solution combined with adjuvant laxative agents for those at risk of bowel preparation [7]. A previous systematic review by Enestvedt et al [8] revealed that 4 L split-dose PEG was better than other bowel preparation comparators including a regimen of 4 L single-dose PEG the night before the procedure and MiraLAX/Gatorade solutions, regardless of adjuvant laxative use. However, in order to evaluate bowel cleanliness of the SSD regimens of PEG and patient tolerance in terms of sleep disturbances and side effects for bowel preparation, we conducted a systematic review and meta-analysis to compare the efficacy and tolerability of SSD PEG-based arm vs large-volume (≥ 3 L) split-dose PEG solutions for bowel preparation before colonoscopy, regardless of adjuvant laxative use.
MATERIALS AND METHODS

Search strategy and study selection
Systemic searches were performed in June 2021 using MEDLINE/PubMed, EMBASE, Web of Science, Google Scholar and Cochrane Library by two independent reviewers. The search strategy used the Medical Subject Heading term along with the keywords “polyethylene glycol, (bowel preparation OR bowel preparation solution), (split dose OR split-dose) and randomized controlled.” Only full texts published in English with one arm using single-dose PEG on the day of colonoscopy, regardless of adjuvant laxative use and the other arm consisting of a split-dose regimen of PEG for bowel preparation before and on the day of the procedure, were included. References from the reviewed articles were also searched to identify relevant articles that may have been missed.

Exclusion criteria consisted of the following: (1) Participants: pediatric patients, cases of prior colorectal resection and incomplete or complete bowel obstruction cases; (2) Non-colonoscopy studies; (3) Interventions: non-PEG-based solution (i.e. sodium phosphate, picosulfate, sodium picosulfate with magnesium citrate agents, etc); and (4) Comparisons: trials comparing evening-before vs split-dose, twice a same-day vs split-dose and low-volume (≤ 2 L) split-dose. A flowchart of the literature search is shown in Figure 1.

Data extraction and methodologic quality assessment
Two authors independently conducted the screening and extracted the data from selected trials with the intention to treat numbers preferred. Results from included studies reported as percentages were converted to absolute numbers.

The methodological quality of each study was graded by two investigators using a modified Jadad scoring system utilized for single (endoscopist) blinding trials[8]. This 5-point scale assigns a single point for each of the following: (1) The study is described as randomized; (2) The randomization method is described and appropriate; (3) The study is described as blind; (4) The blinding method is described and appropriate; and (5) There is a description of withdrawals and drop-outs. A score of 5 suggested excellent quality, and a score of 0 implied a poor-quality randomized controlled trial. Single-blinding rather than double-blinding can be executed logistically for bowel preparation studies. To ensure the adequacy of blinding, all endoscopists were blinded to the bowel preparation, and staff, nurses and patients were instructed not to discuss the bowel preparation with the endoscopist. The funnel plot was used to assess publication bias. The Grades of Recommendation, Assessment, Development and Evaluation approach was presented to rate the certainty of evidence. Points of disagreement were reconciled by a discussion with another author when required.

Outcomes
The primary outcome measure was bowel cleanliness, defined as adequate bowel preparation using validated scales [Ottawa Bowel Preparation Scale (OBPS) or Boston Bowel Preparation Scale (BBPS)]. Secondary outcomes included the willingness to repeat the procedure using the same preparation, sleep disturbance and side effects, including nausea, vomiting, bloating and abdominal pain/cramps.

The total OBPS score was based upon the sum of the right, transverse and left colonic segments (reference range of 0-4 each segment) plus an overall colonic fluid score (range 0-2)[9]. The total score ranged from 0 to 14; the lower the score, the better the preparation. The total BBPS score was the sum of the right colon, mid-colon and left colonic segmental scale. The total score ranged from 0 to 9 (0 = very poor, 9 = excellent)[10].

Statistical analysis
Statistical analysis was conducted with Review Manager (Version 5.4, Cochrane Collaboration, Oxford, GB). The categorical outcomes were analyzed using relative risk ratio (RR) and its corresponding 95% confidence interval (CI). Continuous data were analyzed using mean differences (MD) and corresponding 95%CI. Statistical heterogeneity was measured by graphic examination of forest plots and statistically through a homogeneity test based on the χ² test (P≥50% suggests heterogeneity) in which P < 0.10 was considered significant for heterogeneity. A fixed-effects model was used unless there was significant heterogeneity, in which case a random-effects model was applied. Weighted MDs were used for outcomes measured on different scales. A RR > 1 favored the SSD arm, while a RR < 1 favored the SpDs arm for the favorable outcomes (adequate preparation and willingness to repeat) and the adverse outcomes (sleep disturbance and adverse effects). The MD represented the difference in means between SSD and SpDs (SSD – SpDs = MD); an MD > 0 favored the SSD arm, while an MD < 0 favored the SpDs arm. A higher mean BBPS score indicated better quality of bowel preparation, which was the opposite for OBPS scores. Subgroup analysis was performed to characterize heterogeneity and sensitivity.
Figure 1 Flowchart of the study selection. PEG: Polyethylene glycol; RCT: Randomized controlled trial.

RESULTS

Search results
The initial search identified 490 potentially relevant articles. A total of 422 articles were excluded based on titles and abstracts because they included patients < 18 years of age, non-colonoscopy studies, reviews, retrospective studies or duplications. Sixty-eight articles were reviewed by full text. Overall, 18 articles [11-28] comparing bowel preparation with SSDs vs SpDs PEG were included in this analysis. Figure 1 shows a flowchart of studies from initial results of publication searches to final inclusion or exclusion. Table 1 summarizes the characteristics of the 18 included studies (n = 5464), which consisted of 2793 patients who received SSDs and 2671 patients who received the SpDs regimen. Nine trials evaluated low-volume (2 L) SSD PEG with adjuvant laxative use vs large-volume (≥ 3 L) SpDs PEG [11,12,22-28], four trials compared 4 L SSD PEG vs 4 L SpDs PEG [13,14,19,20], and six trials compared 2 L SSD PEG vs (≥ 3 L) SpDs PEG [11,15-18,21]. Interestingly, in a study by Zhang et al [11], patients were assigned to three groups: 2 L SSD PEG, 2 L SSD PEG with adjuvant laxative (linaclotide) and 4 L SpDs PEG. Bowel cleanliness was evaluated either with BBPS [11,12,14,15,18,23-27] or OBPS [13,16,17,19-22,28]. An adequate bowel preparation was defined as a total BBPS score ≥ 6 with all colon segments scores ≥ 2, or a total OBPS score < 5 (including score < 7 by De Leon, score ≤ 3 by Cesaro) or all colon segment OBPS score < 2. Diet restriction was mentioned in 16 trials and consisted of low residual diet/low-fiber foods [11,14-16,20-25,27-28] or clear liquid diet [13,15,17,19,26,28] before colonoscopy. Colonoscopy was performed with optimal preparation-to-colonoscopy (PC) interval time in only 6 trials [11,12,15,16,21,24], while 9 trials did not mention the PC interval [13,14,20,22,23,25-28].

Quality of bowel cleanliness
Fourteen studies provided dichotomous information on adequate bowel preparation between the SSDs and SpDs groups, regardless of adjuvant laxative use, and significant heterogeneity was observed (P < 0.00001, I² = 76%) in the pooled estimate. Using a random-effects model, no statistically significant difference was found between the two groups (RR = 0.97; 95%CI: 0.92-1.02) (P = 0.19) as shown in Figure 2. Continuous data on right colon BBPS was available in 9 trials (Figure 3). No significant heterogeneity was observed (P = 0.22, I² = 25%). Using a fixed-effects model, we found that there was no significant difference between the two arms (MD = 0.00; 95%CI: -0.04, 0.03).

Five studies provided continuous data on right colon OBPS (Figure 4), and significant heterogeneity was observed (P = 0.001, I² = 78%). Using a random-effects model, no significant difference was found between the two arms (MD = 0.04; 95%CI: -0.27, 0.34) (P = 0.82).
<table>
<thead>
<tr>
<th>Ref.</th>
<th>Type of study</th>
<th>Participants and years of age</th>
<th>Bowel preparation</th>
<th>Patients with SSD/SpDs, n</th>
<th>Diet instruction</th>
<th>Colonoscopy timing</th>
<th>Outcomes</th>
<th>Interval, PC</th>
<th>Jadad score, modified</th>
<th>Use of adjuvant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhang et al [11], 2021</td>
<td>Single-center, single-blind, RCT</td>
<td>Outpatients 18-70 yr</td>
<td>SSD (A): 2 L PEG 6 h before procedure; SSD (B): 290 µg Lin 7 h before + 0.5 L water, 2 L PEG 6 h before colonoscopy; SpDs: 2 L PEG at 21:00 the day prior, 2 L PEG 6 h before colonoscopy</td>
<td>139A/141B/140</td>
<td>1-d LRD</td>
<td>Morning: 8:00-11:30; Afternoon: 13:30-17:00</td>
<td>BBPS</td>
<td>6 h</td>
<td>4</td>
<td>SSD (B): Linaclotide</td>
</tr>
<tr>
<td>Barkun et al [12], 2020</td>
<td>Multicenter, single-blind, RCT</td>
<td>Outpatients ≥ 18 yr</td>
<td>SSD: 2 L PEG 4 h before colonoscopy + 15 mg bis at 14:00 the day before; SpDs: 2 L PEG at 19:00 the day before, 2 L PEG 4-5 h before colonoscopy</td>
<td>583/582</td>
<td>Not described</td>
<td>10:30-16:30</td>
<td>BBPS</td>
<td>2-3 h</td>
<td>5</td>
<td>Bisacodyl</td>
</tr>
<tr>
<td>Castro et al [13], 2019</td>
<td>Single-center, single-blind, RCT</td>
<td>Outpatients ≥ 18 yr</td>
<td>SSD: 4 L PEG at 6:00; SpDs: 2 L PEG at 18:00 the day before, 2 L PEG 6 h before colonoscopy</td>
<td>142/158</td>
<td>CLD after regular breakfast the day before</td>
<td>13:00-16:30</td>
<td>OBPS</td>
<td>Not described</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seo et al [14], 2019</td>
<td>Single-center, single-blind, RCT</td>
<td>Outpatients 40-75 yr</td>
<td>SSD (Mor): 4 L PEG at 5:00; SSD (Aft): 2 L PEG at 7:00 + 2 L PEG at 10:00; SpDs: 2 L PEG at 21:00 the day before, 2 L PEG at 7:00 (Mor) or at 10:00 (Aft)</td>
<td>172/167</td>
<td>LFF for 2 d, soft diet dinner the day prior</td>
<td>Morning 10:00-12:00; Afternoon 13:30-17:00</td>
<td>BBPS</td>
<td>Not described</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Kang et al [15], 2018</td>
<td>Single-center, single-blind, RCT</td>
<td>Patients 18-70 yr</td>
<td>SSD: 2 L PEG 4-6 h before colonoscopy; SpDs: 2 L PEG at 19:00-21:00 the day before, 2 L PEG 4-6 h before colonoscopy</td>
<td>470/470</td>
<td>Regular meal for lunch and CLD or LRD for dinner the day before</td>
<td>Morning 8:30-12:00; Afternoon 13:00-16:00</td>
<td>BBPS</td>
<td>2-4 h</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Zhang et al [16], 2015</td>
<td>Multicenter, single-blind, RCT</td>
<td>Patients 18-75 yr</td>
<td>SSD: 2 L PEG 4-6 h before colonoscopy; SpDs: 1 L PEG at 21:00 the day before, 2 L PEG 4-6 h before colonoscopy</td>
<td>159/159</td>
<td>1-d LRD</td>
<td>Not described</td>
<td>OBPS</td>
<td>2-4 h</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Shah et al [17], 2014</td>
<td>Single-center, single-blind, RCT</td>
<td>Patients ≥ 18 yr</td>
<td>SSD: 2 L PEG at 5:00-7:00; SpDs: 1 L PEG at 18:00-19:00 the day before, 1 L PEG at 6:00-7:00</td>
<td>103/97</td>
<td>1-d liquid diet and CLD after midnight</td>
<td>11:00-16:00</td>
<td>OBPS</td>
<td>≥ 4 h</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Tellez-Avila et al [18], 2014</td>
<td>Single-center, single-blind, RCT</td>
<td>Inpatients ≥ 18 yr</td>
<td>SSD: 2 L PEG at 6:00-8:00; SpDs: 2 L PEG at 17:00-19:00 the day before, 2 L PEG at 6:00-8:00</td>
<td>61/67</td>
<td>Not described</td>
<td>Not described</td>
<td>BBPS</td>
<td>≥ 3 h</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Kotwal et al [19], 2014</td>
<td>Single-center, single-blind, RCT</td>
<td>Inpatients 18-80 yr</td>
<td>SSD: 4 L PEG at 5:00-9:00; SpDs: 2 L PEG at 19:00-21:00 the day before, 2 L PEG at 7:00-9:00</td>
<td>60/60</td>
<td>1-d CLD</td>
<td>After 11:00</td>
<td>OBPS</td>
<td>≥ 2 h</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Kim et al [20], 2014</td>
<td>Single-center, single-blind, RCT</td>
<td>Outpatients 18-75 yr</td>
<td>SSD: 4 L PEG 6 h before colonoscopy; SpDs: 2 L PEG at 18:00 the day before, 2 L PEG 4-6 h before colonoscopy</td>
<td>50/50</td>
<td>Avoid high-fiber foods 3 d prior</td>
<td>Not described</td>
<td>OBPS</td>
<td>Not described</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Seo et al [21], 2013</td>
<td>Single-center, single-blind, RCT</td>
<td>Outpatients 18-85 yr</td>
<td>SSD: 2 L PEG 5 h before colonoscopy; SpDs: 2 L PEG at 18:00 the day before, 2 L PEG 5 h before colonoscopy</td>
<td>103/102</td>
<td>3-d LRD</td>
<td>9:00-17:00</td>
<td>OBPS</td>
<td>≥ 3 h</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Cesaro et al [22], 2013</td>
<td>Single-center, single-blind, RCT</td>
<td>Outpatients 18-85 yr</td>
<td>SSD: 2 L PEG-CS at 6:00 + bis 10-20 mg at 22:00 the day before; SpDs: 3 L PEG at 19:00 the day before, 1 L</td>
<td>50/51</td>
<td>3-d LRD</td>
<td>11:00-18:00</td>
<td>OBPS</td>
<td>Not described</td>
<td>5</td>
<td>Bisacodyl</td>
</tr>
</tbody>
</table>
SSD: Same-day single-dose; SpDs: Split-dose; PC: Preparation-to-colonoscopy; LFF: Low-fiber foods; LRD: Low residual diet; CLD: Clear liquid diet; PEG-CS: Polyethylene glycol with citrates and simethicone; PEG-ASc: Polyethylene glycol ascorbic acid; RCT: Randomized controlled trial; PEG: Polyethylene glycol; Lin: Linaclotide; BBPS: Boston Bowel Preparation Scale; bis: Bisacodyl; OBPS: Ottawa Bowel Preparation Scale; Mor: Morning; Aft: Afternoon; Pru: Prucalopride.

**Subgroup analysis**

**2 L SSD with adjuvant vs SpDs:** Seven trials provided dichotomous information on adequate bowel preparation comparing the 2 L SSDs with adjuvant laxative use to the (≥ 3 L) SpDs regimen. The pooled estimates showed significant heterogeneity within the included studies (P = 0.05, I² = 51%). Using a random-effects model, no statistically significant difference was found between the two groups (RR = 1.00; 95%CI: 0.95, 1.05) (P = 0.99). Continuous data on the right colon BBPS was provided in 7 studies. Pooled estimate results showed no significant heterogeneity (P = 0.12, I² = 41%). Using a fixed-effects model, we found that there was no significant difference between the two groups. (MD = 0.00; 95%CI: -0.05, 0.05) (P = 0.93). Only 1 study reported data on right colon OBPS (Table 2).

**2 L SSD without adjuvant vs SpDs:** Five trials compared 2 L SSDs without adjuvant to ≥ 3 L SpDs regimens and provided categorical data on the adequacy of bowel preparation. The pooled estimate results showed significant heterogeneity within the included studies (P < 0.00001, I² = 90%). Using a random-effects model, no statistical difference was reported between the two groups (RR = 0.86; 95%CI:
SSD: Same-day single-dose; SpDs: Split-dose; BBPS: Boston bowel preparation scale; OBPS: Ottawa bowel preparation scale; cat-RR/con-MD: Categorical-relative risk ratio/continuous-mean differences; CI: Confidence interval.

0.72, 1.02) (P = 0.07).

Two trials provided continuous data on right colon BBPS. The pooled estimates showed no significant heterogeneity between both studies (P = 1.00, F = 0%). Using a fixed-effects model, no significant difference was found between the two groups. (MD = 0.00; 95%CI: -0.07, 0.07) (P = 1.00). Two studies provided continuous data on right colon OBPS. The pooled estimates showed significant heterogeneity (P = 0.003, I² = 89%). Using a random-effects model, no significant difference was found between the two groups. (MD = 0.26; 95%CI: -0.20, 0.72) (P = 0.26) (Table 2).

4 L SSD without adjuvant vs SpDs: Three trials compared the adequacy of bowel preparation between 4 L SSDs without adjuvant and 4 L SpDs regimens. The pooled estimates showed that no significant heterogeneity was present within these studies (P = 0.66, F = 0%). Using a fixed-effects model, we found that there was no significant difference between the two groups (RR = 0.99; 95%CI: 0.94, 1.05) (P = 0.82). Only 1 study reported data on the right colon BBPS.

The right colon OBPS scores were provided in 2 studies. The pooled estimates showed no significant heterogeneity between both studies (P = 0.71, F = 0%). Using a fixed-effects model, no significant difference was found between the two groups. (MD = -0.06; 95%CI: -0.30, 0.18) (P = 0.62) (Table 2).

Secondary outcomes
Fifteen studies provided dichotomous information on sleep disturbance between the SSD and SpDs PEG groups (Table 3). During the pooled estimates, significant heterogeneity was observed (P < 0.00001, F = 74%). Using a random-effects model, a significant difference was found between the two groups (RR = 0.52; 95%CI: 0.40, 0.68) (P < 0.00001). During subgroup analysis, 7 trials comparing 2 L SSD with adjuvant vs SpDs showed no significant difference in sleep disturbance between the two groups (RR = 0.69; 95%CI: 0.43, 1.10) (P = 0.12).

Ten trials provided dichotomous information on patient willingness to repeat the procedure using the same preparation between the SSD and SpDs PEG groups (Table 3). During the pooled estimates, significant heterogeneity was observed (P < 0.00001, F = 90%). Using a random-effects model, a significant difference was found between the two groups (RR = 1.15; 95%CI: 1.03, 1.29) (P = 0.01). Two trials in subgroup analysis of 4 L SSD without adjuvant vs SpDs found no significant difference between the two groups (RR = 0.89; 95%CI: 0.71, 1.13) (P = 0.34).
Table 3 Secondary outcome

<table>
<thead>
<tr>
<th>Secondary outcome</th>
<th>Studies (n)</th>
<th>SSD (n)</th>
<th>SpDs (n)</th>
<th>I² (%)</th>
<th>P value for heterogeneity</th>
<th>Pooled analysis (cat-RR/con-MD)</th>
<th>95%CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep disturbance</td>
<td>15</td>
<td>2591</td>
<td>2463</td>
<td>74</td>
<td>&lt; 0.00001</td>
<td>0.52</td>
<td>(0.40, 0.68)</td>
<td>&lt; 0.00001</td>
</tr>
<tr>
<td>2 L SSD with adjuvant vs SpDs</td>
<td>7</td>
<td>1214</td>
<td>1215</td>
<td>69</td>
<td>0.003</td>
<td>0.69</td>
<td>(0.43, 1.10)</td>
<td>0.12</td>
</tr>
<tr>
<td>2 L SSD without adjuvant vs SpDs</td>
<td>6</td>
<td>1014</td>
<td>1013</td>
<td>80</td>
<td>0.0002</td>
<td>0.45</td>
<td>(0.30, 0.67)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>4 L SSD without adjuvant vs SpDs</td>
<td>3</td>
<td>363</td>
<td>375</td>
<td>67</td>
<td>0.05</td>
<td>0.47</td>
<td>(0.28, 0.78)</td>
<td>0.004</td>
</tr>
<tr>
<td>Willingness to repeat</td>
<td>10</td>
<td>1996</td>
<td>1855</td>
<td>90</td>
<td>&lt; 0.00001</td>
<td>1.15</td>
<td>(1.03, 1.29)</td>
<td>0.01</td>
</tr>
<tr>
<td>2 L SSD with adjuvant vs SpDs</td>
<td>6</td>
<td>1073</td>
<td>1078</td>
<td>89</td>
<td>&lt; 0.00001</td>
<td>1.24</td>
<td>(1.06, 1.45)</td>
<td>0.008</td>
</tr>
<tr>
<td>2 L SSD without adjuvant vs SpDs</td>
<td>3</td>
<td>691</td>
<td>690</td>
<td>82</td>
<td>0.004</td>
<td>1.14</td>
<td>(1.01, 1.29)</td>
<td>0.03</td>
</tr>
<tr>
<td>4 L SSD without adjuvant vs SpDs</td>
<td>2</td>
<td>232</td>
<td>227</td>
<td>54</td>
<td>0.14</td>
<td>0.89</td>
<td>(0.71, 1.13)</td>
<td>0.34</td>
</tr>
<tr>
<td>Side effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>17</td>
<td>2715</td>
<td>2592</td>
<td>68</td>
<td>&lt; 0.0001</td>
<td>0.95</td>
<td>(0.78, 1.16)</td>
<td>0.63</td>
</tr>
<tr>
<td>Vomiting</td>
<td>16</td>
<td>2644</td>
<td>2521</td>
<td>64</td>
<td>0.0002</td>
<td>0.96</td>
<td>(0.66, 1.38)</td>
<td>0.81</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>17</td>
<td>2715</td>
<td>2592</td>
<td>38</td>
<td>0.06</td>
<td>0.75</td>
<td>(0.62, 0.90)</td>
<td>0.002</td>
</tr>
<tr>
<td>Bloating</td>
<td>15</td>
<td>2205</td>
<td>2077</td>
<td>67</td>
<td>0.0001</td>
<td>0.80</td>
<td>(0.63, 1.01)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

SSD: Same-day single-dose; SpDs: Split-dose; cat-RR/con-MD: Categorical-relative risk ratio/continuous-mean differences; CI: Confidence interval.

The incidence of adverse effects, including nausea, vomiting, abdominal pain and bloating, was reported in 17, 16, 17 and 15 trials, respectively (Table 3). No significant difference in nausea (RR = 0.95; 95%CI: 0.78, 1.16), vomiting (RR = 0.96; 95%CI: 0.66, 1.38) and bloating (RR = 0.80; 95%CI: 0.63, 1.01) was found between the two groups. However, there was a significant difference in abdominal pain between the two arms, favoring the SSD group (RR = 0.75; 95%CI: 0.62, 0.90).

**Publication bias**
For the publication bias, in our meta-analysis a better symmetry was present with the use of funnel plots (Figure 5). The Grades of Recommendation, Assessment, Development and Evaluation as one systematic approach rated the certainty of evidence for moderate level in this systematic review and meta-analysis (Table 4).

**DISCUSSION**
This updated meta-analysis reviewed 18 trials comparing the efficacy and tolerability of bowel preparation between SSD PEG-based and large-volume SpDs PEG regimens. In recent years, the split dose of 4 L PEG has been adopted as a standard regimen for bowel preparation. However, patients often complain of the large-volume regimen and sleep disturbance due to frequent bowel movements and abdominal discomfort. To enhance patient compliance with the preparation, several studies have suggested adding other laxatives, such as bisacodyl, linaclotide or prucalopride, to a low-volume PEG bowel preparation to reduce the solution volume[11,12,25]. In the present study, according to the volume of PEG ingested and combination with adjuvant laxative, SSD PEG-based regimens were separated into three subgroups: low-volume (2 L) SSD PEG combined with an adjuvant agent, low-volume (2 L) SSD PEG without adjuvant laxative and large-volume (4 L) SSD PEG without adjuvant laxative. In a pooled analysis, we have shown that SSD PEG was as effective as SpDs PEG-based regimens in terms of bowel cleanliness, regardless of adjuvant laxative use and dosage.
### Table 4 Grades of Recommendation, Assessment, Development and Evaluation rated the certainty of evidence

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>SSD</th>
<th>SpDs</th>
<th>RR (95%CI)</th>
<th>Effect/Absolute</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate bowel cleanliness</td>
<td>14</td>
<td>Randomized trials</td>
<td>No serious risk of bias</td>
<td>Serious¹</td>
<td>No serious indirectness</td>
<td>No serious imprecision</td>
<td>None</td>
<td>2002/2468 (81.1%)</td>
<td>1973/2390 (84.0%)</td>
<td>RR 0.97 (0.92 to 1.02)</td>
<td>25 fewer per 1000 (from 67 fewer to 17 more)</td>
<td>(+++ moderate)</td>
</tr>
<tr>
<td>Right colon BBPS</td>
<td>9</td>
<td>Randomized trials</td>
<td>No serious risk of bias</td>
<td>No serious inconsistency</td>
<td>No serious indirectness</td>
<td>No serious imprecision</td>
<td>None</td>
<td>1869</td>
<td>1869</td>
<td>Md 0 higher (0.04 lower to 0.03 higher)</td>
<td>(++++) high</td>
<td>Critical</td>
</tr>
<tr>
<td>Right colon OBPS</td>
<td>5</td>
<td>Randomized trials</td>
<td>No serious risk of bias</td>
<td>Serious¹</td>
<td>No serious indirectness</td>
<td>No serious imprecision</td>
<td>None</td>
<td>422</td>
<td>422</td>
<td>Md 0.04 higher (0.27 lower to 0.34 higher)</td>
<td>(+++) moderate</td>
<td>Critical</td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>15</td>
<td>Randomized trials</td>
<td>No serious risk of bias</td>
<td>Serious¹</td>
<td>No serious indirectness</td>
<td>No serious imprecision</td>
<td>None</td>
<td>348/2591 (13.4%)</td>
<td>651/2463 (26.4%)</td>
<td>RR 0.52 (0.40 to 0.68)</td>
<td>127 fewer per 1000 (from 85 fewer to 159 fewer)</td>
<td>(++) moderate</td>
</tr>
<tr>
<td>Willingness to repeat</td>
<td>10</td>
<td>Randomized trials</td>
<td>No serious risk of bias</td>
<td>Serious¹</td>
<td>No serious indirectness</td>
<td>No serious imprecision</td>
<td>None</td>
<td>1624/1996 (81.4%)</td>
<td>1269/1855 (68.4%)</td>
<td>RR 1.15 (1.03 to 1.29)</td>
<td>103 more per 1000 (from 21 more to 198 more)</td>
<td>(++) moderate</td>
</tr>
<tr>
<td>Nausea</td>
<td>17</td>
<td>Randomized trials</td>
<td>No serious risk of bias</td>
<td>Serious¹</td>
<td>No serious indirectness</td>
<td>No serious imprecision</td>
<td>None</td>
<td>516/2715 (19.0%)</td>
<td>559/2592 (21.6%)</td>
<td>RR 0.95 (0.78 to 1.16)</td>
<td>11 fewer per 1000 (from 47 fewer to 35 more)</td>
<td>(++) moderate</td>
</tr>
<tr>
<td>Vomiting</td>
<td>16</td>
<td>Randomized trials</td>
<td>No serious risk of bias</td>
<td>Serious¹</td>
<td>No serious indirectness</td>
<td>No serious imprecision</td>
<td>None</td>
<td>191/2644 (7.2%)</td>
<td>202/2521 (8.0%)</td>
<td>RR 0.96 (0.66 to 1.38)</td>
<td>3 fewer per 1000 (from 27 fewer to 30 more)</td>
<td>(++) moderate</td>
</tr>
</tbody>
</table>
Abdominal pain

<table>
<thead>
<tr>
<th>17</th>
<th>Randomized trials</th>
<th>No serious risk of bias</th>
<th>Serious 1</th>
<th>No serious indirectness</th>
<th>No serious imprecision</th>
<th>None</th>
<th>168/2715 (6.2%)</th>
<th>221/2592 (8.5%)</th>
<th>RR 0.75 (0.62 to 0.9)</th>
<th>21 fewer per 1000 (from 9 fewer to 32 fewer)</th>
</tr>
</thead>
</table>

(+) Critical

Bloating

<table>
<thead>
<tr>
<th>15</th>
<th>Randomized trials</th>
<th>No serious risk of bias</th>
<th>Serious 1</th>
<th>No serious indirectness</th>
<th>No serious imprecision</th>
<th>None</th>
<th>322/2205 (14.6%)</th>
<th>415/2077 (20.0%)</th>
<th>RR 0.8 (0.63 to 1.01)</th>
<th>40 fewer per 1000 (from 74 fewer to 2 more)</th>
</tr>
</thead>
</table>

(++) Critical

1 Only a few different studies have shown conflicting results. SSD: Same-day single-dose; SpDs: Split-dose; CI: Confidence interval; RR: Relative risk; BBPS: Boston Bowel Preparation Scale; Md: Moderate; OBPS: Ottawa Bowel Preparation Scale.

Previous meta-analyses by Cheng et al.[29] and Avalos et al.[30] showed a trend to the equivalent efficacy for bowel preparation in terms of bowel cleanliness and adenoma detection rate when compared to same-day (one or two doses) with split-dose bowel preparation regimens regardless of purgative type. Patients with a history of pelvic surgery and colorectal surgery as high-risks of poor bowel preparation were not excluded by the forementioned studies[29,30]. Other identified patient-related risk factors for inadequate bowel preparation include diabetes and constipation[31]. In the present study, patients with a history of constipation and diabetes mellitus were included, and analysis results obtained were consistent with previous studies. We considered that the SSD PEG-based arm had the same efficacy in bowel cleanliness as the SpDs arm for patients at high-risk of poor bowel preparation by complying with the optimal PC interval and diet instruction before colonoscopy.

In a study by Seo et al.[3], multivariate analysis showed that the PC interval, the amount of PEG ingested and compliance with diet instructions were significant contributors to satisfactory bowel preparation, regardless of when the procedure was performed during the day. Colonoscopies performed with a PC interval of 3 to 5 h had the best bowel-cleansing quality throughout the colon, while a PC interval of 3 to 7 h was an acceptable scale for bowel preparation. It has been reported that after the optimal time window, small-bowel contents of bubbles and viscous bile-stained mucous are evacuated into the colon and restrict the visibility of the colonic mucosa, especially in the right colon. Small flat lesions that are difficult to identify in the right colon can easily be missed by the endoscopist if concealed by opaque small bowel effluent. Accordingly, same-day preparation with split-doses and full-doses improves bowel cleansing and increases the detection rate of small adenomas[28].

Compliance with dietary instructions has been documented as another factor affecting the quality of bowel preparation. A meta-analysis by Chen et al.[32] that analyzed factors of inadequate bowel preparation found no significant difference between a low residual diet and a clear liquid diet the day before colonoscopy. In our meta-analysis, in all included trials, patients in both arms followed a low residual diet or clear liquid diet, and no heterogeneity was found for dietary restriction before colonoscopy.
Consistent with a study by Avalos et al[30] we found that significantly less sleep disturbance was associated with the SSD PEG-based regimens without adjuvant laxatives than the SpDs PEG. However, the incidence of sleep disturbance in combination regimens of low-volume (2 L) SSD with an adjuvant laxative (bisacodyl, linaclotide or prucalopride) was comparable with SpDs regimens. It was noted that bowel movements induced by bisacodyl taken on the night before colonoscopy occurred after waking up. De Leone et al[28] suggested that sleeping difficulties were more likely to be attributed to the anxiety for the day-after procedure rather than nocturnal awakenings for defecation or abdominal pain in patients who took the combination regimen consisting of low-volume PEG with bisacodyl. Based on these findings, we conclude that the split-dose regimen taken the night before colonoscopy and anxiety for the procedure play an important role in the sleep quality of patients.

Patient tolerance of bowel preparation regimens mainly depends on sleep disruptions and adverse effects such as nausea, vomiting, abdominal pain/cramping and bloating. Significantly less nocturnal awakenings for defecation were reported in the SSD PEG-based arm than other SpDs PEG regimens, and no significant difference in other adverse effects was found. Given the low incidence of sleep disturbance and abdominal pain, patients were more tolerant to the SSD PEG-based arm for bowel preparation.
Moreover, patients who received the low-volume (2 L) SSD PEG regimens exhibited increased willingness to repeat the procedure using the same preparation. However, the large-volume (4 L) SSD PEG arm was not superior to the SpDs regimens in terms of willingness to repeat the procedure using the same preparation. This finding suggested that patient intolerance to ingestion of large volumes over a short period was a significant factor contributing to non-compliance and decreased willingness to repeat the procedure with the same regimen.

There are several advantages to this meta-analysis. We performed the extensive retrieval strategy and included only randomized controlled trials. Other advantages were related to the quality of the included studies and to the publication bias. The methodological quality assessment of the included studies was moderate to high according to the Cochrane risk of bias tool and modified Jadad score. For the publication bias, in our meta-analysis a rough symmetry was present with the use of funnel plots and the Grades of Recommendation, Assessment, Development and Evaluation approach.

This meta-analysis has several limitations. First, we enrolled only adult patients and excluded those who had undergone colorectal surgery and/or bowel obstruction; accordingly, the findings of our meta-analysis cannot be generalized for all patients that undergo colonoscopy. Moreover, it is widely acknowledged that constipation is a high-risk factor for poor preparation; however, there was a certain level of inconsistency on the proportion and severity of constipation within the included studies. Furthermore, adenoma detection rate was not evaluated as a secondary outcome. Indeed, adenoma detection rate is a quality indicator for colonoscopy and can be influenced by the endoscopist’s level of expertise and the quality of the bowel preparation[33].
CONCLUSION
We found that the SSD regimens of PEG were non-inferior to large-volume (≥ 3 L) SpDs PEG in terms of bowel cleanliness. Better tolerance to SSD PEG was accounted for by less sleep disturbance and abdominal pain than with the SpDs regimens. Given its efficacy and tolerability, the low-volume (2 L) SSD PEG regimen has huge prospects as a superior alternative to SpDs regimens as long as the optimal PC interval and dietary instructions for bowel preparation are respected.

ARTICLE HIGHLIGHTS

Research background
High volume (4 L) split-dose regimens (SpDs) of polyethylene glycol (PEG) have been recommended as the gold-standard regimen for bowel preparation, but its large volume of fluids and poor tolerability have become sources of patient dissatisfaction.

Research motivation
The same-day single-dose (SSD) PEG has been recommended as an alternative for bowel preparation. However, its superiority compared to other regimens is a matter of debate.

Research objectives
To seek one PEG-based regimen for bowel preparation with characteristics of equal cleansing efficacy, reducing the preparation volume and improving patient tolerance.

Research methods
We conducted a systematic review and meta-analysis to compare the efficacy and tolerability of SSD PEG-based arm vs large-volume (≥ 3 L) SpDs PEG solutions for bowel preparation before colonoscopy, regardless of adjuvant laxative use.

Research results
A total of 18 studies were included. There was no statistically significant difference of adequate bowel preparation, right colon Boston Bowel Preparation Scale and right colon Ottawa Bowel Preparation Scale between (2 L/4 L) SSDs and large-volume (4 L/3 L) SpDs, regardless of adjuvant laxative use. The use of SSDs had advantages of less sleep disturbance and lower incidence of abdominal pain. Patients that received low-volume (2 L) SSDs showed more willingness to repeat the procedure than patients receiving SpDs (P < 0.05).

Research conclusions
Regardless of adjuvant laxative use, the (2 L/4 L) SSDs PEG-based arm was considered equal or better than the large-volume (≥ 3 L) SpDs PEG regimen in terms of bowel cleanliness and tolerability.

Research perspectives
Given its efficacy and tolerability, the low-volume (2 L) SSD PEG regimen has huge prospects as a superior alternative to SpDs regimens as long as the optimal preparation-to-colonoscopy interval and dietary instructions for bowel preparation are respected.

FOOTNOTES

Author contributions: Pan H, Fang CY, Chen JS and Wang C contributed to data curation and writing the original draft; Zheng XL and Pan H contributed to the methodology; Zheng XL, Pan H and Fang CY contributed to the project administration; Chen YD, Huang JM and Zhou YS contributed to the supervision; Zheng XL and He LP contributed to the writing, reviewing and editing; all authors have read and approved the final manuscript.

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META-ANALYSIS

Rectal nonsteroidal anti-inflammatory drugs, glyceryl trinitrate, or combinations for prophylaxis of post-endoscopic retrograde cholangiopancreatography pancreatitis: A network meta-analysis

Qing-Qing Shi, Guo-Xiu Huang, Wei Li, Jian-Rong Yang, Xiao-Yi Ning

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification
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Grade B (Very good): 0
Grade C (Good): 0
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Kitamura K, Japan; Trna J, Czech Republic

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Published online: August 6, 2022

Abstract

BACKGROUND
Acute pancreatitis is the most common and severe complication of endoscopic retrograde cholangiopancreatography (ERCP). Recent evidence suggests that combinations based on rectal nonsteroidal anti-inflammatory drugs (NSAIDs) are more beneficial in preventing post-ERCP pancreatitis (PEP). Randomized controlled trials (RCTs) have also demonstrated the efficacy of glyceryl trinitrate (GTN). We conducted a network meta-analysis to compare NSAIDs and GTN for prevention of PEP and to determine whether they are better in combination.

AIM
To compare NSAIDs and GTN for prevention of PEP and to determine whether they are better in combination.

METHODS
A systematic search was done for full-text RCTs of PEP in PubMed, Embase, Science Citation Index, and the Cochrane Controlled Trials database. Inclusion and exclusion criteria were used to screen for eligible RCTs. The major data were extracted by two independent reviewers. The frequentist model was used to conduct this network meta-analysis and obtain the pairwise OR and 95% CI. The data were then extracted and assessed on the basis of the Reference Citation...
**Analysis** (https://www.referencecitationanalysis.com/).

**RESULTS**

Twenty-four eligible RCTs were selected, evaluating seven preventive strategies in 9416 patients. Rectal indomethacin 100 mg plus sublingual GTN (OR: 0.21, 95% CI: 0.09–0.50), rectal diclofenac 100 mg (0.34, 0.18–0.65), sublingual GTN (0.34, 0.12–0.97), and rectal indomethacin 100 mg (0.49, 0.33–0.73) were all more efficacious than placebo in preventing PEP. The combination of rectal indomethacin and sublingual GTN had the highest surface under the cumulative ranking curves (SUCRA) probability of (92.2%) and was the best preventive strategy for moderate-to-severe PEP with a SUCRA probability of (89.2%).

**CONCLUSION**

Combination of rectal indomethacin 100 mg with sublingual GTN offered better prevention of PEP than when used alone and could alleviate the severity of PEP.

**Key Words:** Endoscopic retrograde cholangiopancreatography; Pancreatitis; Diclofenac; Indomethacin; Naproxen; Glyceryl trinitrate

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**Core tip:** Post-endoscopic retrograde cholangiopancreatography pancreatitis (PEP) is a common and serious complication. Several prophylactic measures have been tried. Some guidelines recommend rectal administration of 100 mg diclofenac or indomethacin as routine PEP prophylaxis. Glyceryl trinitrate (GTN) has been reported as an effective drug for preventing PEP. In view of some high-quality randomized controlled trials, we conducted this network meta-analysis to compare nonsteroidal anti-inflammatory drugs and GTN for prevention of PEP and to determine whether they are better in combination. Our analysis showed that combination of rectal indomethacin 100 mg with sublingual GTN was the most effective strategy for preventing PEP and reducing its severity.

**Citation:** Shi QQ, Huang GX, Li W, Yang JR, Ning XY. Rectal nonsteroidal anti-inflammatory drugs, glyceryl trinitrate, or combinations for prophylaxis of post-endoscopic retrograde cholangiopancreatography pancreatitis: A network meta-analysis. *World J Clin Cases* 2022; 10(22): 7859-7871

**URL:** https://www.wjgnet.com/2307-8960/full/v10/i22/7859.htm

**DOI:** https://dx.doi.org/10.12998/wjcc.v10.i22.7859

**INTRODUCTION**

Endoscopic retrograde cholangiopancreatography (ERCP) is a widely used tool for diagnosing and treating biliary and pancreatic diseases. Despite technological advances and improved operator experience, ERCP has a high potential for complications, such as acute pancreatitis, bleeding, perforation, and cholangitis[1,2]. Post-ERCP pancreatitis (PEP) is the most common and serious complication, with an incidence of 3.5%–9.7% and mortality ranging from 0.1% to 0.7%[2]. It often leads to prolonged hospitalization and has a substantial economic impact[3].

Over the past few decades, several prophylactic measures have been explored to solve this thorny problem. These include the placement of pancreatic stents, intravenous fluids, and several pharmacological options[4,5]. Some guidelines recommend rectal administration of 100 mg diclofenac or indomethacin as routine PEP prophylaxis in unselected patients. Its efficacy and safety have been confirmed repeatedly[6]. Nevertheless, increasingly, studies have focused on combination therapy involving nonsteroidal anti-inflammatory drugs (NSAIDs) to investigate whether this might be more effective than NSAIDs alone[5,7].

A meta-analysis has confirmed that glyceryl trinitrate (GTN), an inexpensive and easily administered agent, effectively prevents PEP[8]. It has been suggested that a combination of GTN and NSAIDs may be more effective[9]. Therefore, we conducted a network meta-analysis of RCTs to compare the direct and indirect evidence and identify their effectiveness in preventing PEP.
MATERIALS AND METHODS

Search strategy
A comprehensive search was conducted independently by two review authors (Shi QQ and Ning XY). The following databases were searched: PubMed, Embase, Science Citation Index, and the Cochrane Controlled Trials, from initiation to September 10, 2021. The search terms included “pancreatitis” and “cholangiopancreatography, Endoscopic retrograde” or “Endoscopic retrograde cholangiopancreato-graphy” or “ERCP” and “random or randomized controlled trial” or “RCT”. The terms were limited to “title and abstract” and filtered with “human”. Only articles published in English were selected. The reference lists of related systematic reviews or meta-analyses were manually searched to avoid omitting eligible studies.

Selection criteria
The inclusion criteria were as follows: (1) RCTs published in full text and English, irrespective of whether double-blind; (2) Patients were subjected to ERCP and administration of rectal NSAIDs, sublingual GTN, or transdermal GTN to prevent PEP; and (3) Incidence of PEP was the primary outcome, and the definition of PEP was explicit. We excluded conference proceedings or abstracts, except where the complete information was available from the authors. We also excluded studies without a record of PEP.

Data extraction
The following data were extracted by two independent investigators (Shi QQ and Ning XY) from eligible RCTs using a common data form: first author, year of publication, country of origin, patient characteristics (ratio of men to women, age distribution), details of intervention and control, PEP definition, PEP severity criteria, sample size, and the incidence of PEP and its severity. The type, dose, route, and timing of medication were also extracted. Any conflicts were resolved through discussion or consultation with a third reviewer (Yang JR). The data were then extracted and assessed on the basis of the Reference Citation Analysis (https://www.referencecitationanalysis.com/).

Risk of bias assessment
The Cochrane Risk of Bias Assessment Tool was used by two authors to independently evaluate the risk of bias of individual studies (Li W and Huang GX)[10]. The assessment included the following items: Random sequence generation, allocation concealment, blinding of the participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and additional potential practices. Any disagreements were resolved through discussion or consultation with a third reviewer (Yang JR).

Statistical analysis
This network meta-analysis was undertaken with a Frequentist model using the mumeta and network commands in STATA version 16.0. The pairwise meta-analysis and network meta-analysis were undertaken simultaneously with the random effect model. The OR and 95%CI were used to describe dichotomous outcomes, and the global and local inconsistencies were checked. I² was used to describe the heterogeneity, where < 50% indicated low heterogeneity and > 50% high heterogeneity. P < 0.05 represented statistical significance. The loop-specific inconsistency was used to assess the discordance between direct and indirect evidence in the loop. If the 95%CI of inconsistency factors included zero or RoR included 1, inconsistency results were considered nonsignificant. The network graph was used to present the treatment comparisons. Interventions were ranked by their posterior probability by the surface under the cumulative ranking curve values.

Role of funding source
There was no funding source for this study.

RESULTS

Eligible studies
The literature search yielded 3260 titles, of which 2905 articles were excluded because they were duplicates, systematic reviews or meta-analyses, or not relevant. Of the remaining 355 articles, 52 were screened out by scanning the titles and abstracts (Figure 1). Eventually, 24 RCTs (including 9416 patients) were included in this network meta-analysis. Sixteen RCTs involved NSAIDs[11-26] and eight were of GTN[9,27-33]. Two different studies had the same first author[12,33], and both of them were included. One study stratified the patients based on pancreatitis risk after ERCP[21]. In the treatment group, the average-risk patients only received 100 mg of rectal indomethacin before ERCP, but the high-risk patients received a further 100 mg of rectal indomethacin after ERCP. Therefore, we only extracted
Shi QQ et al. The prophylaxis of post-ERCP pancreatitis

Figure 1 Flowchart of the selection process.

the data of the average-risk patients. One study only included female patients[9], but the baselines between the experimental and control groups were similar, so we included it.

**Characteristics of studies**

The main characteristics and the incidence and severity of PEP are presented in Table 1 and Table 2. Among the RCTs that met the inclusion criteria, the first study was published in 2001, and the most recent was in 2020. The sample size ranged from 74 to 2014 subjects. The proportion of women in the RCTs ranged from 37.74% to 100%. A total of 9416 patients were randomly assigned to one of seven different interventions or placebo. The interventions included NSAIDs (100 mg diclofenac, indomethacin, 50 mg diclofenac, naproxen), GTN (sublingual or transdermal), or a combination (indomethacin plus sublingual GTN). The definition and the degree of severity of PEP varied among the included studies, but most of them (66.67%) used the consensus definition[34], with the others using similar definitions. The incidence of PEP was reported in all studies, but four RCTs have no report about the degree of PEP[13,25,27,30].

**Methodological quality and risk of bias**

Two authors evaluated the methodological quality of the included RCTs using the Cochrane Collaboration’s Risk of Bias tool. A summary assessment of low, unclear, or high risk of bias was given to each study. The results are presented in Figure 2.

**Consistency test and sensitivity analysis**

The inconsistency was not significant ($I^2 = 3.13\%, \ P = 0.37$) among the included RCTs, and no evidence of local or loop inconsistency was seen. A sensitivity analysis was conducted by excluding the studies with the largest ($n = 2014$) and smallest ($n = 74$) sample sizes. This slightly changed the OR and the SUCRA, indicating low heterogeneity ($I^2 = 2.47\%, \ P = 0.48$). The exclusion of two open-label studies[18, 23] also did not change the final results.

**NMA of the PEP incidence**

Figure 3A displays the network of all the interventions included in this network meta-analysis, and Figure 3B displays the network of interventions with details of the incidence of mild or moderate-severe PEP recorded. The network meta-analysis included one head-to-head three-arm RCT comparing different NSAIDs, one head-to-head two-arm RCT comparing combined indomethacin and sublingual GTN with indomethacin. All the others were placebo-controlled RCTs.
Table 1 Characteristics of the included studies

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Country</th>
<th>Intervention</th>
<th>Sample size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Murray et al[11], 2003</td>
<td>Scotland</td>
<td>100 mg diclofenac after endoscopy</td>
<td>220</td>
</tr>
<tr>
<td>Sotoudehmanesh et al[12], 2007</td>
<td>Iran</td>
<td>100 mg indomethacin before ERCP</td>
<td>490</td>
</tr>
<tr>
<td>Khoshbaten et al[13], 2007</td>
<td>Iran</td>
<td>100 mg diclofenac after endoscopy</td>
<td>100</td>
</tr>
<tr>
<td>Elmunzer et al[14], 2012</td>
<td>United States</td>
<td>100 mg indomethacin after ERCP</td>
<td>602</td>
</tr>
<tr>
<td>Otsuka et al[15], 2012</td>
<td>Japan</td>
<td>50 mg diclofenac before ERCP</td>
<td>104</td>
</tr>
<tr>
<td>Döbrönte et al[16], 2014</td>
<td>Hungary</td>
<td>100 mg indomethacin 10-15 min before ERCP</td>
<td>665</td>
</tr>
<tr>
<td>Andrade-Dávila et al[17], 2015</td>
<td>México</td>
<td>100 mg indomethacin after ERCP</td>
<td>166</td>
</tr>
<tr>
<td>Lu et al[18], 2015</td>
<td>Malaysia</td>
<td>100 mg diclofenac after ERCP</td>
<td>144</td>
</tr>
<tr>
<td>Patai et al[19], 2015</td>
<td>Hungary</td>
<td>100 mg indomethacin 1 h before ERCP</td>
<td>539</td>
</tr>
<tr>
<td>Levenick et al[20], 2016</td>
<td>United States</td>
<td>100 mg indomethacin following attempted cannulation</td>
<td>449</td>
</tr>
<tr>
<td>Luo et al[21], 2016</td>
<td>China</td>
<td>100 mg indomethacin within 30 min before ERCP</td>
<td>2014</td>
</tr>
<tr>
<td>Mansour-Ghanaei et al[22], 2016</td>
<td>Iran</td>
<td>500 mg naproxen immediately before ERCP</td>
<td>324</td>
</tr>
<tr>
<td>Patil et al[23], 2016</td>
<td>India</td>
<td>100 mg diclofenac immediately before or during the ERCP</td>
<td>400</td>
</tr>
<tr>
<td>Mohammad et al[24], 2017</td>
<td>Iran</td>
<td>100 mg diclofenac, 100 mg indomethacin or 500 mg naproxen, 30 min before ERCP</td>
<td>246</td>
</tr>
<tr>
<td>Li et al[25], 2019</td>
<td>China</td>
<td>100 mg indomethacin before ERCP</td>
<td>100</td>
</tr>
<tr>
<td>Kato et al[26], 2019</td>
<td>Japan</td>
<td>50 mg diclofenac before ERCP</td>
<td>297</td>
</tr>
<tr>
<td>Sudhindran et al[27], 2001</td>
<td>United Kingdom</td>
<td>Sublingual 2 mg GTN before ERCP</td>
<td>186</td>
</tr>
<tr>
<td>Moreto et al[28], 2003</td>
<td>Spain</td>
<td>Transdermal 15 mg GTN 30 to 40 minutes before ERCP</td>
<td>144</td>
</tr>
<tr>
<td>Kaffes et al[29], 2006</td>
<td>Australia</td>
<td>Transdermal 5 mg GTN before ERCP</td>
<td>318</td>
</tr>
<tr>
<td>Hao et al[30], 2009</td>
<td>China</td>
<td>Sublingual 5 mg GTN 5 min before ERCP</td>
<td>74</td>
</tr>
<tr>
<td>Nøjgaard et al[31], 2009</td>
<td>France</td>
<td>Transdermal 15 mg GTN before ERCP</td>
<td>806</td>
</tr>
<tr>
<td>Bhatia et al[32], 2011</td>
<td>India</td>
<td>Transdermal GTN 30 min before ERCP</td>
<td>250</td>
</tr>
<tr>
<td>Sotoudehmanesh et al[33], 2014</td>
<td>Iran</td>
<td>100 mg indomethacin, plus 5 mg of sublingual GTN before ERCP</td>
<td>300</td>
</tr>
<tr>
<td>Wang et al[34], 2020</td>
<td>China</td>
<td>Indomethacin plus 0.5 mg of sublingual GTN 5 min before ERCP</td>
<td>352</td>
</tr>
</tbody>
</table>

ERCP: Endoscopic retrograde cholangiopancreatography; GTN: Glyceryl trinitrate.

Incidence of PEP
On pairwise comparison with placebo, rectal indomethacin 100 mg plus sublingual GTN (OR: 0.21, 95% CI: 0.09–0.50), rectal diclofenac 100 mg (0.34, 0.18–0.65), sublingual GTN (0.34, 0.12–0.97), and rectal indomethacin 100 mg (0.49, 0.33–0.73) were all more efficacious than placebo in preventing PEP. Rectal indomethacin 50 mg (0.69, 0.22–2.18), transdermal GTN (0.70, 0.37–1.32), rectal naproxen 500 mg (0.80, 0.35–1.83) were found to have no significant effect in preventing PEP (Table 3). Furthermore, the combination of rectal indomethacin 100 mg and sublingual GTN was more effective than rectal naproxen 500 mg (0.26, 0.08–0.86), and transdermal GTN (0.30, 0.10–0.89) in preventing PEP. As shown in Figure 4A, rectal diclofenac 100 mg performed best in the pairwise comparisons of prophylaxis between NSAIDs. Rectal indomethacin 100 mg ranked second. Regarding GTN, sublingual administration was more effective than transdermal in preventing PEP, but the combination achieved the best results.

Incidence of mild PEP
On pairwise comparison with placebo, rectal indomethacin 100 mg plus GTN (0.27, 0.11–0.67), rectal diclofenac 100 mg (0.46, 0.23–0.94), rectal indomethacin 100 mg (0.59, 0.40–0.88) were all more efficacious than placebo in preventing mild PEP (Table 4). The combination of indomethacin with sublingual GTN was also the most effective measure for preventing mild PEP (Figure 4B).

Incidence of moderate-severe PEP
On pairwise comparison with placebo, rectal indomethacin 100 mg plus GTN (0.19, 0.08–0.48), rectal diclofenac 100 mg (0.27, 0.09–0.79), and rectal indomethacin 100 mg (0.43, 0.28–0.66) were all more
## Table 2 Incidence and severity of post-endoscopic retrograde cholangiopancreatography pancreatitis

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Group</th>
<th>Case (n)</th>
<th>PEP</th>
<th>Mild PEP</th>
<th>Moderate to severe PEP</th>
<th>Sex (M:F)</th>
<th>Age (yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shi et al [1], 2003</td>
<td>Diclofenac 100 mg</td>
<td>110</td>
<td>7</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td></td>
<td>Placebo</td>
<td>110</td>
<td>15</td>
<td>2</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Sotoudehmanesh et al [12], 2007</td>
<td>Indomethacin</td>
<td>245</td>
<td>7</td>
<td>0</td>
<td>111:134</td>
<td>58.4 ± 17.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>245</td>
<td>10</td>
<td>5</td>
<td>115:130</td>
<td>58.4 ± 16.8</td>
<td></td>
</tr>
<tr>
<td>Elmunzer et al [14], 2012</td>
<td>Indomethacin</td>
<td>295</td>
<td>14</td>
<td>13</td>
<td>66:29</td>
<td>44.4 ± 13.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>307</td>
<td>25</td>
<td>27</td>
<td>60:47</td>
<td>46.0 ± 13.1</td>
<td></td>
</tr>
<tr>
<td>Otaka et al [15], 2012</td>
<td>Diclofenac 50 mg</td>
<td>51</td>
<td>2</td>
<td>0</td>
<td>20:31</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>53</td>
<td>7</td>
<td>3</td>
<td>33:20</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>Döbrönte et al [16], 2014</td>
<td>Indomethacin</td>
<td>347</td>
<td>16</td>
<td>4</td>
<td>133:214</td>
<td>65.66 ± 16.21</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>318</td>
<td>18</td>
<td>4</td>
<td>106:212</td>
<td>67.68 ± 15.56</td>
<td></td>
</tr>
<tr>
<td>Andrade-Dávila et al [17], 2015</td>
<td>Indomethacin</td>
<td>82</td>
<td>3</td>
<td>1</td>
<td>31:51</td>
<td>51.59 ± 18.55</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>84</td>
<td>14</td>
<td>4</td>
<td>25:59</td>
<td>54.0 ± 17.85</td>
<td></td>
</tr>
<tr>
<td>Lua et al [18], 2015</td>
<td>Diclofenac 100 mg</td>
<td>69</td>
<td>4</td>
<td>3</td>
<td>34:35</td>
<td>50.3 ± 17.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>75</td>
<td>4</td>
<td>0</td>
<td>25:50</td>
<td>49.6 ± 16.8</td>
<td></td>
</tr>
<tr>
<td>Patai et al [19], 2015</td>
<td>Indomethacin</td>
<td>270</td>
<td>15</td>
<td>3</td>
<td>89:181</td>
<td>66.25 (23-100)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>269</td>
<td>33</td>
<td>4</td>
<td>88:181</td>
<td>64.51 (20-95)</td>
<td></td>
</tr>
<tr>
<td>Levenick et al [20], 2016</td>
<td>Indomethacin</td>
<td>223</td>
<td>16</td>
<td>0</td>
<td>105:118</td>
<td>64.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>226</td>
<td>9</td>
<td>2</td>
<td>108:118</td>
<td>64.3</td>
<td></td>
</tr>
<tr>
<td>Luo et al [21], 2016</td>
<td>Indomethacin</td>
<td>992</td>
<td>22</td>
<td>7</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>1022</td>
<td>48</td>
<td>17</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Mansour-Ghanaei et al [22], 2016</td>
<td>Naproxen</td>
<td>162</td>
<td>8</td>
<td>4</td>
<td>84:78</td>
<td>46.3 ± 8.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>162</td>
<td>18</td>
<td>10</td>
<td>89:73</td>
<td>44.7 ± 9.7</td>
<td></td>
</tr>
<tr>
<td>Patil et al [23], 2016</td>
<td>Diclofenac 100 mg</td>
<td>200</td>
<td>6</td>
<td>0</td>
<td>72:128</td>
<td>45.44</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>200</td>
<td>14</td>
<td>9</td>
<td>77:23</td>
<td>47.86</td>
<td></td>
</tr>
<tr>
<td>Mohammad et al [24], 2017</td>
<td>Diclofenac 100 mg</td>
<td>124</td>
<td>2</td>
<td>3</td>
<td>58:66</td>
<td>56.5 ± 18.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Indomethacin</td>
<td>122</td>
<td>3</td>
<td>4</td>
<td>57:65</td>
<td>58.0 ± 16.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Naproxen</td>
<td>126</td>
<td>7</td>
<td>12</td>
<td>60:66</td>
<td>54.8 ± 13.7</td>
<td></td>
</tr>
<tr>
<td>Kato et al [26], 2019</td>
<td>Diclofenac 50 mg</td>
<td>147</td>
<td>7</td>
<td>1</td>
<td>82:65</td>
<td>74.3 ± 11.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>150</td>
<td>4</td>
<td>1</td>
<td>95:55</td>
<td>74.0 ± 12.7</td>
<td></td>
</tr>
<tr>
<td>Mohammad et al [24], 2017</td>
<td>Diclofenac 50 mg</td>
<td>147</td>
<td>7</td>
<td>1</td>
<td>82:65</td>
<td>74.3 ± 11.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>150</td>
<td>4</td>
<td>1</td>
<td>95:55</td>
<td>74.0 ± 12.7</td>
<td></td>
</tr>
<tr>
<td>Katoh et al [28], 2003</td>
<td>tra-GTN</td>
<td>71</td>
<td>2</td>
<td>1</td>
<td>44:27</td>
<td>66.7 ± 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>73</td>
<td>10</td>
<td>1</td>
<td>43:30</td>
<td>65.2 ± 2</td>
<td></td>
</tr>
<tr>
<td>Kaffes et al [29], 2006</td>
<td>tra-GTN</td>
<td>155</td>
<td>9</td>
<td>2</td>
<td>59:96</td>
<td>60 (47-72)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>163</td>
<td>6</td>
<td>4</td>
<td>57:106</td>
<td>65 (54-75)</td>
<td></td>
</tr>
<tr>
<td>Knüppel et al [31], 2009</td>
<td>tra-GTN</td>
<td>401</td>
<td>4</td>
<td>14</td>
<td>164:237</td>
<td>67 (18-95)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>405</td>
<td>9</td>
<td>20</td>
<td>168:237</td>
<td>65 (19-96)</td>
<td></td>
</tr>
<tr>
<td>Bhatia et al [32], 2011</td>
<td>tra-GTN</td>
<td>124</td>
<td>12</td>
<td>0</td>
<td>36:88</td>
<td>42 (18-76)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>126</td>
<td>13</td>
<td>0</td>
<td>47:79</td>
<td>42.5 (19-90)</td>
<td></td>
</tr>
<tr>
<td>Sotoudehmanesh et al [33], 2014</td>
<td>Indomethacin+sub-GTN</td>
<td>150</td>
<td>8</td>
<td>2</td>
<td>76:74</td>
<td>58.4 ± 17.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
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<td>19</td>
<td>4</td>
<td>70:80</td>
<td>58.6 ± 17.5</td>
<td></td>
</tr>
<tr>
<td>Wang et al [9], 2020</td>
<td>Indomethacin+sub-GTN</td>
<td>176</td>
<td>5</td>
<td>4</td>
<td>Female</td>
<td>63.5 ± 14.4</td>
<td></td>
</tr>
</tbody>
</table>
PEP: Endoscopic retrograde cholangiopancreatography; M: Male; F: Female; NA: Not available; sub-GTN: Sublingual glyceryl trinitrate; tra-GTN: Transdermal glyceryl trinitrate.

Table 3 League table with OR estimates of each pair of interventions accompanied by 95%CI according to the prevention of total PEP (significant difference when OR < 1 and CI < 1)

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Placebo</th>
<th>176</th>
<th>14</th>
<th>20</th>
<th>Female</th>
<th>66.87 ± 13</th>
</tr>
</thead>
</table>

GTN: Glyceryl trinitrate; sub-GTN: Sublingual glyceryl trinitrate; tra-GTN: Transdermal glyceryl trinitrate.

Table 4 League table with OR estimates of each pair of interventions accompanied by 95%CI according to the prevention of mild PEP (significant difference when OR < 1 and CI < 1)

GTN: Glyceryl trinitrate; sub-GTN: Sublingual glyceryl trinitrate; tra-GTN: Transdermal glyceryl trinitrate.

DISCUSSION

PEP remains the most common and serious complication of ERCP. Various preventive strategies have been used to try to solve this tough problem. Common measures include pancreatic stents, pharmacotherapy, and hydration[7,35]. The prophylactic effect of pancreatic stents and rectal NSAIDs has been recognized by European clinical guidelines[6]. Nevertheless, pancreatic stents have obvious disadvantages, including injury to the pancreatic orifice and failure of placement, which significantly increases the risk of PEP. Recently, more attention has been paid to pharmacotherapy, especially NSAIDs, due to their effectiveness, cheapness and convenience. Both RCTs and meta-analyses found that rectal administration of NSAIDs was better at preventing PEP compared to oral or intramuscular administration.
Table 5 League table with OR estimates of each pair of interventions accompanied by 95%CI according to the prevention of moderate-to-severe PEP (significant difference when OR < 1 and CI < 1)

<table>
<thead>
<tr>
<th>Indomethacin+GTN</th>
<th>Diclofenac 100 mg</th>
<th>Indomethacin</th>
<th>Diclofenac 50 mg</th>
<th>tra-GTN</th>
<th>Naproxen</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.71 (0.17, 2.96)</td>
<td>0.61 (0.20, 1.87)</td>
<td></td>
<td>0.66 (0.07, 6.62)</td>
<td>1.07 (0.13, 8.55)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.47 (0.05, 4.40)</td>
<td>0.39 (0.11, 1.36)</td>
<td>0.63 (0.30, 1.34)</td>
<td>0.59 (0.07, 4.95)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.28 (0.09, 0.85)</td>
<td>0.34 (0.11, 1.02)</td>
<td>0.55 (0.24, 1.27)</td>
<td>0.52 (0.06, 4.65)</td>
<td>0.88 (0.32, 2.46)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.24 (0.07, 0.82)</td>
<td>0.27 (0.09, 0.79)</td>
<td>0.43 (0.28, 0.66)</td>
<td>0.41 (0.05, 3.11)</td>
<td>0.69 (0.37, 1.28)</td>
<td>0.78 (0.35, 1.77)</td>
<td></td>
</tr>
</tbody>
</table>

GTN: Glyceryl trinitrate; sub-GTN: Sublingual glyceryl trinitrate; tra-GTN: Transdermal glyceryl trinitrate.

Figure 2 Consensus risk of bias assessment of randomized control trials included in this network meta-analysis. A: Risk of bias summary; B: Risk of bias graph.

administration[7,36,37].

We did a network meta-analysis of 24 RCTs with a total of 9416 patients to identify the prophylactic efficacy of seven different interventions on PEP and to identify the best-performing dose and best route of administration. We found that rectal diclofenac 100 mg was the most effective rectal NSAID, consistent with the previous meta-analysis[7]. Sublingual GTN administration was more useful than transdermal in preventing PEP. Furthermore, the combination of indomethacin and sublingual GTN might be the best preventive strategy for PEP.

Severe PEP is a well-known complication with significant consequences for patients undergoing ERCP. Therefore, we also concentrated on this challenging complication. A network meta-analysis was also performed on 20 RCTs with a total of 8956 patients, to identify the prophylactic effect of six different interventions on mild or moderate-to-severe PEP. Since the two sublingual GTN studies did not record the severity of the PEP episodes[27,30], the preventive strategy using sublingual GTN was not included in this analysis. We found that rectal diclofenac 100 mg was also the most effective among rectal NSAIDs for preventing mild or moderate-to-severe PEP. The combination of indomethacin with sublingual GTN had the best preventive effect for mild PEP and moderate-to-severe PEP. Based on our results, rectal diclofenac 50 mg, transdermal GTN, and rectal naproxen 500 mg did not prevent or alleviate PEP better than placebo.

The exact mechanism, by which the NSAIDs prevent PEP is still a subject of debate, and there are several hypotheses. It is widely accepted that inflammatory mediators play a vital role in the pathogenesis of pancreatitis and the subsequent inflammatory response[38]. The severity of pancreatitis is also determined by the intensity of the inflammatory cascade and the systemic response. NSAIDs are potent inhibitors of phospholipase A2, which is thought to play a critical role early in the inflammatory
cascade[39]. This might explain the ability of NSAIDs to prevent PEP or reduce its severity.

The mechanism of GTN in preventing PEP has not been completely elucidated. The main hypothesis is that the GTN relaxes smooth muscle, which increases pancreatic parenchymal blood flow and lowers the basal pressure and contraction amplitude in the sphincter of Oddi[40]. More studies are needed to confirm the mechanism.

Despite that we believe the combination of NSAIDs with sublingual GTN might be the best preventive strategies in PEP. This analysis had some limitations. First, rectal diclofenac 100 mg is the most efficacious among rectal NSAIDs for PEP prevention, but there was no research on the combination of rectal diclofenac and sublingual GTN. There were only two studies on the combination of indomethacin and sublingual GTN[33,34], and more RCTs are needed to explore this issue in the future. Second, we only searched for RCTs published in English, which may have resulted in sample and geographical biases. Finally, few included studies had results about hyperamylasemia, post-ERCP pain, or perforation. Therefore, we could not compare these complications.

CONCLUSION

In conclusion, this network meta-analysis confirmed that, of the NSAIDs, rectal diclofenac 100 mg was the best for PEP prophylaxis and sublingual was more effective than transdermal GTN in preventing PEP. Combination of rectal indomethacin 100 mg with sublingual GTN was the most effective strategy.
Figure 4 Ranking of treatment strategies based on probability of prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis with the cumulative ranking area. A: Incidence of post-endoscopic retrograde cholangiopancreatography pancreatitis (PEP); B: Mild PEP; C: Moderate-to-severe PEP.

for preventing PEP and alleviating its severity. These findings help establish PEP prophylaxis for future study and practice; however, more high-quality, double-blind RCTs are needed for further network meta-analysis.
ARTICLE HIGHLIGHTS

Research perspectives
Clinical application of drugs.

Research conclusions
The combination of rectal indomethacin 100 mg with sublingual glyceryl trinitrate (GTN) offered better prevention of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP) than when used alone and could alleviate the severity of PEP. This conclusion needs to be explored in more randomized controlled trials (RCTs) with large samples.

Research results
Twenty-four eligible RCTs were selected, evaluating seven preventive strategies in 9416 patients. Rectal indomethacin 100 mg plus sublingual GTN, rectal diclofenac 100 mg, sublingual GTN, and rectal indomethacin 100 mg were all more efficacious than placebo in preventing PEP. The combination of rectal indomethacin and sublingual GTN had the highest surface under the cumulative ranking curves (SUCRA) probability of 92.2% and was the best preventive strategy for moderate-to-severe PEP with a SUCRA probability of 89.2%.

Research methods
A systematic search was done for full-text RCTs of PEP in PubMed, Embase, Science Citation Index, and the Cochrane Controlled Trials database. Inclusion and exclusion criteria were used to screen for eligible RCTs. The major data were extracted by two independent reviewers. The Frequentist model was used to conduct this network meta-analysis and obtain the pairwise odds ratios and 95% CI.

Research objectives
To compare NSAIDs and GTN in the prevention of PEP and to determine whether they are better in combination.

Research motivation
To explore the role of NSAIDs and GTN for prevention of PEP.

Research background
Post-endoscopic retrograde cholangiopancreatography pancreatitis.

FOOTNOTES

Author contributions: Yang JR and Li W designed the study; Li W and Huang GX carried out critical appraisal of the included studies; Shi QQ and Ning XY performed the literature search, extracted the data; Shi QQ wrote the manuscript; Yang JR and Huang GX helped to revise the manuscript; all authors critically reviewed the manuscript and approved this study to be published.

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Effect of celecoxib on improving depression: A systematic review and meta-analysis

Zhi Wang, Qiao Wu, Qing Wang

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Abstract
BACKGROUND
Anti-inflammation drugs were uncovered to be a potential therapy for depression. Celecoxib as a selective COX2 inhibitor is also one anti-inflammation drugs. Celecoxib is widely used in the clinic, which is well known by medical workers. It is uncertain whether celecoxib has efficacy in improving depression.

AIM
To estimate the effect of celecoxib on improving depression.

METHODS
All literature was searched until 2022. The databases included PubMed, OVID database, Cochrane library, Web of Science, CNKI, Clinicaltrials.gov database and Wanfang database. The random effects model was used to estimate the standardized mean differences with 95% CIs. With determined diagnostic criteria, studies containing patients with depression in the celecoxib group and the control group were included in the meta-analysis. The primary outcome measures were set for depression scale scores.

RESULTS
Twenty-nine randomized controlled studies were included in the meta-analysis (including 847 subjects with depression and 810 control subjects). The meta-analysis showed that celecoxib had an effect of anti-depression. At the same time, heterogeneity was observed ($I^2 = 82.1\%$, $P = 0.00$), and meta-regression was implemented to estimate the source of heterogeneity, which showed that the type...
of depression scale and depression type may lead to the heterogeneity. Subgroup analysis with respect to depression scale and depression type suggested that depression type was the possible main source of heterogeneity. Moreover, Egger’s test, Begg’s test, funnel plot and Doi plot was implemented, and publication bias was found to be significant. Next, the trim and fill method was used to estimate the influence of publication bias on the outcome of the meta-analysis, which showed that the outcome of the meta-analysis was reliable. Sensitivity analysis was estimated by deleting a study one by one, and the outcome of the meta-analysis was significantly stable. The quality of all randomized controlled trial studies was assessed by risk of bias, which indicated the rank of evidence in the meta-analysis was high.

CONCLUSION
Celecoxib could be effective for improving depression.

Key Words: Celecoxib; Depression; Systematic review; Meta-analysis; Inflammation

Core Tip: There is inconsistency about the efficacy of celecoxib in improving depression. This is an updated systematic review and meta-analysis that includes more than 10 additional clinical trials compared to the previous meta-analysis. We compared the depression scale scores between the celecoxib group and the control group, and celecoxib had a significant reduction in depression scale scores and could be effective in improving depression.

INTRODUCTION
Depression as a psychiatric disorder severely threatens human health and life quality. The World Health Organization reported that over 300 million people are currently living with depression in 2018[1]. Depression has a wide array of symptoms affecting somatic, cognitive, affective and social processes[2]. Depression is closely associated with suicide[3]. In addition, depression is associated with morbidity and mortality of cardiovascular disease[4]. According to the number, type and severity of symptoms, depressive disorder is classified as mild, moderate and major depression. Depression disorder also includes bipolar depression. The pathology of depression is still uncovered. Recently, the relationship between inflammation and depression is gaining more attention. Inflammation is likely a critical disease modifier, promoting susceptibility to depression[5]. Inflammation as a potential target in the treatment of depression has led to the exploration of clarifying the efficacy of anti-inflammation drugs on improving depression.

Celecoxib is a COX2 inhibitor and an anti-inflammation drug. Celecoxib has an Food and Drug Administration indication for the management of acute pain in adult women and primary dysmenorrhea[6]. Celecoxib is widely used in inflammation diseases such as rheumatoid arthritis, and celecoxib is widely used in the clinic. Due to its clinical popularity, celecoxib is well known by many doctors and patients. Interestingly, if celecoxib has an effect of anti-depression, it would be meaningful to uncover a new function in the clinic. From the view of anti-inflammation, it is necessary to explore the efficacy of anti-depression.

The data on the efficacy of celecoxib on improving depression are inconsistent. Some studies showed celecoxib could improve depression[8,9]. On the contrary, a study showed that celecoxib was not superior to placebo for the treatment of bipolar depression[10]. A meta-analysis[11] about celecoxib on depression was published in 2014, and the number of randomized controlled trials (RCT) was only five. Another meta-analysis[12] in 2019 estimated the efficacy of celecoxib on bipolar depression, and the number of RCT was only three. Obviously, the number of RCT included in previous meta-analyses was not enough. Therefore, it is necessary to estimate the effect of celecoxib on depression by including more clinical trials. This meta-analysis aimed to estimate whether celecoxib could improve depression including bipolar depression, major depression and so on.
MATERIALS AND METHODS

The meta-analysis was made up of four parts including search strategy, study selection, quality assessment and data extraction and data synthesis.

Search strategy
Conducting and reporting meta-analysis data were strictly in accordance with PRISMA statement guidelines. The PICOS scheme was followed in the selected studies. A systematic literature search was implemented by two researchers (Wang Z and Wu Q). Retrieval fields included “celecoxib,” “celebrex,” “depression” and so on. Retrieval mode included basic retrieval and advanced retrieval. The process of retrieval was presented in Supplementary Table 1. We searched databases including PubMed, OVID database, Cochrane library, Web of Science, CNKI, Clinicaltrials.gov database and Wanfang database. There was no language restriction in the retrieval process. No restrictions about humans, clinical trials or RCT were used, which was aimed at the comprehensiveness of retrieval. In addition, we retrieved the references using the Reference Citation Analysis database. For searching all databases, the latest time was until 2022.

Study selection
Studies that reported celecoxib and depression were screened.

Inclusive criteria: (1) RCT included celecoxib group and control group; (2) With determined criteria, patients were diagnosed with depression including bipolar depression or unipolar depression or major depression and so on; and (3) Patients diagnosed with depression were comorbid with other non-mental diseases such as cancer.

Exclusive criteria: (1) With the diagnostic depression, patients were also diagnosed with other mental diseases such as Alzheimer’s disease; (2) Clinical trials that lacked a control group; (3) Case reports, letters, editorials and conference abstracts; and (4) Data about depression scores could not be obtained.

To retrieve more relevant studies, the references were also searched. According to the PRISMA literature-searching method, the primary inclusions were obtained through scanning titles and abstracts. Then, the full texts were screened carefully. Two researchers (Wang Z and Wu Q) searched the literature and determined the selected studies independently. The final inclusions were decided through consultations.

Quality assessment
Based on the Cochrane Handbook for Systematic Reviews, risk of bias was used to evaluate the quality of all selected studies. Bias evaluation was conducted by estimating seven items including random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment, incomplete outcome data (attrition bias), selection reporting (reporting bias) and other bias. All selected studies were evaluated according to above seven items. Finally, risk of bias graph and risk of bias summary plot were plotted by RevMan 5.3 software.

Data extraction and data synthesis
All data were extracted from all selected studies. A standardized data extraction form was used: name of the first author, year of publication, diagnostic criteria, study design, number of the celecoxib group and control group, type of depression scale and depression scale scores in the celecoxib group and control group. If the clinical trial included multiple treatment groups (different intervention), we only extracted data about the celecoxib and control groups. Based on the Cochrane Handbook for Systematic Reviews, if the clinical trial contained different doses and intervention periods, the trial will be divided into different trials with the same control group. The process of abstraction was administered by two researchers (Wang Z and Wu Q). They were in agreement with the outcome of the extraction.

We collected data including mean ± SD and n from selected studies. If the study provided mean ± SEM, data transformation would be implemented by the formula: SD = SEM × square root n.

Statistical analysis
All processes included forest plots, meta-regression analysis, funnel plot and Egger’s tests and were finished by STATA 16. Heterogeneity was assessed by the Cochran’s Q statistic and the F’ score. Heterogeneity was divided into homogeneity, moderate heterogeneity and high heterogeneity by F’ values of 0%-25%, 25%-50% and > 50%, respectively. If heterogeneity was significant, the random effects model was applied to estimate the standardized mean differences with 95%CI. Meta-regression and Galbraith plot were used to find the source of heterogeneity. With F’ values less than 50%, heterogeneity was considered to be small, and the fixed effects model was used.
Results

Characteristics of the included studies and assessment of quality
In total, 825 potentially relative records were identified, which was the sum of each database mentioned in the search strategy. After screening the titles, 338 duplicates were removed. Then, 474 records (review or meta-analysis, 71; animal experiment, 67; case report or letters, 19; no relationship or others, 317) were removed, and 13 records were obtained after screening the abstract. Because we could not obtain the raw data, three articles[13-15] were removed. Then, 10 records[8-10,16-22] were included in the meta-analysis. Except one study[19], the other studies were divided into separate studies according to a different period of therapy. Finally, 29 studies were included in the meta-analysis. All procedures were shown in Figure 1. The baseline characteristics in all included studies were presented in Supplementary Table 2. Twenty-nine case-control studies included 847 subjects in the celecoxib group and 810 subjects in the control group. Study type of all studies was RCT. Major matched factors for the celecoxib group and control group were mainly composed of publication year, diagnostic criteria, depression type, period of therapy, design of experiment group, design of control group, dose of celecoxib and depression scale. Based on the risk of bias graph and risk of bias summary plot, the quality of all studies was high (Figure 2). All data was shown as mean ± SD. Results of some studies were shown as mean ± SEM. SEM was transformed into SD according to sample size and SEM.

Meta-analysis
All data of the 29 studies were pooled in the meta-analysis. The outcome was shown in the forest plot (Figure 3). The depression scores in the celecoxib group were significantly lower than the control group (standardized mean difference = -0.49, 95% CI: -0.74 to -0.25, P < 0.05). Heterogeneity was observed to be severe (P = 82.1% and P < 0.001), and the random effect model was applied.

Meta-regression
A multivariate meta-regression analysis was used to estimate the source of heterogeneity. We conducted meta-regression including three aspects (study design, depression scale and depression type). The results showed that the depression scale (regression coefficient: 0.268; P = 0.016; 95% CI: 0.054-0.483) and depression type (regression coefficient: 0.157; P = 0.020; 95% CI: 0.027-0.287) were the possible...
After meta-regression, subgroup analysis about the depression scale and depression type was implemented to identify the possible source of heterogeneity (Figure 4A and B). Heterogeneity in the subgroup analysis about depression type was decreased, which showed that depression type may be the main source of heterogeneity. Moreover, subgroup analysis about the period of therapy was plotted (Figure 4C), which indicated that celecoxib could improve depression whether the period was ≤ 4 wk or > 4 wk.

Sensitivity analysis
Sensitivity analysis was conducted by deleting the studies one by one, and the outcome of meta-analysis was significantly stable.

Publication bias
Funnel plot (Figure 5A), Egger’s test (Figure 5B), Begg’s test (Figure 5C) and Doi plot (Figure 5D) were implemented to estimate publication bias. Funnel plot, Egger’s test, Begg’s test and Doi plot showed publication bias was significant. Further, the trim and fill method was used to estimate the influence of publication bias on the outcome of the meta-analysis. The result of the trim and fill method (standardized mean difference = -0.679, 95%CI: -0.961 to -0.398, P < 0.01) indicated the outcome of the meta-analysis was reliable.
Figure 3 The pooled quantitative synthesis for depression scores in the celecoxib group and control group. Twenty-nine studies were included in the meta-analysis. With the random effect model, the depression scores were calculated through using standardized mean differences (grey squares with small black squares) with 95% CIs (horizontal lines through gray squares) and pooled-effect sizes (blue diamonds).

DISCUSSION

The result of the meta-analysis showed that celecoxib could improve depression. Depression type in all studies was different. This meta-analysis aimed to estimate the efficacy of celecoxib on depression. Future meta-analyses of celecoxib based on the specific type of depression should be implemented when the number of RCT studies increases. In this meta-analysis, the publication bias was significant. The result of the trim and fill method showed that this meta-analysis was still reliable. Obviously, heterogeneity was significant, and the depression scale and depression type were the main sources of heterogeneity by meta-regression and subgroup analysis. The result of the meta-analysis was likely interpreted by obvious heterogeneity. More studies would decrease the heterogeneity.

The results indicated that the anti-inflammation may be the potential target of anti-depression. Celecoxib, a COX2 inhibitor and a nonsteroidal anti-inflammatory drug, was used in the clinic. Other nonsteroidal anti-inflammatory drugs were shown to be effective for improving depression in some studies[23,24]. Extensive studies have confirmed the proinflammatory status in depression and causal relationships with neurotransmitter dysregulation[25]. On the contrary, a trial failure of anti-inflammation drugs in depression was published in 2020[26]. According to the trial failure, the authors replied and indicated that drug selection and certain inflammation status in depression status were the necessary consideration. This meta-analysis did not estimate the inflammation status for celecoxib in depression due to lack of inflammation data in most studies. Therefore, the relationship between inflammation and depression for celecoxib needs to be analyzed in the future.

On the other hand, not all depression patients coexist with abnormal inflammation levels. In these patients, it is possible that celecoxib would not improve depression. Of course, the above issues are weaknesses in the meta-analysis. Currently, there are not enough studies to support the meta-analysis regarding celecoxib on improving depression with inflammation status or without inflammation status, which is also the possible source that caused the heterogeneity. Comparing with other anti-inflammation drugs such as aspirin, data on the efficacy of improving depression are lacking. Before comparing the efficacy between celecoxib and other anti-inflammation drugs on improving depression, the issue whether inflammation status or non-inflammation status are associated with the efficacy of anti-inflammation should be resolved. If the issue is not resolved, then the result of the comparison between celecoxib and other anti-inflammation drug is not credible.
Wang et al. Meta-analysis of celecoxib improving depression

A
Depression scores and author (year)

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<tr>
<th>Study</th>
<th>Effect (95% CI)</th>
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<td>HAMD-17</td>
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<td></td>
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<td>-1.16 (-2.83, -0.49)</td>
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<td>N. Miller-4 (2004)</td>
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<td>N. Miller-5 (2004)</td>
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<tr>
<td>Subgroup, DL (g &lt; 0.39) p = 0.000</td>
<td>-0.70 (-1.02, -0.36)</td>
<td>67.90</td>
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B
Depression type and author (year)

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<th>Drug-naive Depression</th>
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<tr>
<td>Marson Majid-1 (2015)</td>
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<td>Subgroup, ES (I^2 = 0%, p = 0.657)</td>
<td>-0.62 (-1.44, -0.20)</td>
<td>5.74</td>
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<th>Depressive or mixed phases of bipolar disorder</th>
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<td>Fabiano G. Nery-1 (2017)</td>
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<td>3.37</td>
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<td>Fabiano G. Nery-2 (2017)</td>
<td>-0.54 (-1.30, 0.23)</td>
<td>3.15</td>
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<tr>
<td>Fabiano G. Nery-3 (2017)</td>
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<td>S. Jafari (2015)</td>
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<td>S. Jafari (2015)</td>
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<td>Subgroup, ES (I^2 = 66.2%, p = 0.085)</td>
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<td>Payam Mohammadi(1) (2015)</td>
<td>-1.61 (-2.45, -0.10)</td>
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<td>Subgroup, DL (g = 79.1%, p = 0.029)</td>
<td>-2.54 (-3.47, -1.59)</td>
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<td>3.44</td>
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<td>Subgroup, ES (I^2 = 0% , p = 0.374)</td>
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<td>Bernhard T. Baune-3 (2021)</td>
<td>0.37 (0.07, 0.67)</td>
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</tr>
<tr>
<td>Mohammad lateral Huasen-2 (2020)</td>
<td>0.14 (-0.20, 0.45)</td>
<td>4.14</td>
</tr>
<tr>
<td>Mohammad lateral Huasen-3 (2020)</td>
<td>0.12 (-0.32, 0.45)</td>
<td>4.14</td>
</tr>
<tr>
<td>Mohammad lateral Huasen-4 (2020)</td>
<td>-0.11 (-0.48, 0.27)</td>
<td>4.14</td>
</tr>
<tr>
<td>Subgroup, ES (I^2 = 0%, p = 0.723)</td>
<td>0.04 (0.03, 0.21)</td>
<td>10.57</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment-resistant bipolar depression</th>
<th>Effect (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angelos Halari-1 (2018)</td>
<td>0.09 (-0.02, 0.48)</td>
<td>3.60</td>
</tr>
<tr>
<td>Angelos Halari-2 (2018)</td>
<td>0.11 (-0.01, 0.62)</td>
<td>3.60</td>
</tr>
<tr>
<td>Subgroup, ES (I^2 = 0%, p = 0.802)</td>
<td>0.12 (-0.09, 0.33)</td>
<td>7.21</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Neuropsychiatric depression</th>
<th>Effect (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>N. Miller-1 (2006)</td>
<td>-0.10 (-0.72, 0.52)</td>
<td>3.50</td>
</tr>
<tr>
<td>N. Miller-2 (2006)</td>
<td>-0.25 (-0.65, 0.14)</td>
<td>3.50</td>
</tr>
<tr>
<td>N. Miller-3 (2005)</td>
<td>-0.37 (-1.03, 0.29)</td>
<td>3.45</td>
</tr>
<tr>
<td>N. Miller-4 (2004)</td>
<td>-0.51 (-1.25, 0.23)</td>
<td>3.21</td>
</tr>
<tr>
<td>N. Miller-5 (2005)</td>
<td>-0.36 (-1.03, 0.32)</td>
<td>2.80</td>
</tr>
<tr>
<td>N. Miller-6 (2006)</td>
<td>-0.56 (-1.04, 0.40)</td>
<td>2.89</td>
</tr>
<tr>
<td>Subgroup, ES (I^2 = 0%, p = 0.951)</td>
<td>-0.32 (-0.69, -0.02)</td>
<td>19.10</td>
</tr>
</tbody>
</table>

| Heterogeneity between subgroups, p = 0.000 | Overall, DL (g = 82.27%, p = 0.000) | -0.49 (-0.74, -0.25) | 100.00 |
Figure 4 Subgroup analysis about the depression scale, depression type and period of therapy. A: Depression scale; B: Depression type; C: Period of therapy. With the random effect model, the depression scores were calculated through using standardized mean differences (grey squares with small black squares) with 95%CIs (horizontal lines through gray squares) and pooled-effect sizes (blue diamonds).

The relationship between inflammation and depression was explored by more studies. Inflammation is usually a reflection of cell damage caused by infections, physical injury or the response of tissues to an antibody challenge.[27] However, it has become apparent that psychological stress can also initiate the inflammatory response, thereby linking inflammation to both physical and mental ill health recently.[27] The inflammosome complex is expressed in microglia located in the hippocampus and other mood-regulating regions that are particularly vulnerable to the effects of chronic stress, which was linked to depression.[27] Stress plays a critical role in depression, ultimately leading to pervasive mental status changes and chronic low-grade inflammatory reaction.[25] Stress-induced activation of the immune response alters neurotransmission leading to neurotransmitter imbalances such as serotonergic deficiency, which was the possible mechanism of inflammation and depression.[25] Interestingly, inflammation plays a key role in depression pathogenesis for a subset of depressed individuals.[28]

Further, the bidirectional relationship between inflammation and depression was mentioned. Depression can promote intestinal permeability, i.e. greater inflammation-inducing endotoxin translocation, described as a “leaky gut” and inflammatory mediators can also induce clinical depression.[28] Therefore, the mechanism pathway between inflammation and depression is complex. Other factors such as gut microbiota, stress and so on can also participate in the complex net of inflammation and depression. The complex relationship and mechanism of inflammation and depression need more research.

Moreover, the dose of celecoxib in depression deserves exploration. Nearly all RCTs in the meta-analysis described 400 mg/d of celecoxib. No gradient of dose for celecoxib could be explored in this meta-analysis. More studies about different doses of celecoxib should be included to estimate the relationship between dose and depression. Safety of celecoxib was not mentioned in the meta-analysis due to few descriptions in the primary RCT. All in all, celecoxib is likely effective for improving depression. Weaknesses mentioned in the above context need to be resolved in the future work.

CONCLUSION

In summary, the results of this meta-analysis demonstrated that celecoxib could be effective for improving depression. Depression scale scores in the celecoxib group were less than the control group. For depression with or without inflammation, the efficacy of celecoxib on improving depression needs
to be estimated separately in the future.

ARTICLE HIGHLIGHTS

Research background
There is inconsistency about the efficacy of celecoxib for improving depression.

Research motivation
To estimate the efficacy of celecoxib for improving depression.

Research objectives
To provide more evidence to support the efficacy of celecoxib for improving depression.

Research methods
The meta-analysis was pooled.

Research results
Depression scores in the celecoxib group were lower than the control group.

Research conclusions
Celecoxib has an effect on improving depression.

Research perspectives
The meta-analysis was explored from the view of a COX2 selective inhibitor, an anti-inflammation drug.
ACKNOWLEDGEMENTS

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FOOTNOTES

Author contributions: Wu Q and Wang Z contributed to database search, data extraction and data analysis; Wang Q contributed to paper writing and revision; All authors confirmed the final version of the manuscript.

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Rectal mature teratoma: A case report

Jia-Li Liu, Ping-Liang Sun

**BACKGROUND**
Rectal mature teratoma is rare and has been reported as a case report in this study. Herein, clinical presentation, magnetic resonance imaging findings, and immunohistochemistry showed a pelvic rectal mature teratoma. The case report and the surgical treatment procedure have been discussed below.

**CASE SUMMARY**
A 29-year-old Chinese female showed up with over a 1-mo history of perianal mass that emerged after defecation. Physical examination indicated that the mass was 4 cm × 3 cm × 3 cm. The intraoperative procedure involved ligation of the sigmoid colon 10 cm above the upper edge of the tumor, followed by ligation of the rectum 3.5 cm above the upper edge of the tumor, and subsequent complete removal of the mass. The histopathology confirmed the mature teratoma.

**CONCLUSION**
The tumor can be completely removed using surgery to prevent its recurrence.

**Key Words:** Rectal; Mature teratoma; Therapy; Case report

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**Core Tip:** Herein, a rectal mature teratoma patient was reported. However, only a few similar cases have been reported. Currently, it is difficult to diagnose mature rectal teratoma using a computed tomography scan. However, complete removal of the tumor using surgery can prevent its recurrence.
INTRODUCTION
Teratoma is a tumor caused by pluripotent cells, especially the embryonic stem or seed cells in the gonad or embryonic part of the body. It occurs in the midline or on both sides of the body. It often originates from the Hensen’s node, the location of pluripotent stem cells. Teratoma also occurs in the sacral region where pluripotent cells are located[1]. Teratoma is mostly benign with low malignant potential, but it can also develop into a malignancy[2]. Rectal teratoma is rare, and there are few reports worldwide. Mature teratoma is a benign tumor (dermoid cyst) and accounts for over 95% of teratomas. Mature teratoma mostly occurs in women of childbearing age and sometimes in young girls and postmenopausal women. It rarely occurs in males[3]. This study aimed to review the diagnosis and treatment of rectal teratoma and to determine the clinical characteristics associated with this rare tumor.

CASE PRESENTATION

Chief complaints
A 29-year-old female, G1P0, with over a 1-mo history of a perianal mass that emerged after defecation, was hospitalized in the First Affiliated Hospital of Guangxi Chinese Medicine University.

History of present illness
She reported a 1-mo medical history of perianal mass that emerged after defecation and complained about the anal bulge. The patient had not used contraceptives, was not injured, had no pain, chills, or fever, and no difficulty during defecation.

History of past illness
The patient had no past illness.

Personal and family history
The patient had a history of artificial abortion and no family history of rectal mature teratoma. The condition was diagnosed as a rectal mass (nature to be investigated).

Physical examination
The mass was 4 cm × 3 cm × 3 cm inside the anus with a dentate line distance of about 6 cm and was smooth upon palliation. A non-tender mass was seen outside the anus.

Laboratory examinations
Hematological examinations, including serum electrolyte levels, human chorionic gonadotropin, comprehensive metabolic panel, and complete blood count, were normal.

Imaging examinations
Electronic colonoscopy: Rectal mass (nature to be investigated) (Figure 1).

The computed tomography (CT) scan revealed: (1) A 6.3 cm × 4.7 cm × 5.1 cm round mass, flaky low-density shadow and calcification on center, enhanced scanning lesions with circular mild enhancement, non-enhancement on center, and clear boundary on the pelvis (unclear if this is a teratoma); and (2) Double-sided adnexal area low-density shadow (cyst) (Figure 2).

A rectal mass resection was performed via laparoscopy under anesthesia to alleviate the patient’s symptoms.

FINAL DIAGNOSIS
The condition was diagnosed as mature rectal teratoma based on the above physical examinations and imaging data.
TREATMENT

Surgical procedure
A rectal mass resection was conducted via laparoscopy under anesthesia. Intraoperative ligation was conducted on the sigmoid colon 10 cm above the upper edge of the tumor and on the rectal area 3.5 cm above the upper edge of the tumor, followed by complete removal of the mass. Full hemostasis, sigmoid colon and rectal suture repair, placement of a negative pressure drainage tube in the anus and abdominal cavity, and layer-by-layer suture repair of the incision was then conducted (Figure 3).

Pathological examination
In the intestinal section, two connected tumors, about 6 cm × 5 cm × 4 cm and 2 cm × 2 cm × 2 cm, were seen in the intestinal mucosa and intestinal serosal layer, respectively. In the microscopic view, skin and appendages, glands, fat, bone tissue, bone marrow tissue, and brain tissue indicated mature teratoma. No tumor tissue was seen at the two ends (upper and lower margins) after the examination. Six lymph nodes were found, and no tumor metastasis was identified (0/6). Therefore, the condition was diagnosed as mature teratoma (Figure 4).

OUTCOME AND FOLLOW-UP
Postoperatively, the patient was discharged after healing. She returned for a follow-up in August 2018. On examination, there was evident wound healing and no tumor recurrence. Additionally, the patient was free of discomfort, pain, and fecal incontinence.
The colonoscopy and CT scan revealed a rectal mass, 6 cm × 5 cm × 4 cm in the intestinal mucosa and 2 cm × 2 cm × 2 cm in the intestinal serosal layer, which was diagnosed as mature rectal teratoma. Laparoscopic tumor resection was conducted to remove the tumor. No tumor metastasis was found 6 mo after successful 1-mo treatment. The teratoma was located in the rectal wall, which is close to the pelvic cavity. The teratoma volume increases and breaks into the intestinal wall, and bulging occurs to the posterior wall of the rectum. The teratoma then comes out of the anus and can only be returned by hand.

DISCUSSION

Clinical reports of teratoma are common in the sacrococcygeal, appendix, ovary, testis, retroperitoneum, mediastinum, etc. Several studies have shown that the incidence of teratoma may be related to various
Factors, such as genetic, environmental, and gene-level regulation [4,5]. Teratoma can be divided into benign and malignant transformations based on the degree of tissue differentiation. Teratoma incidence is about 1:35000-1:40000 [6] and mostly occurs in women (the ratio of male to female is about 1:2-4) with few occurrences in children and postmenopausal women [7,8]. Although mostly reported in the ovary and testis, it also occurs in the midline of the mediastinum, appendix, sacrococcygeal, pineal body, mediastinum, posterior peritoneal cavity, omentum, uterine rectum, vagina, and cervix [9-12]. Immature teratomas occur in adolescents. Most malignancies transform into cancer (squamous cell carcinoma). About 1%-2% of teratoma cases are malignant and are common in young women (the average age of onset is 11 years to 19 years) with poor prognosis [13-15]. CT images of mature teratoma reveal calcification, adipose tissue, bone, tooth, and obviously cysts [16,17].

CT scan is sensitive to calcification and fat, common and quick, and combined with enhanced scan can evaluate the soft tissue composition well. However, it lacks specificity for differentiating between tumor types. While magnetic resonance imaging has a higher resolution of fat and soft tissue, which helps to determine the retrorectal tumors and their relationships to surrounding structures and cystic degeneration, but it poorly shows calcification [18,19]. To some extent, magnetic resonance imaging is more accurate than CT to estimate the possible complications such as torsion, rupture, and malignant transformation.

Badmos et al. [20] reported that laparoscopic surgery can enlarge the field of view, reducing the incision and intraoperative blood loss. Lee et al. [21] also reported that laparoscopic surgery could significantly reduce the body’s inflammatory response compared to open surgery. Chansoon et al. [22] reported a case of complicated duodenal mature teratoma, which was resected via laparoscopic surgery. Herein, the mature cystic teratoma was identified, and the patient was discharged after the operation. No recurrence occurred after 6 mo of follow-up. Laparoscopic pelvic and teratogenic teratoma surgery is widely used because of the minimally invasive advantages. Laparoscopic surgery completely removes the tumor without damaging adjacent tissues and organs, avoiding the rupture of the tumor and preventing leakage of the teratoma, thus inhibiting malignant transformation, recurrence, and metastasis [23,24].

Murdoch and Abbas [25] reported that an anorectal cystic teratoma transabdominal approach is necessary, which can be done laparoscopically safely and successfully, even for a large lesion. Wang et al. [26] reported that it is generally not recommended to use preoperative biopsy of retrorectal tumors because of the risk of infection or tumor seeding in the pelvis. As such, a definitive diagnosis is best obtained by following complete resection of the tumor. Resection of retrorectal teratoma is generally regarded as appropriate because of the malignant potential.

Aiken et al. [27] reported that the diagnosis can be made with endoscopy alone by the presence of hair over the mass. Nam and Kim [28] reported that the mass was removed by polypectomy because the patient’s lesion was a pedunculate polyp measuring approximately 4 cm and located approximately 15 cm from the anus. Endoscopic resection was performed to make a diagnosis. Endoscopic resection is indicated for a pedunculate polyp that measures < 4 cm. If the diagnosis is unclear or malignancy cannot be excluded, surgical resection is preferable. The summaries of reported cases of rectal mature teratoma are shown in Table 1.

**CONCLUSION**

Rectal teratoma remains a rare disease despite a recent uptick in diagnoses. Radiological imaging is helpful to preoperative diagnosis and planning. Complete surgical excision is the treatment of choice, and regular follow-up after surgery is needed to prevent recurrence. The prognosis of mature teratomas

### Table 1 Reported cases of rectal mature teratoma

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Year</th>
<th>Age/sex</th>
<th>Symptoms</th>
<th>Previous history</th>
<th>Method</th>
<th>Final diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Murdoch and Abbas [25]</td>
<td>2010</td>
<td>26/female</td>
<td>Right-sided pelvic pain radiating down her lower extremities</td>
<td>Transanal drainage of a presumed presacral abscess</td>
<td>Laparoscopic abdomino-paracoccygeal resection</td>
<td>Anorectal cystic teratoma</td>
</tr>
<tr>
<td>Wang et al [26]</td>
<td>2019</td>
<td>44/female</td>
<td>Submucosal rectal mass</td>
<td>Not described</td>
<td>Laparoscopic tumor resection</td>
<td>Mature retrorectal teratoma</td>
</tr>
<tr>
<td>Aiken et al [27]</td>
<td>2020</td>
<td>47/female</td>
<td>Bleeding from the rectum for 10 d</td>
<td>Not described</td>
<td>Partial resection of the rectum</td>
<td>Rectum mature teratoma</td>
</tr>
<tr>
<td>Nam and Kim [28]</td>
<td>2021</td>
<td>68/female</td>
<td>Hemanatochezia</td>
<td>Not described</td>
<td>Polypectomy</td>
<td>Primary mature teratoma of the rectum</td>
</tr>
<tr>
<td>Our case</td>
<td>2021</td>
<td>29/female</td>
<td>Perianal mass that emerged after defecation</td>
<td>Not described</td>
<td>Laparoscopic</td>
<td>Rectal mature teratoma</td>
</tr>
</tbody>
</table>
is excellent, and we report this case to raise awareness of this disease.

FOOTNOTES

Author contributions: Liu JL and Sun PL designed the research and equally contributed to this work; Liu JL and Sun PL provided figure legends; Liu JL and Sun PL drafted the manuscript; All authors reviewed and approved the final submitted manuscript.

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Liu JL et al. Rectal mature teratoma


Antibiotic and glucocorticoid-induced recapitulated hematological remission in acute myeloid leukemia: A case report and review of literature

Xiao-Yun Sun, Xiao-Dong Yang, Xiao-Qiu Yang, Bo Ju, Nuan-Nuan Xiu, Jia Xu, Xi-Chen Zhao

Abstract

BACKGROUND
Leukemic hematopoietic cells acquire enhanced self-renewal capacity and impaired differentiation. The emergence of symptomatic leukemia also requires the acquisition of a clonal proliferative advantage. Untreated leukemia patients usually experience an aggressive process. However, spontaneous remission occasionally occurs in patients with acute myeloid leukemia (AML), most frequently after recovery from a febrile episode, and this is generally attributed to the triggering of antineoplastic immunity. There may be another explanation for the spontaneous remission as implicated in this paper.

CASE SUMMARY
A 63-year-old Chinese man presented with high fever, abdominal pain and urticaria-like skin lesions. He was diagnosed with AML-M4 with t(8;21)(q22;q22)/RUNX1-RUNX1T1 based on morphological, immunological, cytogenetic and molecular analyses. He had a complex chromosome rearrangement of 48,XY,t(8;21)(q22;q22),+13,+13[9]/49,idem,+mar[9]/49,idem,+8[2]. He also had a mutated tyrosine kinase domain in fms-like tyrosine kinase 3 gene. He was treated with antibiotics and glucocorticoids for gastrointestinal infection and urticaria-like skin lesions. The infection and skin lesions were quickly resolved. Unexpectedly, he achieved hematological remission along with resolution of the febrile episode, gastrointestinal symptoms and skin lesions. Notably, after relapse, repeating these treatments resulted in a return to hematological remission. Unfortunately, he demonstrated strong resistance to antibiotic and glucocorticoid treatment after the second relapse and died of sepsis from...
bacterial infection with multidrug resistance. The main clinical feature of this patient was that symptomatic AML emerged with flaring of the gut inflammatory disorder and it subsided after resolution of the inflammation. Learning from the present case raises the possibility that in a subgroup of AML patients, the proliferative advantage of leukemia cells may critically require the presence of inflammatory stresses.

**CONCLUSION**

Inflammatory stresses, most likely arising from gastrointestinal infection, may sustain the growth and survival advantage of leukemic cells.

**Key Words:** Acute myeloid leukemia; Fms-like tyrosine kinase 3 tyrosine kinase domain; Glucocorticoid; Antibiotic; Spontaneous remission; Gastrointestinal infection; Case report

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**Core Tip:** Untreated leukemia patients usually experience an aggressive process. However, spontaneous remission occasionally occurs in a small number of patients with acute myeloid leukemia. Here, we report an acute myeloid leukemia (AML) patient with t(8;21) translocation who achieved recapitulated spontaneous remissions after antibiotic and dexamethasone treatments for febrile episodes and skin lesions. These antibiotic and dexamethasone treatment-induced spontaneous remissions indicated that inflammatory stresses, most likely arising from gastrointestinal infection, sustained the growth and survival advantage of the leukemia cells. Inflammation-sustained proliferation may represent a specific subgroup of AML.

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**Citation:** Sun XY, Yang XD, Yang XQ, Ju B, Xiu NN, Xu J, Zhao XC. Antibiotic and glucocorticoid-induced recapitulated hematological remission in acute myeloid leukemia: A case report and review of literature. *World J Clin Cases* 2022; 10(22): 7890-7898

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**INTRODUCTION**

Acute myeloid leukemia (AML) is a highly heterogeneous group of malignant hematological diseases caused by somatic mutations in multipotential hematopoietic cells. Leukemic hematopoietic cells acquire enhanced self-renewal capacity and impaired differentiation. The emergence of symptomatic leukemia not only requires the acquisition of enhanced self-renewal capacity but also critically requires the acquisition of clonal growth and survival advantages. It is the growth and survival advantages that lead to the accumulation and infiltration of transformed hematopoietic cells in the bone marrow, taking up the hematopoietic pool, inhibiting normal hematopoiesis and ultimately resulting in a reduced capacity to produce mature blood cells[1–4].

Chemotherapy is currently the main initial treatment for AML, the aim of which is to reduce the number of leukemia cells and to achieve complete hematological remission. Untreated AML patients usually experience an aggressive process[1]. However, spontaneous remission occasionally occurs in a small number of AML patients, which frequently follows a febrile episode and is generally attributed to the overproduction of proinflammatory cytokines and the activation of antineoplastic activities[5]. This spontaneous remission could occur not only in patients with fused genes in recurrent chromosome rearrangements and other cytogenetic abnormalities but also in patients with mutated genes in recurrent molecular abnormalities and other transcription factors. Here, we report an AML patient with the recurrent chromosome rearrangement t(8;21)(q22;q22)/RUNX1-RUNX1T1 who achieved unexpected spontaneous remission after antibiotic and glucocorticoid treatment for his gastrointestinal infection and urticaria-like skin lesions. After relapse, repeating this treatment resulted in a second remission. The recapitulated treatment responses confirmed the spontaneous remissions to be induced by the antibiotic and glucocorticoid treatments. Learning from the present case raises the possibility that in a subgroup of AML patients, the proliferative advantage of leukemia cells may critically require the presence of inflammatory stresses.
CASE PRESENTATION

Chief complaints
Abdominal pain and fever for 3 d and pruritic skin lesions for 2 d.

History of present illness
A 63-year-old Chinese man presented with abdominal pain and fever for 3 d in the absence of headache, chest pain, dyspnea, cough and sputum. The highest body temperature was 39.7 °C. Oral administration of antibiotics could not resolve the febrile episode or gastrointestinal symptoms. Urticaria-like pruritic skin lesions occurred 2 d before, and treatment with astemizole could partially relieve the pruritus but could not completely resolve the skin lesions. Within the last month, his performance status exacerbated, with gradually aggravated fatigue, dizziness and palpitation.

History of past illness
The patient had no history of diseases in the hematological or other systems.

Personal and family history
No family history of hematological diseases, autoimmune diseases or malignant diseases was recorded.

Physical examination
His height was 1.71 m, body weight 74.5 kg. His body temperature was 38.3 °C, breathing rate 21 bp per minute, heart rate 92 bp per minute, and blood pressure 17.6/10.4 Kpa (132/78 mmHg). Upon physical examination, prominent signs were panabdominal tenderness and urticaria-like skin lesions. Conspicuous mucocutaneous hemorrhage and jaundice were not found. No significant signs in the nervous system, respiratory system, cardiovascular system, urogenital system or skeletal musculature system were identified.

Laboratory examinations
Routine laboratory examinations: On admission, complete blood count (CBC) revealed the following results: White blood cells (WBCs), $19.13 \times 10^9$/L; absolute neutrophil count (ANC), $4.55 \times 10^9$/L; absolute monocyte count (AMC), $8.88 \times 10^9$/L; red blood cells (RBCs), $2.38 \times 10^9$/L; hemoglobin level (Hb), 80 g/L; platelets (Plts), $32 \times 10^9$/L; absolute reticulocyte count (Ret), $5.61 \times 10^9$/L; and C-reactive protein (CRP), 142.7 mg/L. The coagulation profile and the urine examination did not show any abnormalities. Fecal examination revealed the presence of increased pyocytes. Biochemical analysis found elevated serum levels of lactate dehydrogenase (2834 IU/L), hydroxybutyric dehydrogenase (2394 IU/L) and β2-microglobulin (47.3 mg/L) in the absence of abnormalities in liver and renal functions. Pathogenic culture of his blood was sterile. Serological tests for hepatitis A, B, and C virus and human immunodeficiency virus were negative. Biomarkers of neoplasms were also negative.

Morphological, immunophenotyping, cytogenetic and molecular biological analysis of leukemic hematopoietic cells: Morphological evaluation of the bone marrow smears showed a heavily hypercellular bone marrow, with substantially increased percentages of monoblasts (accounting for 44.5% of the total nucleated hematopoietic cells) and premonocytes (24.5%). Morphological evaluation
of the blood smears showed a highly increased number of WBCs, with substantially increased percentages of premonocytes (accounting for 44% of the total nucleated cells) and monocytes (46%) (Figure 1). Two groups of abnormal myeloid precursors were detected in the bone marrow samples by flow cytometric immunophenotyping analysis. One group (accounting for 32.53% of the total nucleated cells) expressed CD13, CD33, CD14, CD11b, CD36, CD64, CD123 and human leukocyte antigen-DR (HLA-DR); another group (accounting for 48.95% of the total nucleated cells) expressed CD34, CD117, CD38, HLA-DR, CD13, CD33, CD11b, CD56 and CD123. Cytogenetic analysis by culturing the bone marrow cells reported a karyotype of 48,XY,t(8;21)(q22;q22),+13,+13[9]/49,idem,+mar[9]/49, idem,+8[2] (Figure 2). Molecular biological analysis revealed the presence of a fused AML1–ETO gene and a mutated tyrosine kinase domain in fms-like tyrosine kinase 3 (FLT3-TKD) gene.

Imaging examinations
No positive findings were observed in the chest computed tomography (CT) images. However, abdominal CT imaging revealed striking bowel wall thickening in the small and large intestines, abnormally gas-filled small intestine, and paper-like dilation of the small intestines and sigmoid colon with perienteric hypervascular fat proliferation, together with the symptoms and signs of the gastrointestinal tract indicating the presence of gut inflammatory lesions.

FINAL DIAGNOSIS
He was made a definitive diagnosis of AML-M4 with the recurrent chromosome arrangement of t(8;21)(q22;q22)/RUNX1-RUNX1T1[1,5].

TREATMENT
Because of the presence of obvious gastrointestinal infection and his poor performance status, cytostatic therapies were deferred. He was treated with piperacillin-tazobactam and etimicin for his febrile disease and with dexamethasone for his urticaria-like skin lesions. He was also prescribed an oral administration of polyglycol electrolyte solution (1500 mL daily for 2 d) followed by rifaximin (200 mg, four times daily) and berberine (0.3 g, three times daily) in an attempt to quickly eliminate the pathogens and their metabolites from the intestines.

OUTCOME AND FOLLOW-UP

Unexpected hematological remission by antibiotic and glucocorticoid treatment
The febrile episode, gastrointestinal symptoms and urticaria-like skin lesions quickly resolved after antibiotic and glucocorticoid treatment. Unexpectedly, his hematological parameters gradually improved. Along with a decline in the AMC and CRP, the ANC, Plts and Ret rapidly increased, and the RBCs and Hb steadily increased. On day 31, CBC showed the following results: WBCs, 10.83 × 10^9/L; ANC, 6.24 × 10^9/L; AMC, 1.62 × 10^7/L; RBCs, 2.74 × 10^12/L; Hb, 93 g/L; Plts, 253 × 10^9/L; and Ret, 112.45 × 10^9/L. When the blood smears were examined, there were no evident morphological abnormalities in the blood cells except for the left shift in neutrophils. The significantly improved hematological parameters and the absence of leukemia cells on blood smears indicated clearance of the leukemia cells from the peripheral blood and an achievement of clinical hematological remission. Because he declined chemotherapy and hypomethylation therapy, he was discharged from our center.

Recapitulated hematological remission by antibiotic and glucocorticoid treatment after relapse
He maintained a good performance status for approximately three weeks since he was discharged from our center. On day 51, he was sent to our center with identical symptoms as when he was first hospitalized. The CBC results and the morphological evaluation of the blood smear confirmed disease recurrence. Because of the history of the achievement of a hematological response to antibiotic and glucocorticoid treatment and because of the existence of an obvious gastrointestinal infection, he was tentatively treated with the same modality as when he was first hospitalized. As we anticipated, repeating the treatment resulted in a second clinical and hematological remission.

He refused chemotherapy and hypomethylation therapy again, and he was discharged. During the follow-up, he experienced a second relapse on day 105 with the same symptoms, but this time, he demonstrated strong resistance to antibiotic and glucocorticoid treatment and eventually died of an overwhelming infection at another hospital. Pathogenic culture of his blood samples reported a positive result for *Acinetobacter baumannii* infection with multidrug resistance.
Cytogenetic analysis for the bone marrow culture. Cytogenetic analysis by culture of the bone marrow sample reported a karyotype of 48,XY,t(8;21)(q22;q22),+13,+13[9]/49,idem,+mar[9]/49,idem,+8[2].

Figure 2

Cytogenetic analysis for the bone marrow culture. Cytogenetic analysis by culture of the bone marrow sample reported a karyotype of 48,XY,t(8;21)(q22;q22),+13,+13[9]/49,idem,+mar[9]/49,idem,+8[2].

Results of CBCs during the treatments in our center
Hematological examinations of WBCs, ANC, AMC, Hb, Plt and Ret levels during the treatments in our center are outlined in Figure 3.

DISCUSSION
In the present case, the presence of increased percentages of blasts and CD34+ progenitors, the identification of the chromosome rearrangement of t(8;21)(q22;q22) and the fused AML1–ETO gene fulfilled the diagnostic criteria for AML with the recurrent chromosome rearrangement of t(8;21)(q22;q22)/RUNX1-RUNXIT1[1,4]. On admission, he presented with the major complaints of high fever, overt gastrointestinal symptoms and urticaria-like skin lesions. In this setting, chemotherapy was deferred. He was prescribed antibiotics to treat the febrile episode, dexamethasone to treat urticaria-like skin lesions and a gut-cleansing preparation to remove gastrointestinal pathogens and their metabolites. His gastrointestinal infection and skin lesions were quickly resolved. Along with the resolution of the gastrointestinal infection and the skin lesions, his hematological profile significantly improved. The disappearance of the leukemia cells from his blood smears suggested an achievement of clinical hematological remission, although bone marrow aspiration was not performed at that time.

Because he declined chemotherapy and hypomethylation therapy, we had the opportunity to observe the recapitulated treatment response after disease relapse. The relapse-remission regularity was that symptomatic AML emerged with flaring of the gastrointestinal infection, and symptomatic AML subsided after resolution of the gastrointestinal infection by antibiotic and glucocorticoid treatments. These recapitulated treatment responses indicated that hematological remission was induced by antibiotic and glucocorticoid treatments. This raises the possibility that the clonal growth and survival advantage of the leukemia cells were sustained by the inflammatory stresses, probably derived from the gut inflammatory condition. With effective treatment of the gut inflammatory condition, the leukemia cells lost their proliferative advantage, and normal hematopoiesis was restored.

AML is highly heterogeneous in clinical presentation and treatment responses, which results from the high diversity of impaired genes, not only driving genes in the transformation of hematopoietic progenitors and in the acquisition of proliferative advantage but also nondriving genes affecting the clinical and biological activities of transformed leukemia cells. To date, hundreds of genes have been found to be associated with leukemia pathogenesis, each of which has a distinctive impact on disease development, progression and treatment responses[1-4]. The natural history of AML is generally aggressive, leading to death usually within weeks to months after the emergence of symptomatic disease in the absence of specific treatments[1,4]. However, spontaneous remission occasionally occurs in a small number of AML patients[5].

Although spontaneous remission is a rare event, more than 100 adult AML cases have been recorded. Spontaneous remission was reported in AML patients with various recurrent cytogenetic abnormalities, such as t(8;21)(q22;q22)/RUNX1-RUNXIT1[6-9], t(15;17)(q31;q22)/PML-RAR-α[10], t(v;11q23)/KMT2A rearrangement[11-13], inv(16)(p13;q22) or t(16;16)(p13;q22)/CBFB-MYH11[14,15] and t(8;16)(p11;p13)/MOZ-CBP[16]. Spontaneous remission was also reported in AML patients with a normal karyotype and other cytogenetic abnormalities, with +8 being the most frequently observed cytogenetic abnormality[17-21]. Spontaneous remission has been reported in AML patients with recurrent gene mutations such as...
as nucleophosmin 1 and RUNX1[22-24], with gene mutations in epigenetic modulation such as Ten-Eleven Translocation-2, BCOR, isocitrate dehydrogenase 1 and 2; splicing factors such serine/arginine-rich splicing factor 1, U2AF1 and pre-mRNA processing factor 8; and cell growth receptors and their signaling pathway components such as FLT3-ITD, BRAF, NRAS, KRAS and neurofibromatosis type 1 (NF1)[22-26]. Spontaneous remission even occurs in relapsed AML patients many years after allogeneic hematopoietic stem cell transplantation[13,27]. These AML patients encompassed M0-M6 subtypes with monocyte differentiation accounting for approximately half of the reported cases[6,10,11,14,16]. Patient bone marrow may be either hypercellular or hypocellular, and WBCs may be either elevated or reduced, with reduced WBCs occurring in a large proportion of reported cases.

In the majority of reported cases, the emergence of AML was concomitant with the flaring of an infectious episode, and spontaneous remission occurred after recovery from the infectious disease by treatment with antibiotics, corticosteroids, recombinant human granulocyte colony stimulating factor (rH-GSF) and/or surgical drainage. Infections range from localized infections[5,6,9,15] to fulminant sepsis[5,6,28,30]. Several extrapolations have been proposed to explain the occurrence of spontaneous remission in AML: (1) Overproduced inflammatory cytokines suppress the proliferation and promote the apoptosis of leukemia cells[31-33]; (2) Restored or acquired cellular and innate immune responses target leukemia cells[11,34]; (3) Restored or acquired humoral immune response targets leukemia cells [8,35]; (4) Acquired graft-versus-leukemia effects suppress the proliferation of leukemia cells[13,21,27]; (5) Glucocorticoids promote the apoptosis of leukemia cells[9]; and (6) Granulocyte CSF promotes the differentiation of leukemia cells[7,10,17]. However, these mechanisms do not legitimately explain the features of spontaneous remissions in our present case. This raises the possibility that an inflammation-sustained proliferative advantage of leukemia cells promotes the emergence of symptomatic disease, which may be the best explanation for these antibiotic and glucocorticoid treatment-induced hematological remissions. Symptomatic AML emerged when the inflammatory stresses flared, and the symptomatic AML subsided after the inflammatory stresses had been resolved by effective treatments. In other reported cases, spontaneous remissions occurred frequently after recovery from a febrile episode in response to diverse treatments rather than during the flaring of the infectious episode, also indicating an inflammation-sustained proliferative advantage, at least in a fraction of the reported cases.

It is generally accepted that constitutionally activated growth factor receptor signaling pathways are responsible for the growth and survival advantage of leukemic stem cells. Activated growth factor receptors and their signaling pathway components, such as the formation of fused genes involving ABL, FGFR1 and platelet-derived growth factor receptor and mutated genes involving FLT3, KIT, interleukin-3R, RAS, CBL, PTPN11 and NF1, result in autonomous proliferation[1-4]. In some AML patients, activation of certain mutated genes may not be autonomous but instead ligand-dependent, resembling mutated genes in the B-cell receptor signaling pathway during lymphoma pathogenesis in which the antigen-dependent growth and survival advantages have been well described[36-39]. In this setting, mutated genes in growth factor receptor signaling pathways may play a tonic role in intensifying prolif-
ervative signaling after ligands bind to their receptor, thereby acquiring growth and survival advantages. While clonal B cells proliferate in response to antigens binding to B-cell receptors,[36-39], myeloid hematopoietic progenitors proliferate in response to ligands binding to pattern recognition receptors, cytokine receptors and colony-stimulating factor receptors[40-42]. Inflammatory cytokines and colony-stimulating factors could directly promote the growth and survival of leukemia cells[43-47]. In our present case, the FLT3-TKD mutation was identified, which might be responsible for the proliferative advantage in inflammatory conditions.

This study has several limitations. First, the diagnosis of spontaneous remission was dependent on hematological improvements and the disappearance of leukemia cells from blood smears, lacking morphological evaluation of bone marrow smears and cytogenetic and molecular monitoring. Second, the exact ligands responsible for the proliferative advantage were not identified. Therefore, additional studies are merited to confirm the extrapolation.

CONCLUSION

The recapitulated hematological remissions provide strong evidence for the treatment responses being induced by antibiotic and glucocorticoid treatments. AML is a highly heterogeneous hematological malignancy. In our present case, removing the underlying infection could induce a transient hematological remission, suggesting that the growth and survival advantage in this subgroup of leukemia cells may be sustained by inflammation. The ligands may be infection-related components such as microbes or their metabolites, inflammatory cytokines or colony-stimulating factors produced in response to infection. This phenomenon warrants further investigation and may aid in investigating AML pathogenesis and in improving therapeutic outcomes in this subgroup of AML patients.

FOOTNOTES

Author contributions: Sun XY, Yang XD and Yang XQ analyzed the data and drafted the manuscript; Sun XY, Yang XD, Ju B, Xiu NN, Xu J participated in the treatment of this patient; Zhao XC supervised the treatment and finally decided on the manuscript; and all authors have read and approved the final version of the manuscript.

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Non-secretory multiple myeloma expressed as multiple extramedullary plasmacytoma with an endobronchial lesion mimicking metastatic cancer: A case report

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Abstract

BACKGROUND
Non-secretory multiple myeloma (MM) is a rare condition that accounts for only 3% of MM cases and is defined by normal serum and urine immunofixation and a normal serum free light chain ratio. Non-secretory MM with multiple extramedullary plasmacytomas derived from endobronchial lesions is extremely rare and can be misdiagnosed as metastasis of solid cancer.

CASE SUMMARY
A 36-year-old man presented with progressive facial swelling and nasal congestion with cough. Various imaging studies revealed an endobronchial mass in the left bronchus and a large left maxillary mass with multiple destructive bone metastatic lesions. He initially presented with lung cancer and multiple metastases. However, pathologic reports showed multiple extramedullary plasmacytomas in the left maxilla and the left bronchus. There was no change in the serum and urine monoclonal protein levels, and no abnormalities were observed in laboratory examinations, including hemoglobin, calcium, and creatinine levels. The bone marrow was hypercellular, with 13.49% plasma cells. The patient was diagnosed with non-secretory MM expressed as multiple extramedullary plasmacytomas with endobronchial lesions in a rare location. Radiation therapy for symptomatic lesions with high-dose dexamethasone was started, and the size of the left maxillary sinus lesion dramatically decreased. In the future, chemotherapy will be administered to control lesions in other areas.
CONCLUSION
We present a rare case of non-secretory MM with multiple extramedullary plasmacytoma with an endobronchial lesion.

Key Words: Maxillary mass lesion; Destructive bone metastatic lesion; Multiple extramedullary plasmacytoma; Endobronchial lesion; Non-secretory multiple myeloma; Case report

INTRODUCTION
Multiple myeloma (MM) is a mature B cell neoplasm that accounts for 10% of all hematologic malignancies and is defined by the presence of ≥ 10% of clonal plasma cells in the bone marrow or biopsy-proven extramedullary plasmacytoma and the presence of related tissue or organ damage[1]. Symptomatic MM is defined by the presence of a monoclonal protein in the serum or urine, plasma cells in the bone marrow (at least 10%), and presence of related organ disorders (hypercalcemia, renal insufficiency, anemia, and bone lesions)[1,2]. MM is primarily observed in older patients and considered difficult to treat[3]. Over the past decade, the median survival of patients with myeloma has increased with the development of therapeutic agents, including immunomodulatory drugs (thalidomide and lenalidomide) and proteasome inhibitors (bortezomib). High-dose therapy followed by autologous stem cell transplantation (ASCT) has also contributed to this improvement in the survival rate[4].

In most patients, plasma cell proliferation is restricted to the bone marrow. However, in some cases, extramedullary plasma cell proliferation is also observed in other tissues, such as the nasal cavity, lung, and pleura[5]. Endobronchial plasmacytoma has been reported in several cases. Although exceedingly rare, according to published reports, most cases were reported in solitary lesions or advanced MM[6]. Here, we report the first diagnosed case of multiple extramedullary plasmacytoma with endobronchial lesions in non-secretory MM.

CASE PRESENTATION

Chief complaints
A 36-year-old man presented to our hospital for evaluation of progressively worsening facial swelling and nasal congestion. He was initially diagnosed with a nasal polyp with sinusitis and underwent polyp removal with antibiotic therapy.

History of present illness
The patient visited our hospital for further evaluation after redeveloping facial swelling and nasal congestion, this time accompanied by a gradually worsening cough with sputum and blurred vision in the left eye.

History of past illness
The patient had no previous medical history.

Personal and family history
The patient is a non-alcoholic and non-smoker. He has no family history.
Physical examination
The patient showed painful facial swelling and blurred vision. The patient's respiratory rate was 22 breaths per minute, blood pressure was p (B) = 15.99/10.7 kPa, and oxygen saturation in room air was 90%.

Laboratory examinations
Based on laboratory findings, the hemoglobin level was 11.9 g/dL (normal range, 12-16 g/dL), and the creatinine level was 0.7 mg/dL (normal range, 0.5-1.3 mg/dL). Monoclonal proteins could not be detected by serum and urine protein immunofixation electrophoresis. The albumin level was 3.77 g/dL (normal range, 3.5-5.5 g/dL) and beta-2-microglobulin level was 4.2 mg/L (normal range, 0.0-2.4 mg/L). The lactate dehydrogenase level was 271 U/L (normal range, 125-220 U/L).

Imaging examinations
Computed tomography of the neck and thorax revealed a solid mass occupying the left maxillary sinus and an endobronchial lesion in the left main bronchus (Figure 1).
Positron emission tomography/computed tomography revealed a hypermetabolic mass in the left maxillary sinus extending to the left ethmoid sinus and nasal cavity and multiple hypermetabolic metastatic nodules in both the cervical and left supraclavicular areas. Multiple hypermetabolic osseous metastases had spread to the sternum, ribs, right scapula, right humerus, thoracic and lumbar spines, pelvic bone, and left femur. Focal hypermetabolic nodular lesions in the left main bronchus were also observed (Figure 1). Primary lung cancer with multiple bone metastases was initially suspected, but double primary lung cancer with maxillary sinus cancer was excluded. We immediately performed a pathologic examination of the maxillary sinus mass and the endobronchial mass using bronchoscopy. Bronchoscopic findings showed a 1.5-cm protruding mass with pedicles arising from the anterior wall of the left proximal main bronchus (Figure 1), which was suspected to be primary lung cancer. Initially, the maxillary mass had pathologic findings of monomorphic plasmacytoid cytoplasm (positive for CD138, kappa light chain, and negative for CD3, CD20, and lambda light chain) (Figure 2), and it was subsequently diagnosed as a plasmacytoma, which was confirmed by the bronchoscopic biopsy result (Figure 2).

Further diagnostic workup
The patient was referred to the hematology department to undergo an evaluation for systemic MM. Biochemical tests revealed normal calcium and creatinine levels, and serum and urine immunofixation were negative for monoclonal proteins. However, the bone marrow biopsy from the iliac crest showed hypercellularity for his age with diffusely infiltrated plasma cells (13.49%) (Figure 3). Although the patient had no anemia and the serum creatinine levels were normal, a diagnosis of non-secretory MM was considered based on the bone marrow biopsy findings and the multiple lesions, including confirmation of the maxillary sinus and endobronchial lesions as plasmacytoma.

FINAL DIAGNOSIS
The patient was finally diagnosed with non-secretory MM, expressed as multiple extramedullary plasmacytomas with an endobronchial lesion. The International Staging System stage at the time of diagnosis was II.

TREATMENT
The left maxillary sinus mass extended to the nasopharynx and left ethmoid sinus, which had caused severe facial edema and blurred vision in the left eye. Moreover, endobronchial lesions also caused severe respiratory distress symptoms. Therefore, we started high-dose steroid therapy with dexamethasone 40 mg for 4 days. Palliative radiation therapy of the left maxillary sinus lesion was performed simultaneously. After steroid administration, facial edema dramatically decreased, and respiratory distress symptoms improved (Figure 4). We continued radiation therapy on the symptomatic lesions to a total dose of 15 Gy.

OUTCOME AND FOLLOW-UP
Finally, the facial mass and symptoms almost regressed, and the patient will subsequently undergo chemotherapy with bortezomib, thalidomide, and dexamethasone, followed by ASCT.
Figure 1 Imaging at admission. A: Contrast-enhanced neck computed tomography shows a bulky mass in the left maxillary sinus extending to the orbit, nasal cavity, ethmoid sinus, infratemporal fossa, and pterygopalatine fossa; bone destruction extends to the nasal cavity; B: Contrast-enhanced chest computed tomography shows an enhanced nodule approximately 0.8 cm in size in the left main bronchus; C-E: 18F-fluorodeoxyglucose positron emission/computed tomography shows a large expansile hypermetabolic mass in the left maxillary sinus and hypermetabolic focal activity in the nasopharynx, multiple metastatic lymphadenopathies in both cervical and left supraclavicular areas, and multiple osseous metastases. There is a focal hypermetabolic nodular lesion in the left main bronchus; F and G: Bronchoscopy shows a 1.0-cm sized nodular lesion with pedicles arising from the anterior wall of the left main bronchus.

DISCUSSION

In the initial stage of diagnosis, our patient was strongly considered as having primary lung cancer with multiple bone metastases or double primary lung cancer with maxillary sinus cancer. Our patient’s laboratory tests showed normal results. For this reason, we excluded the possibility of plasmacytoma or non-secretory MM. However, the biopsy confirmed an extramedullary plasmacytoma. In addition, bone marrow examination showed more than 10% plasma cell infiltration without alterations in serum or urine paraprotein and immunoglobin subtype. Thus, we diagnosed the patient with non-secretory MM based on bone marrow examination and biopsy results.

Extramedullary plasmacytoma is a variant of a plasma cell tumor involving organs outside the bone marrow without any sign of systemic involvement (primary solitary plasmacytoma) or secondary to MM[7]. The differential diagnosis of plasma cell dyscrasias is vital because these diseases may exhibit diverse clinical courses and prognoses. Extramedullary plasmacytoma is most often located in the upper respiratory tract and nasopharynx, and involvement of the lower respiratory tract is rarely observed[8]. Endobronchial plasmacytoma is a rare manifestation of extramedullary plasmacytoma[6], with very few cases reported in the literature. Most endobronchial plasmacytoma cases were solitary plasmacytomas with no systemic involvement of MM[9-12]. Our patient showed systemic involvement of a plasma cell malignancy.

Extramedullary plasmacytoma is associated with adverse prognoses in patients with newly diagnosed and relapsing MM[13]. Almost all patients show multiple extramedullary plasmacytomas as the terminal event of their MM[13,14], whereas this patient showed multiple extramedullary plasmacytomas at the initial diagnosis of MM.

Non-secretory MM is a rare variant that accounts for 1%-5% of all cases of MM. It is characterized by the absence of monoclonal gammapathy in the serum and urine[15]. In this case, monoclonal gammapathy was not observed, and there was no organ dysfunction. Due to the inability to detect monoclonal proteins, it is difficult to establish an accurate diagnosis, and misdiagnosis of this condition as a solitary plasmacytoma delays systemic treatment[16,17].
Figure 2 Microscopic examination of the specimen using hematoxylin and eosin staining and immunohistochemistry staining. A-F: In the bronchus, plasmacytoid large atypical cells are densely infiltrated beneath the surface epithelium. These cells are immunoreactive for kappa-light chain (B) and CD138 (F) but not for lambda-light chain (C), CD3 (D), and CD20 (E); G-I: The lesion in the nasal cavity also shows densely packed plasmacytoid cells and is positive for kappa-light chain (H) and negative for lambda light chain (I).

Figure 3 Bone marrow biopsy. Plasma cells are present in the biopsy. Arrow: Plasma cell.

CONCLUSION
Initially, this patient was diagnosed with primary lung cancer with multiple metastases because there was no reversal of the A/G ratio or increase in serum monoclonal protein levels. However, bone marrow and tissue biopsy results showed systemic involvement of MM. Thus, we present a case of non-secretory MM expressed as multiple extramedullary plasmacytoma with an endobronchial lesion.
Figure 4 Imaging after radiotherapy. A: Before radiotherapy; B: During radiotherapy; and C: After completion of radiotherapy, bulky mass of the left maxillary sinus decreased after radiotherapy.

Such cases are extremely rare and can be easily misdiagnosed as solid cancers of the upper respiratory tract until histologic confirmation. These clinical situations are extraordinarily heterogeneous, and care must be taken before making a diagnosis. These cases should be considered as having high-risk myeloma systemic involvement and treated appropriately.

FOOTNOTES

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Latamoxef-induced severe thrombocytopenia during the treatment of pulmonary infection: A case report

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**Abstract**

**BACKGROUND**

Latamoxef shows excellent antibacterial activity against anaerobic bacteria such as *Bacteroides fragilis*. Reports of thrombocytopenic toxicity of latamoxef are limited. This report presents a case of severe thrombocytopenia possibly induced by latamoxef, an infrequent adverse drug reaction in a young patient with tuberculosis and Crohn's disease in China.

**CASE SUMMARY**

We reported a case of severe thrombocytopenia induced by latamoxef in a 28-year-old man with tuberculosis and Crohn's disease. On admission, the patient presented with a cough productive of bloody sputum, a chest computed tomogram suggested scattered mottled, high-density shadows in both lungs. Laboratory tests indicated a platelet count of 140000/μL. Considered a pulmonary bacterial infection, the patient received anti-infection therapy with latamoxef (dose: 2.0 g) intravenously Q12h. On the 9th day of treatment, the platelet count decreased to 44000/μL. On the 12th day, scattered purpura and ecchymosis appeared on the patient's limbs and trunk, and the platelet count decreased to 9000/μL after latamoxef treatment for 15 d. Three days after discontinuation of latamoxef, the platelet count recovered to 157000/μL, and the area of scattered purpura and ecchymosis on the limbs and trunk decreased. The platelet counts remained in the normal range, and no thrombocytopenia was found at follow-up 15 mo after discharge.
CONCLUSION

For patients treated with latamoxef, platelet counts should be carefully followed, and caregivers should be vigilant for the appearance of scattered ecchymosis.

Key Words: Thrombocytopenia; Latamoxef; Adverse drug reactions; Young onset; Case report

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Core Tip: We described a case of severe thrombocytopenia likely induced by latamoxef, an infrequent adverse drug reaction in a young patient with tuberculosis and Crohn's disease. We followed the changes in platelet counts and the appearance of purpura during latamoxef treatment and after drug withdrawal and excluded other possible causes of thrombocytopenia. Our findings suggested that the patient's thrombocytopenia was caused by latamoxef. This is the first reported case of severe thrombocytopenia induced by latamoxef in a young Chinese patient to the best of our knowledge.

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INTRODUCTION

Latamoxef is a new semisynthetic oxacephem antibiotic structurally similar to third-generation cephalosporins. Latamoxef has excellent antibacterial activity against anaerobic bacteria such as Bacteroides fragilis. It is stable against β-lactamases produced by most Enterobacteriaceae, mediated by plasmids or partially by chromosomes[1]. The primary associated adverse reactions are rash, drug fever, hepatic and renal dysfunction, neutropenia, and eosinophilia, followed by coagulation dysfunction, with an incidence of 12.45%[2,3]. Thrombocytopenia is a common blood disorder characterized by the destruction of circulating platelets and inhibition of platelet production[4]. Although several studies have reported that latamoxef could cause thrombocytopenia[5-7], thrombocytopenia induced by latamoxef in the Chinese population is rare and clinicians often overlook latamoxef-induced thrombocytopenia. This case report presents the first case of severe thrombocytopenia and multiple ecchymoses caused by latamoxef in a young Chinese patient. We defined thrombocytopenia as a platelet count less than 100000/μL[8].

CASE PRESENTATION

Chief complaints
A 28-year-old male patient presented to the hospital with a fever for one month and a cough for more than ten days.

History of present illness
He developed a fever at about 38℃ without obvious inducement one month prior and went to another hospital’s emergency department. He received a diagnosis of upper respiratory tract infection. The symptoms subsided after symptomatic treatment. More than 10 days before presentation, the patient had a paroxysmal cough with white sticky sputum and was diagnosed with pneumonia. Symptoms did not improve after expectorant treatment. In the days before the presentation, he had developed yellow and bloody sputum accompanied by night sweats.

History of past illness
The patient had a history of Crohn’s disease for more than five years and took mesalazine sustained-release tablets. Half a year prior, he stopped the mesalazine and switched to adalimumab injection once every two weeks, and he was in stable condition at presentation.

Personal and family history
There is no specific family history of illness.
Physical examination
Several enlarged lymph nodes were found on the left and right sides of the patient's neck. The skin color was normal without ecchymosis, and respiratory rate and vital signs were normal.

Laboratory examinations
White blood cell (WBC) count was below the normal range, while hemoglobin (HGB) and platelet count were at normal levels (Figure 1). Other test indicators were in the normal ranges.

Imaging examinations
A chest computed tomogram suggested scattered mottled, high-density shadows in both lungs, mediastinal and hilar lymph node enlargement, and several nodules in the spleen.

Final diagnosis
Secondary tuberculosis with sputum smear-negative, initial treatment; Cervical lymphatic tuberculosis; Splenic tuberculosis; Crohn's disease; Thrombocytopenia; Leukopenia.

Treatment
Because the diagnosis of tuberculosis was not clear initially, we considered it a bacterial infection. The patient first received anti-infective therapy with latamoxef (2.0 g) intravenously every 12 h and leucogen tablets (20.0 mg) three times per day for leukocytopenia. The timeline of the overall treatment process is presented in Table 1.

On day 9 (18:00 h) after initiation of latamoxef treatment, the patient developed chills and fever to 38.2 °C without shivering and cough with a small amount of sputum. On day 10, after initiation of latamoxef treatment, the patient received isoniazid tablets (0.3 g/d) and rifampicin capsules 0.6 g daily, considering his history of immunosuppressive agents and positive T SPOT-TB testing results, and latent infection with Mycobacterium tuberculosis was evident. On day 11, cervical lymph node aspirate fluid grew Mycobacterium tuberculosis complex sensitive to rifampicin. Pathological examination of a biopsy specimen from a left cervical lymph node revealed chronic granulomatous lymphadenitis with coagulative necrosis. Considering the presence of secondary pulmonary tuberculosis, cervical lymph node tuberculosis, and splenic tuberculosis, we added pyrazinamide 0.5 g three times per day and ethambutol 1.0 g daily in combination with isoniazid and rifampicin.

On the 12th day, the patient’s body temperature returned to normal but scattered purpura and ecchymosis appeared on his limbs and trunk. The platelet count decreased to 7000/μL. Considering that this might be thrombocytopenia induced by rifampicin, we replaced rifampicin with levofloxacin sodium chloride injection, 0.5 g intravenous drip once a day. Following consultation with hematology, we added subcutaneous injection of recombinant human thrombopoietin at 15000 units per day and intravenous infusion of human immunoglobulin (20.0 g/d), 15 units of platelets, and 5 mg of dexamethasone. The patient developed hemoptysis on day 13, and we added intravenous infusion of tranexamic acid sodium chloride (0.5 g/d), etamsylate (2.0 g/d) and spearhead agkistrodon hemocogulase (2.0 U/d) for hemostasis.

On the 15th day, the platelet count decreased to 9000/μL, suggesting that the patient was in a critical state. Because the patient could not afford the medications, pharmacists simplified the prescriptions. We recommended discontinuing latamoxef 2.0 g Q12H and adding an intravenous injection of 10 mg of vitamin K1 once a day, and the clinicians agreed. On the 16th day, the platelet count increased to 57000/μL. We discontinued the human immunoglobulin injection and recombinant human thrombopoietin. On the 17th day, the platelet count rapidly recovered to 157000/μL. We discontinued vitamin K1 and dexamethasone. Since then, the patient did not use latamoxef and was discharged on the 24th day taking isoniazid, ethambutol, pyrazinamide, and levofloxacin for tuberculosis treatment. Figure 1 display the fluctuation of peripheral blood WBC, HGB, and platelets, respectively, along with medications. Figure 2 display the ecchymoses before discontinuation of latamoxef and before discharge, respectively.

Outcome and follow-up
The patient was followed up at the first, third, and fifth week and monthly after discharge. The platelet counts and the HGB concentrations remained stable and in the normal range. Prothrombin and activated partial thromboplastin were normal from admission to platelet recovery. No thrombocytopenia was found at follow-up 15 mo after discharge.
Table 1: Timeline of the treatment process

<table>
<thead>
<tr>
<th>Time</th>
<th>Symptom</th>
<th>Platelet counts</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>Bloody sputum, scattered mottled, high-density shadows in both lungs</td>
<td>140000/μL</td>
<td>Latamoxef (dose: 2.0 g) intravenously Q12H</td>
</tr>
<tr>
<td>Day 9</td>
<td>Chills and fever to 38.2 °C (18:00)</td>
<td>44000/μL (8:00 am)</td>
<td>-</td>
</tr>
<tr>
<td>Day 10</td>
<td>Positive T SPOT-TB testing results</td>
<td>-</td>
<td>Added isoniazid tablets 0.3 g QD, rifampicin capsules 0.6 g QD</td>
</tr>
<tr>
<td>Day 11</td>
<td>Secondary pulmonary tuberculosis, cervical lymph node tuberculosis, and splenic tuberculosis were confirmed</td>
<td>-</td>
<td>Continued adding pyrazinamide 0.5 g TID, ethambutol 1.0 g QD</td>
</tr>
<tr>
<td>Day 12</td>
<td>Body temperature returned to normal but scattered purpura and ecchymosis appeared on his limbs and trunk's skin</td>
<td>7000/μL</td>
<td></td>
</tr>
<tr>
<td>Day 13</td>
<td>Hemoptysis</td>
<td>44000/μL</td>
<td>Continued adding tranexamic acid sodium chloride (0.5 g/d), etamsylate (2.0 g/d) and spearhead agkistrodon hemocoagulase (2.0 U/d) for hemostasis</td>
</tr>
<tr>
<td>Day 15</td>
<td>Critical state</td>
<td>9000/μL</td>
<td>Discontinued latamoxef 2.0 g Q12H and added vitamin K1 (10 mg/d)</td>
</tr>
<tr>
<td>Day 16</td>
<td>-</td>
<td>57000/μL</td>
<td>Discontinued the human immunoglobulin injection and recombinant human thrombopoietin</td>
</tr>
<tr>
<td>Day 17</td>
<td>-</td>
<td>157000/μL</td>
<td>Discontinued vitamin K1 and dexamethasone</td>
</tr>
<tr>
<td>Day 23</td>
<td>-</td>
<td>255000/μL</td>
<td>-</td>
</tr>
<tr>
<td>Day 24</td>
<td>Discharged</td>
<td>-</td>
<td>Took isoniazid, ethambutol, pyrazinamide, and levofloxacin for tuberculosis treatment</td>
</tr>
<tr>
<td>The 1, 3, 5 wk, and 15-mo after discharge</td>
<td>-</td>
<td>Normal</td>
<td>Took isoniazid, ethambutol, pyrazinamide, and levofloxacin for tuberculosis treatment</td>
</tr>
</tbody>
</table>

Thrombocytopenia: Platelet count less than 100000/μL. Abnormal values are given in italic font.

DISCUSSION

Our patient’s thrombocytopenia induced by latamoxef was unique. To our best knowledge, this is the first documented case in a young Chinese patient. Vayne et al.[9] reported that drug-mediated immune thrombocytopenia often gave rise to a higher risk of bleeding. Generally, thrombocytopenia occurs after 5 to 10 d of drug exposure, and the median platelet count is usually less than 20000/μL. Platelet counts usually begin to recover at four to five half-lives or within two to three days after discontinuation[8,9]. The literature suggested that rifampicin had a strong tendency to cause thrombocytopenia with an incidence of between 1% and 10%[10]. A systematic evaluation of 153 drugs conducted by Arnold et al[11] found that the most drugs contributing to drug-induced immune thrombocytopenia were rifampicin, quinine, vancomycin, and ceftriaxone.

The patient started oral rifampicin on the 10th day and stopped on the 12th day. We excluded rifampicin-induced immune thrombocytopenia based on the following criteria: (1) The time of occurrence was not in line with expectations. Before taking rifampicin, the patient received latamoxef alone. At that time, the platelet count decreased significantly from 140000/μL to 44000/μL (by 68.57%); (2) The exposure time of rifampicin was short (only two days), far less than the exposure time of five to ten days; this exposure was not sufficient to cause a decline in the platelet count[8,9,12]; and (3) The elimination half-life of rifampicin is three to five hours, and the patient had been off rifampicin for three days before the recurrence of thrombocytopenia; this time-course was inconsistent with the reported recovery of platelet counts after four to five half-lives. We transfused 15 units of platelets and administered human immunoglobulin, glucocorticoid after discontinuation of rifampicin to retard platelet clearance; however, the patient’s platelet count remained at 9000/μL on the 4th day after discontinuation of rifampicin. These results suggest that rifampicin was not the primary cause of drug-induced immune thrombocytopenia.

According to an approach proposed by Arnold et al[13], the diagnosis of drug-induced immune thrombocytopenia is based on the following four criteria: (1) Severity of thrombocytopenia: platelet count nadir below 20000/μL; (2) Clinical signs: Any bleeding; (3) Time to onset: Platelet counts fall 5-10 d after initiation of a new drug or exposure to a drug previously taken; and (4) Use of drugs already identified as responsible for drug-induced immune thrombocytopenia (with clinical and laboratory
tests), with the drug previously associating with drug-induced immune thrombocytopenia by clinical and laboratory criteria[13]. The first three criteria matched our patient’s presentation. Because of our hospital's limited laboratory conditions, we could not directly measure drug-dependent platelet antibodies using immunoassay or flow cytometry. Therefore, the fourth criterion could not be confirmed.

We excluded possible causes of thrombocytopenia such as tuberculosis of the spleen, pseudothrombocytopenia, primary immune thrombocytopenia, other drug-induced immune thrombocytopenia, food and beverages, infections, hypersplenism due to chronic liver disease, excessive alcohol intake, nutritional deficiencies, rheumatologic diseases, thrombotic microangiopathy, myelodysplasia, cancer with disseminated intravascular, coagulation, cancer with bone marrow infiltration or suppression, and post-transfusion purpura. On the Naranjo scale, our patient scored six, placing him in the category of potential drug-related toxicity[14]. We could not rechallenge the patient with latamoxef for apparent reasons. According to our findings, latamoxef was the cause of the drug-induced immune thrombocytopenia.

The original instructions for latamoxef did not mention thrombocytopenia or coagulation dysfunction. Some studies mentioned that the N-methyl tetrazolium side-chain in latamoxef could lead to prothrombin deficiency, thrombocytopenia, platelet dysfunction, and bleeding. In such cases, one should supplement with vitamin K to reduce adverse reactions such as coagulation dysfunction and bleeding[2,15]. We searched PubMed, Embase, CNKI, Wan-Fang, and VIP database, and located four articles related to thrombocytopenia caused by latamoxef[5-7,16]. Although several studies reported that latamoxef could cause thrombocytopenia, thrombocytopenia induced by latamoxef in the Chinese population has never been reported previously. The literature suggests that one should use latamoxef cautiously in elderly patients with hepatic and renal dysfunction, history of ulcers, long-term use of broad-spectrum antibiotics, poor coagulation function, bleeding tendency, or use of anticoagulant and antiplatelet drugs[5,6,16]. The patient in our case had none of these risk factors; however, he had recurrent fevers for more than one month. Fever leads to high metabolic rates, and disseminated
tuberculosis is a consumptive disease that reduces immunity. He also had Crohn’s disease for more than five years and was treated with adalimumab as immunosuppressive therapy. Overall, the patient’s tolerance to drug-induced thrombocytopenia was lower than that of healthy adults. Therefore, we suggested that latamoxef should be discontinued immediately when patients with thrombocytopenia suspected to be caused by latamoxef, the platelet count is less than 20000/μL and complicated by bleeding or blood loss anemia. Moreover, first-line drug treatment such as corticosteroid, human immunoglobulin, platelet-raising drugs, and transfusion of platelets or coagulation factor should be considered to alleviate the symptoms as soon as possible. We also recommend that thrombocytopenia be included among the adverse effects in the Chinese instructions for latamoxef.

CONCLUSION

This is the first case of severe thrombocytopenia induced by latamoxef in a young Chinese patient. For patients treated with latamoxef, platelet counts should be carefully monitored, and clinicians should be vigilant for the appearance of scattered ecchymoses. Clinicians should discontinue latamoxef immediately when thrombocytopenia occurs in the context of latamoxef treatment, especially for patients with tuberculosis, malnutrition, polypharmacy, and immunosuppressive states, all of which are potential predisposing factors.

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FOOTNOTES

Author contributions: Zhang RY proposed and supervised the study; Zhang JJ assisted with data analysis, Li JM, Xu YY and Xu YH managed the patient and collected samples; Cai XJ evaluated data and modified the manuscript; all authors contributed to the design and interpretation of the study and to further drafts.

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Zhang RY et al. Severe thrombocytopenia induced by latamoxef

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Multicentric reticulohistiocytosis with prominent skin lesions and arthritis: A case report

Xiao-Li Xu, Xiao-Hong Liang, Juan Liu, Xu Deng, Lu Zhang, Zhi-Gang Wang

Abstract

BACKGROUND
Multicentric reticulohistiocytosis (MRH) is a rare non-Langerhans histiocytosis of unknown etiology characterized by papulonodular skin lesions and progressive, erosive arthritis. To date, there have been approximately 300 cases of MRH reported worldwide. The majority of patients are Caucasian from western countries, and Asian patients are rare. Here, we report a case of MRH in a Chinese patient.

CASE SUMMARY
A 38-year-old male was admitted to the hospital with a rash that had persisted for over 2 years and bilateral knee pain for over 1 year. The patient’s symptoms had previously been misdiagnosed as eczema when there were only skin symptoms and was finally diagnosed as MRH after a skin biopsy of the left upper back. The patient was treated with glucocorticoids combined with an immunosuppressive regimen. While the skin lesions on both arms, abdomen, and back subsided, the skin lesions on the rest of the body did not increase. The interphalangeal joints of both thumbs and bilateral knee joints remained swollen and painful.

CONCLUSION
The case will help clinicians better identify and treat this disease in the absence of epidemiological studies or randomized controlled data.
Key Words: Multicentric reticulohistiocytosis; Papulonodular skin lesions; Arthritis; CD68; Case report

Core Tip: Multicentric reticulohistiocytosis (MRH) is a rare non-Langerhans histiocytosis of unknown etiology characterized by papulonodular skin lesions and progressive, erosive arthritis. To date, there have been approximately 300 cases of MRH reported worldwide. However, the majority of patients are Caucasian from western countries, and Asian patients are rare. Here, we report a case of MRH in a Chinese patient. We also review the relevant literature and comprehensively analyze the clinical characteristics of MRH. This case report and comprehensive analysis will help clinicians better identify and treat this disease in the absence of epidemiological studies or randomized controlled data.

INTRODUCTION
Multicentric reticulohistiocytosis (MRH) is a rare multisystemic disease of unknown etiology characterized by papulonodular skin lesions and erosive arthritis. MRH is classified as non-Langerhans cell histiocytosis class II b according to the recommendations of the Histiocyte Society. There is currently no published data on the incidence and prevalence of MRH. To date, there have been approximately 300 reported cases of MRH worldwide. Moreover, the majority of patients are Caucasian from western countries and Asian patients are rare. Here, we report a case of MRH in China and provide a comprehensive analysis of the clinical characteristics of MRH.

CASE PRESENTATION

Chief complaints
A 38-year-old male was admitted to our hospital with a rash that had persisted for over two years and bilateral knee pain for over one year.

History of present illness
In May 2017, a small red dotted rash appeared on the inner side of the patient’s right thigh slightly above the skin surface, without itching. By September 2017, the rash on the patient’s right thigh had gradually increased in size from a small dot to a chrysanthemum-like pattern. In July 2018, millet-like, brownish-red papules appeared on the left thigh, symmetrically positioned with the right leg. This was followed by the appearance of similar rashes on the back of the ear, neck, shoulder, and back. The patient was diagnosed with eczema by a foreign hospital and was prescribed an ointment (details unknown) for external application without improvement. In September 2018, he was diagnosed with MRH following a skin biopsy obtained from the left upper back in our hospital. In November 2018, the patient was administered oral treatment with tripterygium glycosides for two months at Peking Union Medical College Hospital (exact dosage unknown). He subsequently ceased taking the medicine upon the development of liver damage. From September 2019, red macules and millet-like brown-red papules appeared on the anterior chest area, waist, and abdomen. After re-visitng our hospital, he began taking 8 mg/d oral methylprednisolone, and was administered 0.6 g cyclophosphamide in October 2019 by venous transfusion. Subsequently, the patient took 8 mg/d oral methylprednisolone irregularly without improvement of the skin lesions and joint symptoms. In January 2020, multiple round and oval nodules that were brownish red, hard, with a smooth surface, no rupture, approximately 2-8 mm in size appeared on the back of both hands. The patient had difficulty making a fist with both hands and exhibited a deformity in the distal interphalangeal joints of both hands in flexion. Beginning in July 2020, sesame-sized maculopapules appeared on both of the patient’s arms; pain in both knees was aggravated with swelling; and squatting was limited. The patient had no fever, myalgia, oral ulcers, or Raynaud’s phenomenon, was in good spirits, and had no loss of appetite. No significant changes were observed regarding the patient’s weight throughout the course of the illness.
History of past illness
The patient had no previous medical history.

Personal and family history
The patient denied a history of smoking and alcohol consumption; denied drug addiction; no history of exposure to industrial poisons, dust, and radioactive substances. There is no similar family history and family genetic disease is denied.

Physical examination
On physical examination, the patient was in a good general condition. A brownish-red maculopapular rash densely covered behind the ears, neck, shoulder, anterior chest, back, waist, abdomen, arms, and inner thighs. Multiple round and oval nodules, 2-8 mm in size, reddish-brown, hard, without rupture, and without pressure pain were observed on the back of both hands (Figure 1) and was associated with poor mobility. The oral mucosa and tongue were not involved. Grade V muscle strength of the extremities was observed. The patient had a "gooseneck-like" deformity involving 2-5 fingers of both hands, swelling of the interphalangeal joints of both thumbs, difficulty making a fist, swelling of the bilateral knee joints with pressure-associated pain, and limited capacity for squatting.

Laboratory examinations
The laboratory tests revealed that liver function, biochemistry, blood lipid level, erythrocyte sedimentation rate, tumor markers, and thyroid function were normal. The complete set of autoantibodies was negative. The patient was negative for anti-keratin antibodies and anti-cyclic citrullinated peptide antibodies < 5 relative units (RU)/mL. Anti-anti-neutrophil cytoplasmic antibody (anti-ANCA) was negative, anti-myeloperoxidase (anti-MPO), and anti-proteinase 3 (anti-PR3) were < 20 RU/mL. Routine blood count: platelets 361 × 10^9/L and monocyte count 0.63 × 10^9/L. Bone turnover marker: type I collagen carboxy-terminal peptide 1198.00 pg/mL. Immune function: immunoglobulin G 16.3 g/L, and C3 0.76 g/L.

Imaging examinations
Radiographs of both hands revealed that multiple interphalangeal joints and the intercarpal joints of both hands were narrowed. In addition, the bone density of the constituent bones of the joints was reduced, cystic translucent areas were observed, and the left radial carpal joint was narrowed (Figure 2A). Knee MRI revealed a Grade 2 injury to the anterior and posterior angles of the medial and lateral menisci of the left knee; degeneration of the left knee, osteochondral injury to the patellofemoral articular surface; dotted film shadow of the synovial membrane around the left knee; possible synovitis; and effusion in the left knee joint cavity and suprapatellar bursa (Figure 2B). Chest CT revealed interstitial inflammation in both lungs; bilateral interlobular cleft nodules with recommended follow-up; fibrous foci in both lower lobes of the lungs; and cystic foci in the right subscapularis muscle (Figure 2C).

PATHOLOGICAL EXAMINATION
Microscopic, pathological analysis of a skin biopsy taken from the left upper back revealed that the epidermis was generally normal. The dermal papillae showed an increase in the number of histiocytes and multinucleated giant cells with abundant cell cytoplasm and hairy glass-like changes, with a little lymphatic and eosinophilic infiltration around them (Figure 3A). Immunohistochemistry showed CD68(+), CD1a(-), and S100(-) (Figure 3B-D). In an iliac bone aspiration biopsy, the morphological analysis of the bone marrow cells did not exhibit any significant abnormalities in the granulocyte-red-macro triad. The pathological examination revealed hematopoiesis. There was an approximately 40%-60% fat, granulocyte-red ratio < 2.5:1, Alip-, and scattered megakaryocyte lineage, with no obvious tumor component.

FINAL DIAGNOSIS
The final diagnosis of the presented case is MRH.

TREATMENT
As treatment, the patient began taking 16 mg/d oral methylprednisolone tablets regularly on November 2020. The methylprednisolone was reduced to 12 mg/d during February 2021-April 2021, and methyl-
Figure 1 Skin lesions of the patient. A-E: Skin-colored, brownish-red, millet to mung bean-sized maculopapules were observed on the patient’s neck, chest, waist, abdomen, and arms; F: Multiple round or oval nodules, 2-8 mm in size, reddish-brown, hard, and unbroken were observed on both hands.

Figure 2 Imaging examinations of the patient. A: Radiographs of both hands. Narrowing of the interphalangeal and intercarpal joint spaces in both hands, reduced bone density of the joint components, visible cystic translucent areas, and narrowing of the radial carpal joint on the left side were observed; B: Knee MRI. Osteochondral damage of the patellofemoral articular surface and fluid accumulation in the left knee joint cavity and suprapatellar capsule were observed; C: HRCT of the chest. There was interstitial inflammation present in both lungs; bilateral interlobular fissure nodules; focal fibrosis in both lower lobes of the lungs; and cystic foci in the right subscapularis muscle.

Prednisolone was reduced to 8 mg/d from May 2021 onwards. On 30 November and 15 December 2020, 0.4 g cyclophosphamide was intravenously administered once. On 29 December 2020 and 26 January 2021, 0.6 g cyclophosphamide was intravenously administered once. Since then, 0.8 g cyclophosphamide has been administered regularly every month, and blood count, liver, and kidney function have been monitored (Figure 4).

OUTCOME AND FOLLOW-UP

At present, skin lesions on both arms, abdomen, and back had subsided, while the skin lesions on the rest of the body had not increased elsewhere. The interphalangeal joints of both thumbs and bilateral knee joints remained swollen and painful. Thus, we recommend TNF-α antagonists as treatment for patients who are under consideration. The patient treatment and follow up are ongoing.
MRH is a rare multisystemic granulomatous disease and non-Langerhans histiocytosis. Papulonodular skin lesions and destructive arthritis are the two prominent features of MRH. MRH was first identified and reported by Weber and Frudenthal in 1937 and termed Multicentric reticulohistiocytosis by Goltz and Laymon in 1954[1]. While the pathogenesis of MRH remains unclear and may be related to the infiltration of a large number of macrophages in the skin and synovial tissues, it may also be associated with the differentiation of monocytes into osteoclasts, which ultimately leads to joint destruction[2]. To date, there have been approximately 300 cases of MRH reported worldwide. The data demonstrate that most patients are Caucasian and from western countries, whereas Asian patients are rare. The peak age at onset is 40-50 years old, with a male to female ratio of 1:3[3,4].

Skin lesions
The skin is the most frequently involved site of MRH. Skin lesions may be the first symptom and are primarily distributed on the face, scalp, behind the ears, neck, anterior chest, back, waist, and abdomen[Adamopoulos, 2006 #12]men, arms, hands, and thigh. The manifestations of skin lesions include papular nodules and macules. Papular nodules appear above the skin surface, are hemispherical in shape, hard in texture, millet to soy size, and are usually not accompanied by pruritus. The papular nodules can be of various colors, including skin color, red, and reddish-brown. The small papules are arranged in a linear “coral bead” pattern at the nail folds. In severe cases, facial lesions may have a “lion-like appearance”[5]. Macula is another form of skin lesions that manifest as brown-red and purplish red edematous spots, similar in morphology and distribution to dermatomyositis rash, which is occasionally accompanied by dermatomyositis, and can easily be misdiagnosed. In addition, MRH can also involve mucous membranes (e.g., oral mucosa, gingival mucosa, and laryngeal mucosa).

MRH-associated arthritis
Arthritis is one of the predominant clinical symptoms of MRH and can appear as the first symptom of MRH, and can occur simultaneously with skin lesions. MRH-associated arthritis can be characterized as diffuse, symmetric, progressive, and destructive. MRH is most commonly involved in the hand joints, especially the distal interphalangeal joint, followed by the knee joint, the shoulder, elbow, hip, ankle, and metatarsophalangeal joint. The affected joints exhibit swelling, pain, an increase in skin temperature, joint effusion, and some patients can also experience morning stiffness. Joint erosion is characterized by the gradual progression from the joint edges to the entire joint surface, eventually leading to an enlargement of the joint cavity, loss of articular cartilage, and resorption of subchondral bone. Unlike other forms of inflammatory arthritis, MRH is mainly free of bone loss and abnormal new bone formation[1,6]. However, joint destruction progresses rapidly and can eventually lead to joint deformities, hypofunction, or loss. Without prompt and effective treatment, this destruction of the proximal interphalangeal and distal interphalangeal joints may result in “opera-glass hand”[1]. It has
also been reported that some patients with severe hip destruction require hip arthroplasty\[7\]. Therefore, X-ray examination can play an important role in the early detection of MRH and in the screening of MRH from other types of arthritis.

**Other clinical manifestations**

MRH can involve additional organs. Patients with muscle involvement present with myalgia or decreased muscle strength. Electromyography may exhibit myogenic lesions in some patients\[3\]. Patients with lung involvement exhibited dyspnea, pulmonary nodules, pleural effusion, or pulmonary interstitial fibrosis\[8\]. Patients with heart involvement have been reported as having pericardial effusion and myocarditis\[9\]. Patients with laryngeal involvement exhibit hoarseness, foreign body sensation in the larynx, or laryngeal abnormalities\[4\]. In addition, patients with thyroid involvement showed hypothyroidism\[10\]. Thrombosis has also been reported in patients with MRH\[11,12\]. A small number of patients have extensive systemic involvement of the larynx, lungs, spleen, and plasma membranes at the same time. In addition to organ involvement, MRH may also present with systemic symptoms, including fatigue, fever, and weight loss.

**Laboratory results**

The laboratory tests for patients with MRH are nonspecific. Some patients may have increased leukocytes, decreased hemoglobin, accelerated sedimentation, and elevated lipids. Positivity for rheumatoid factor, anti-cyclic citrullinated antibodies, and antinuclear antibodies is rare, except for the combination with a systemic autoimmune disease\[13\].

**Figure 4** Timeline summarizing the patient's disease process.
Histopathology
The diagnosis of MRH is primarily based on a biopsy of the skin or synovial tissue. The histopathological manifestations include a large number of histiocytes and multinucleated giant cells with an eosinophilic cytoplasm and hairy glass-like changes. Immunohistochemistry indicated that the macrophage marker CD68 is positive, which may be considered an essential criterion for MRH characterization. The Langerhans cell tissue markers S-100, CD1a and B cell markers CD19 and CD20 are negative. It has been reported that vimentin, CD45, CD43, Mac387, and lysozyme are positive in varying degrees in some patients[14,15].

MRH-associated diseases
Patients with MRH may also have a variety of systemic autoimmune diseases including systemic lupus erythematosus, rheumatoid arthritis, Sjögren’s syndrome, dermatomyositis, hypothyroidism, diabetes, and tuberculosis[10,11,16,17]. It is important to note that MRH can be associated with malignancies and the combination rate can be as high as 25%, covering almost all solid tumors and hematologic malignant diseases[3,18]. It has been reported that some patients have also experienced remission of the skin and joint symptoms following tumor treatment; thus, MRH is considered to be a paraneoplastic syndrome [19]. While this view remains controversial, clinicians should be on alert for the presence of malignancies in patients with MRH.

Differential diagnosis
MRH is prone to be misdiagnosed as a systemic autoimmune disease due to similar skin and joint symptoms. MRH is also misdiagnosed as it often coexists with systemic autoimmune diseases, including rheumatoid arthritis, dermatomyositis, Sjögren’s syndrome, fibroelastic rheumatism, and systemic lupus erythematosus. The diseases most commonly confused with MRH include rheumatoid arthritis and dermatomyositis. Here, we will summarize the key points that distinguish MRH from these two diseases based on relevant literature and clinical experience. Unlike rheumatoid arthritis, joint destruction in MRH is rapid, and the distal interphalangeal joints can be involved during the early stages. MRH is mostly free of bone loss and abnormal new bone formation[1] and synovial biopsy can effectively distinguish MRH from rheumatoid arthritis (Table 1). Unlike dermatomyositis, the main skin lesions in MRH are papular nodules and macules, whereas Gottron papules, heliotrope rash, Gottron signs, erythema along the light site, heterochromia, nail fold changes, scalp involvement, and skin calcification are observed in dermatomyositis. The histopathological manifestations of MRH consist of a large number of histiocytes and multinucleated giant cells with an eosinophilic cytoplasm and hairy glass-like changes. In contrast, the histopathological manifestations of dermatomyositis are dominated by the sporadic or focal infiltration of lymphocytes, plasma cells, and histiocytes. Moreover, the musculoskeletal symptoms of MRH are featured as arthritis, whereas proximal muscle weakness is observed in dermatomyositis[20,21] (Table 2).

Treatment and prognosis
There is currently no consensus regarding the treatment of MRH, which mainly consists of empirical and individualized therapy. The initial treatment of MRH patients primarily consists of glucocorticoids combined with immunosuppressants regimens. Commonly used immunosuppressants include methotrexate, cyclophosphamide, hydroxychloroquine, and leflunomide. These combination regimens provide varying degrees of relief for the skin lesions and early joint symptoms; however, it is difficult to control joint erosion effectively. It has been reported that bisphosphonates can decrease macrophage-osteoclast differentiation, promote osteoclastic apoptosis, and inhibit osteoclastic resorptive activity. Moreover, bisphosphonates are potent inhibitors of osteoclast activity and can effectively prevent joint erosion[22,23]. Bisphosphonates have also been reported to be effective for both skin and joint symptoms. The mechanism by which bisphosphonates improve skin symptom remains unclear.

As the study progressed, it was found that pro-inflammatory cytokines (TNF-α, IL-1β, IL-6, and IL-12) were overexpressed in the MRH skin lesions and levels of TNF-α, IL-1β, IL-6, and IL-8 were also elevated. However, their expression levels in the serum were significantly increased after symptom relief by treatment[24]. Based on these theories, biological agents have been used for the treatment of MRH. The most commonly used biological agents are TNF-α antagonists (e.g., etanercept, adalimumab, and infliximab), IL-6 receptor antagonists (tocilizumab), and IL-1 receptor antagonists (anakinra)[25,26]. The effects of biological agents on the relief of skin and joint symptoms varied greatly among individuals. In addition, it is difficult to assess the superiority of one biological agent over another due to the low number of case reports. It has been reported that biological agents may be taken into consideration when first-line treatments are unable to achieve any effective disease control within 4–6 wk[27]. However, additional prospective investigations are required to standardize their application, including dosage, frequency, duration, and side effects.
Table 1 Comparison of multicentric reticulohistiocytosis and rheumatoid arthritis

<table>
<thead>
<tr>
<th></th>
<th>MRH</th>
<th>RA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joint involvement</td>
<td>Hand joint, knee joint, the shoulder, elbow, hip, ankle, and metatarsophalangeal joint</td>
<td>Double hand joint, wrist joint, foot joint, etc.</td>
</tr>
<tr>
<td></td>
<td>The distal interphalangeal joints involvement is frequent</td>
<td>The distal interphalangeal joints involvement is rare</td>
</tr>
<tr>
<td>Rate of joint destruction</td>
<td>Rapid</td>
<td>Slow</td>
</tr>
<tr>
<td>Radiologic characteristics</td>
<td>Enlargement of joint cavity</td>
<td>Periarticular osteopenia</td>
</tr>
<tr>
<td></td>
<td>Loss of articular cartilage and resorption of subchondral bone; no bone loss and abnormal new bone formation</td>
<td>Narrowing of the joint space, and bone erosion</td>
</tr>
</tbody>
</table>

MRH: Multicentric reticulohistiocytosis; RA: Rheumatoid arthritis; DIP: Distal interphalangeal; PIP: Proximal interphalangeal joint; MCP: Metacarpophalangeal joints.

Table 2 Comparison of multicentric reticulohistiocytosis and dermatomyositis

<table>
<thead>
<tr>
<th></th>
<th>DM</th>
<th>MRH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amyasthenia</td>
<td>More than 90% showed a symmetrical proximal muscle weakness</td>
<td>Rare</td>
</tr>
<tr>
<td>Increased myoenzyme</td>
<td>Almost all patients with DM (except CADM) have at least one myoenzyme level at some point in the disease course</td>
<td>Rare</td>
</tr>
<tr>
<td>Skin manifestations</td>
<td>Gottron papules and heliotrope rash are the definitive features of DM; Gottron signs, erythema along the light site, heterochromia, nail fold changes, scalp involvement, and skin calcification are also typical manifestations of DM</td>
<td>The manifestations of skin lesions include popular nodules and macules. Skin lesions are primarily distributed on the face, scalp, behind the ears, neck, anterior chest, back, waist, and abdomen, arms, hands, and thigh</td>
</tr>
<tr>
<td>Skin biopsy</td>
<td>The sporadic or focal infiltration of lymphocytes, plasma cells, and histiocytes</td>
<td>A large number of histiocytes and multinucleated giant cells with an eosinophilic cytoplasm and hairy glass-like changes</td>
</tr>
</tbody>
</table>

MRH: Multicentric reticulohistiocytosis; DM: Dermatomyositis; CADM: Clinically amyopathic dermatomyositis.

CONCLUSION

MRH is a rare non-Langerhans histiocytosis of unknown etiology with the characteristic clinical features of papulonodular skin lesions and progressive, destructive arthritis. MRH can also co-exist or be confused with a variety of systemic autoimmune diseases. Moreover, MRH may also be associated with various types of malignancies. Laboratory tests are not specific and the diagnosis is primarily based on skin or synovial tissue biopsies. Histopathological analyses revealed a large number of histiocytes and multinucleated giant cells with an eosinophilic cytoplasm and hairy glass-like changes. The immunohistochemical analysis indicates that the samples were positive for the macrophage marker, CD68, but negative for the Langerhans cell tissue markers, S-100, CD1a, as well as B cell markers CD19 and CD20. Most initial treatment for MRH consists of a combined regimen of glucocorticoids and immunosuppressants. Recently, while biological agents have been gradually used to treat MRH, an evaluation of the long-term efficacy and safety requires further evaluation. This case is representative of MRH and we also summarized the characteristics of MRH (Table 3) compared to common differential diagnoses (e.g., rheumatoid arthritis and dermatomyositis). We hope that our work will help clinicians better identify and treat this disease in the absence of epidemiological studies or randomized controlled data. The incidence of MRH is higher in Europe than in Asia according to existing reports; however, no significant differences have been found regarding clinical features, and prognosis between the two regions. Therefore, we will continue to pay attention to this disease in the future.
# Table 3 The clinical characteristics of multicentric reticulohistiocytosis

<table>
<thead>
<tr>
<th>Clinical manifestation</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Skin lesions</strong></td>
<td>The skin is the most frequently involved site of MRH. Skin lesions may be the first symptom and are primarily distributed on the face, scalp, behind the ears, neck, anterior chest, back, waist, and abdomen, arms, hands, and thigh. The manifestations of skin lesions include popular nodules, and macules. MRH can also involve mucous membranes (e.g., oral mucosa, gingival mucosa, and laryngeal mucosa).</td>
</tr>
<tr>
<td><strong>MRH-associated arthritis</strong></td>
<td>Arthritis can appear as the first symptom of MRH and also can occur simultaneously with skin lesions. MRH-associated arthritis can be characterized as diffuse, symmetric, progressive, and destructive. MRH is most commonly involved in the hand joints, especially the distal interphalangeal joint, followed by the knee joint, the shoulder, elbow, hip, ankle, and metatarsophalangeal joint. The affected joints exhibit swelling, pain, increase in skin temperature, joint effusion, and some patients can also experience morning stiffness.</td>
</tr>
<tr>
<td><strong>Other clinical manifestations</strong></td>
<td>Muscle involvement: Myalgia or decreased muscle strength; Electromyography (EMG) may exhibit myogenic lesions in some patients; Lung involvement: Dyspnea, pulmonary nodules, pleural effusion, or pulmonary interstitial fibrosis; Heart involvement: Pericardial effusion and myocarditis; Laryngeal involvement: Hoarseness, foreign body sensation in the larynx, or laryngeal abnormalities; Thyroid involvement: Hypothyroidism; Thrombosis has also been reported in patients with MRH. A small number of patients have extensive systemic involvement of the larynx, lungs, spleen, and plasma membranes at the same time. Systemic symptoms: Fatigue, fever, and weight loss.</td>
</tr>
<tr>
<td><strong>Laboratory tests</strong></td>
<td>Non-specific. Some patients may have increased leukocytes, decreased hemoglobin, accelerated sedimentation, and elevated lipids.</td>
</tr>
<tr>
<td><strong>Histopathology</strong></td>
<td>Histopathological manifestations: a large number of histiocytes and multinucleated giant cells with an eosinophilic cytoplasm and hairy glass-like changes.</td>
</tr>
<tr>
<td><strong>Immunohistochemistry</strong></td>
<td>Macrophage marker CD68 is positive; the Langerhans cell tissue markers S-100, CD1a, and B cell markers CD19 and CD20 are negative; CD45, CD43, Mac387, and lysozyme are positive to varying degrees.</td>
</tr>
<tr>
<td><strong>MRH-associated diseases</strong></td>
<td>Systemic autoimmune diseases: systemic lupus erythematosus, rheumatoid arthritis, Sjogren’s syndrome, dermatomyositis, hypothyroidism, diabetes, and tuberculosis.</td>
</tr>
<tr>
<td><strong>Malignancy</strong></td>
<td>Covering almost all solid tumors and hematologic malignant diseases.</td>
</tr>
<tr>
<td><strong>Differential diagnosis</strong></td>
<td>MRH is most easily confused with rheumatoid arthritis, dermatomyositis, and psoriatic arthritis.</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Initial treatment: Glucocorticoids combined with immunosuppressants regimens. Commonly used immunosuppressants include methotrexate, cyclophosphamide, hydroxychloroquine, and leukofluoride. Biological agents: TNF-α antagonists (e.g., etanercept, adalimumab, and infliximab), IL-6 receptor antagonists (tocilizumab), and IL-1 receptor antagonists (anakinra).</td>
</tr>
<tr>
<td><strong>Prognosis</strong></td>
<td>The prognosis of MRH patients varies greatly among individuals; It is related to treatment choice, response to drug therapy, and comorbidities.</td>
</tr>
</tbody>
</table>

**MRH**: Multicentric reticulohistiocytosis; **TNF-α**: Tumor necrosis factor-α; **IL**: Interleukin.

**FOOTNOTES**

**Author contributions**: Xu XL, Liang XH, and Liu J contributed to the conception of the study; Deng X participated in the pathological examination and analysis of the patients; Lu J performed the data analyses; Liang XH and Wang ZG helped perform the analysis with constructive discussions; Xu XL wrote the manuscript; all authors have read and approved the final manuscript.

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Xu XL et al. Multicentric reticulohistiocytosis


CASE REPORT

Brainstem abscesses caused by *Listeria monocytogenes*: A case report

Jie Wang, Yu-Chen Li, Ke-Yu Yang, Jing Wang, Zan Dong

**Abstract**

**BACKGROUND**

Intracranial Listeria infections are common in newborns and immunocompromised individuals, but brainstem abscesses are rare.

**CASE SUMMARY**

We report a rare case of brainstem abscesses caused by *Listeria monocytogenes* in a previously healthy adult patient. The patient’s magnetic resonance imaging examination showed multiple brain abscesses, and his second cerebrospinal fluid culture test indicated the presence of *Listeria monocytogenes*. Despite early empirical therapy, the patient’s condition progressively deteriorated. Because the patient’s abscesses were located in the brainstem and multiple lobes, surgery was not possible. The patient died 40 d after admission.

**CONCLUSION**

This case highlights the importance of rational clinical use of drugs to avoid potentially serious infectious complications.

**Key Words:** *Listeria monocytogenes*; Brainstem abscesses; Drug; Brain MRI; Therapy; Prognosis; Case report

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Core Tip: *Listeria monocytogenes*, an opportunistic pathogen, can be life-threatening when it infects the central nervous system (CNS). Herein, we report the case of a patient presenting with fever, headache, emesis, and perturbed consciousness. His condition rapidly deteriorated after empiric antibiotic therapy. He was finally diagnosed with *Listeria monocytogenes* infection after re-examination. Despite a timely change in his medication regimen, the patient died. This case highlights the importance of rational clinical antibiotic therapy to avoid potentially serious infectious complications. When empiric antibiotic therapy fails, and *Listeria* infection of the CNS is suspected, bacterial culture should be repeated for timely adjustment of antibiotics.

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DOI: https://dx.doi.org/10.12998/wjcc.v10.i22.7924

INTRODUCTION

*Listeria monocytogenes* is a Gram positive bacterium that can opportunistically cause listeriosis, including bacteremia and neurolisteriosis. Listeriosis is rarely seen in humans but has a high mortality rate of approximately 30%[1]. Patients diagnosed with neurolisteriosis develop meningitis and cerebral hemisphere inflammation, with a 20%–30% mortality[1]; brainstem encephalitis appears in 17% of patients, with a 51% mortality[1,2]. The percentage of cases with brain abscess is low (2%)[1], and those formed in the brainstem are more rare, with only a few case reports described. Despite clinically appropriate antibiotic therapy, the mortality rate remains high, owing to the difficulty in diagnosis, resistance to cephalosporin, and rapid progression of the disease. Early diagnosis and appropriate and adequate anti-microbial therapy are essential to decrease mortality and sequelae.

Here, we report the case of a patient whose cerebrospinal fluid (CSF) culture was positive for *Listeria* and who accepted positive anti-infective therapy. Multiple abscesses formed at the brainstem and both cerebral hemispheres rapidly during the course of treatment. The patient’s condition subsequently deteriorated, and he ultimately died. This case report aims to optimize the anti-infection treatment protocols for brainstem abscesses caused by *Listeria monocytogenes* and to provide a reference for rational drug administration by clinicians.

CASE PRESENTATION

Chief complaints
A history of fever and headache for 6 d, emesis for 1 d, and disturbance of consciousness for 4 h.

History of present illness
The patient began to experience headache and fever, and vomiting and disturbance of consciousness appeared later.

History of past illness
The patient was previously healthy.

Personal and family history
The patient had no personal and family history.

Physical examination
At the time of admission, the patient’s body temperature was 38 ℃; neurological examination showed confusion and irritability; his bilateral pupils were equally large and round and insensitive to light; the shallow sensation on the right limb was lower than that on the left limb; the Kernig sign was positive; and neck resistance was observed, at the submental three horizontal fingers. Both lungs produced an audible sputum sound, and the right external auditory canal had purulent secretion.

On the 14th day, the patient’s condition suddenly worsened and included drowsiness, left pupil dilation, a slow light response, and limited left and right abduction. On the 24th day, the patient was in shallow-moderate coma and left eyelid insufficiency. On the 39th day, his body temperature rose up to 41.3 ℃, and he develop vomiting, a rapid heart rate, and a decrease in blood oxygen saturation to approximately 70%.
Laboratory examinations
Lumbar puncture was performed that day, and the pressure exceeded 330 mmH2O. CSF cytology revealed a white blood cell (WBC) count of 2520/mm³, and the proportions were 68% neutrophilic granulocytes, 25% monocytes, and 7% lymphocytes. CSF biochemistry showed high protein (2875 mg/L), low glucose (1.34 mmol/L), and low chloride (100.9 mmol/L). No abnormalities were found in the CSF smear. The WBC count was 21.5 × 10⁹/L, the neutrophilic granulocyte percentage was 91.7%, and the original calcitonin was 3.28 ng/mL in the blood tests. Cultures of blood, CSF, and purulent secretions were examined simultaneously.

On the 7th day, a lumbar puncture reexamination showed a decrease in CSF WBC count (32/mm³), with 100% lymphocytes, but an increase in protein (3938 mg/L). Blood tests indicated a decrease in WBC count to the normal range. On the 14th day, CSF analysis revealed a WBC count of 401/mm³ (62% neutrophils, 14% monocytes, and 23% lymphocytes), glucose level of 4.37 mmol/L, chloride level of 114 mmol/L, and protein level of 1990 mg/L. The results of the second CSF culture test indicated the presence of *Listeria monocytogenes* (but repeated medical history did not include questions about the history of contaminated food intake), and drug susceptibility testing indicated sensitivity to teicoplanin, linezolid, erythromycin, and amikacin. A blood culture was negative, and sputum culture showed hydrocarbon-resistant *Acinetobacter baumannii*. On the 24th day, abnormal liver function, electrolyte disorder (low sodium, chloride, and calcium), and hypoproteinemia gradually appeared during the course of the disease. On the 27th day, the lumbar puncture was reexamined. The CSF WBC count was 30/mm³, with 100% lymphocytes, the glucose level was 3.91 mmol/L, the chloride level was 113 mmol/L, and the protein level was 1270 mg/L. CSF culture suggested methicillin-resistant staphylococcus, and sensitivity to teicoplanin and linezolid. On the 39th day, blood gas analysis suggested type I respiratory failure.

Imaging examinations
At admission, computed tomography (CT) of the head showed brain swelling, and CT of the chest suggested pulmonary infection. On the fifth day, a head CT reexamination showed no significant change, whereas a chest CT reexamination showed serious infection of the right lower lung, with clear consolidation. On the 14th day, head CT revealed a new oval slightly low-density shadow in the right frontal lobe. On the 15th day, head magnetic resonance imaging (MRI) examination was completed, and multiple abnormal signal shadows were found in the right basal ganglia region, lateral ventricle, bilateral frontal lobes, left craniocerebral foot, pons, right bridge-arm, left ventricle trigonometry, and bilateral parioicciptal-temporal sulcus (Figure 1). On the 27th day, head MRI showed multiple abnormal signal shadows in the right basal ganglia region, lateral ventricle, bilateral frontal lobe, left cranio-cerebral foot, thalamus, pons, medulla oblongata, and left temporal horn, which had become enlarged (Figure 2).

FINAL DIAGNOSIS
Brainstem abscesses caused by *Listeria monocytogenes*.

TREATMENT
On admission, the patient was treated with vancomycin (1 g, every 12 h) and ceftriaxone (2 g, every 12 h) to resist infection; mannitol and glycerol fructose to decrease the intracranial pressure; and other treatments for his symptoms. On the fifth day, treatment was adjusted to vancomycin (1 g, every 12 h) and cefoperazone and sulbactam sodium (3 g intravenous infusion once every 8 h). On the 15th day, the antibiotics were adjusted to a combination of teicoplanin, penicillin, cefoperazone, and sulbactam sodium.

OUTCOME AND FOLLOW-UP
On the 40th day and, the patient died outside the hospital.

DISCUSSION
Listeria are food-borne bacteria whose food sources in China are mainly meat and poultry products. In addition, dairy products are possible sources [3]. *Listeria* can adapt to harsh environments, such as high salinity, low temperature, and acidic or alkaline pH [4]. Because the incubation period varies widely,
Wang J et al. Brainstem abscesses caused by *Listeria monocytogenes*

Figure 1 The first magnetic resonance imaging of the patient. A, B, and C. The fluid-attenuated inversion recovery (A), diffusion-weighted imaging (B), and T2 sequence (C) of the brainstem and right frontal lobe of the patient revealed obvious abnormal signal shadows.

ranging from 3 to 70 d[5], identifying the source of infection is difficult in most patients. Despite repeated questioning, the history of intake of contaminated food intake by this patient was not obtained. Studies have suggested that *Listeria* can cross the blood-brain barrier, be transported by migratory immune cells, or be transmitted in a retrograde manner through nerves, such as the trigeminal and olfactory nerves[6-8]. Most patients with central nervous system (CNS) *Listeria* infection are the elderly, pregnant women, or those who have immunodeficiency, immunosuppression, diabetes, or cirrhosis[9]. However, patients with brainstem encephalitis are often healthy individuals, and this condition is believed to be associated with the typing of *Listeria* now[10]. Experimental studies have found that some subtypes of *Listeria* are neurotropic, and can cause brainstem encephalitis through food-borne transmission, and symptoms such as abnormal gait and balance or dyskinesia in mice, despite being negative in the blood. Other strains can enter the brain only if the high levels are present in the blood, and most cause meningoencephalitis not involving the brainstem[10]. According to previous studies, the pathogen affecting our patient may have been the neurotropic *Listeria* subtype, but this possibility has not been confirmed. Patients with central *Listeria* infection may have symptoms of systemic infection, such as fever, headache, vomiting, and diarrhea, as well as symptoms of nervous system damage or irritation, such as disturbance of consciousness, epilepsy, aphasia, hemiplegia, cranial nerve palsy, ataxia, or dysarthria[11]. Most patients are in critical condition after admission, and approximately 33% require endotracheal intubation; 19% develop multiple organ failure after a long hospitalization (15-33 d); approximately 44% have neurological sequelae; and 30% die within 3 mo after diagnosis[1]. Our patient showed signs of improvement several times during hospitalization but was unable to survive. This outcome was considered to be associated with an enlarged brainstem abscess. Patients with CNS *Listeria* infection often present with mild abnormalities in the CSF and are diagnosed on the basis of the detection of *Listeria* in the CSF, or unexplained neurological symptoms together with the detection of *Listeria* in the blood (other pathogens are negative)[1]. Previous diagnosis has mainly relied on culture of CSF and blood or PCR techniques. In recent years, large-scale clinical investigations have shown that the positive rate in blood culture is 63%, the positive rate in direct detection of CSF is 32%, the positive rate in culture is 84%, and the positive rate in PCR detection of CSF is 62.5%[1]. In patients with brain abscesses, the positive rate in CSF culture is even lower. A retrospective study has reported that although blood cultures from patients with *Listeria* brain abscesses were higher (28 out of 33 (86%)), only 11 (38%) of 29 patients with CSF reports were positive[12], thus hindering early diagnosis of patients with *Listeria* brain abscesses. In recent years, second-generation sequencing has been able to
detect pathogens in the CSF of culture-negative patients with CNS Listeria infection, thus improving the diagnostic efficiency\[13,14]\.

In our case, the initial CSF assay hinted at a significantly high WBC count, high protein, and low sugar and chlorine. The first cultures of the blood and CSF were negative, and the results of the second CSF culture suggested Listeria positivity after the patient’s condition had worsened. Antibiotics were adjusted according to the results of drug susceptibility testing, and our patient’s condition improved and then worsened, and eventually died. Our case suggested that, although Listeria infection of the CNS is rare, the CSF and blood cultures should be tested early and even repeatedly if the first results are negative but the patient’s condition fluctuates. If necessary, second generation sequencing can be used to improve the early pathogen detection rate to enable timely treatment and improve the prognosis. Regarding imaging, MRI is better than CT for observing lesions. Previous studies have reported that most patients with Listeria brain abscesses have a single abscess lesion, but 22% have more than one. MRI showed that most multiple abscesses were located in one hemisphere and distributed along the white matter fiber bundles, thus supporting the hypothesis that Listeria is transduced along the nerve axons\[15]\.

In our case, head CT was performed many times in the anterior region over 12 d but did not hint at an abscess lesion. Because of the patient’s poor condition (mechanical assistance) in early stages, head MRI was unable to be completed. The CT showed a new large frontal lobe abscess on the 14th day after the patient’s condition worsened, and the head MRI on the 15th day showed not only the frontal lobe abscess detected 1 d before but also several new abscess lesions in both the cerebral hemisphere and brainstem. All abscesses had increased in size according to the follow-up MRI. We suggest that intracranial Listeria infection progresses rapidly, and head MRI examination is important in early stages if conditions permit. Large-scale clinical studies have suggested that amoxicillin combined with gentamicin is the first-line drug for Listeria infection\[1\]. In addition, studies have shown that penicillin, ampicillin, linezolid, and other antibiotics are effective in intracranial Listeria infection\[1,16,17]\.

Notably, Listeria is sensitive to many common antibiotics but resistant to cephalosporins\[17]\.

Because of the difficulty of diagnosis, up to 90% of patients are treated empirically with cephalosporins because the pathogen is not detected. In addition to drug therapy, surgical procedures such as abscess puncture, drainage, and excision have been reported for the treatment of Listeria brain abscesses in patients who have not responded to antibiotic therapy\[12]\.

In our case, there was no intracranial lesion in the initial stage, and no positive results were found in the culture of CSF and blood. Only vancomycin and third generation cephalosporin were used empirically. Later, according to the results of the culture of CSF and drug sensitivity testing, the antibiotics were replaced with teicoplanin and penicillin, but the patient nonetheless died. Because the patient's abscesses were...
located in the brainstem and multiple lobes, surgery was extremely risky, and a surgical approach was not possible. In retrospect, the patient’s condition fluctuated after early empirical anti-infective therapy, and the number of CSF cells decreased significantly in the initial stage. However, the abscesses continued to expand, and the patient experienced recurrence and eventually died. Analysis of the reasons for this outcome led us to the following conclusions. First, because of the lack of awareness of CNS Listeria infection, targeted antibiotics such as penicillin and gentamicin were not used early in the treatment course. Second, Listeria infection is a dangerous disease; and the patient's condition was exacerbated by brainstem abscess, and the patient eventually died.

CONCLUSION

In summary, we describe a rare case of multiple abscesses in the brainstem and cerebral hemispheres after Listeria infection. Our findings suggest that intracranial infection with Listeria may improve during the course of disease, but the disease is nonetheless dangerous. Although the disease is more common in immunocompromised patients, CNS Listeria infections should be considered in previously healthy patients with intracranial infection. In terms of treatment, antibiotics should be given as early and sufficiently as possible, and should be adjusted in a timely manner according to the results of CSF culture and second-generation sequencing. In addition, repeated searching for pathogens and reexamination of head images are necessary to track changes in patients. Because of the non-specific CSF/blood findings and low positivity rate of cultures, early diagnosis of Listeria infections remains a clinical challenge. Large-scale clinical studies to identify prognostic factors and the efficacy of empiric and definitive antibiotic treatments are also important.

FOOTNOTES

Author contributions: Dong Z and Wang J contributed to conceptualization and data collection; Yang KY reviewed the literature and contributed to manuscript drafting; Wang J and Li YC performed data interpretation; Wang J was responsible for the revision of the manuscript for important intellectual content; all authors have read and approved the final manuscript.

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Brainstem abscesses caused by *Listeria monocytogenes*


Primary hypertension in a postoperative paraganglioma patient: A case report

Jian-Hui Wei, Hai-Li Yan

Abstract

BACKGROUND
Primary hypertension is a common clinical disease. Pheochromocytoma and paraganglioma is a rare cause of secondary hypertension. The diagnosis of the latter is still difficult, and the relationship between the two is not clear. The successful diagnosis of this case confirmed that standardized etiological investigation of secondary hypertension is necessary, contributes to the accurate diagnosis of rare diseases, and is conducive to the formulation or optimization of treatment plans. It shows an example of the coexistence of primary hypertension and secondary hypertension.

CASE SUMMARY
The patient was a 54-year-old male and was hospitalized with high blood pressure for 4 years. The patient’s blood pressure was measured at 150/100 mmHg during physical examination 4 years ago and had no paroxysmal or persistent elevated blood pressure, no typical triad of headache, palpitation, and sweating, without postural hypotension. After taking nifedipine sustained release tablets intermittently, the blood pressure did not meet the standard. Physical examination revealed blood pressure of 180/120 mmHg. There was no abnormality in cardiopulmonary and abdominal examination. The results of blood and/or urinary catecholamines/metanephrine and normetanephrine before and after operation were normal. Fundus examination revealed retinal arteriosclerosis in both eyes. There was a history of paraganglioma diagnosed by pathology after retroperitoneal tumor resection, a family history of hypertension, and a history of passive smoking. The clinical diagnosis was subclinical paraganglioma, primary hypertension, and hypertensive fundus lesions. The patient’s blood pressure was regulated, blood lipid was reduced, and anti-inflammatory, and symptomatic support were given. After treatment, the blood pressure was stable and up to standard without discomfort symptoms.

CONCLUSION
Subclinical paraganglioma and primary hypertension can coexist. The holistic thinking in clinical practice is helpful to the early diagnosis of rare diseases.

**Key Words:** Paraganglioma; Primary hypertension; Secondary hypertension; Diagnosis and Differential diagnosis; Genetic; Case report

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**Core Tip:** Pheochromocytoma and paraganglioma (PPGL) is a rare cause of secondary hypertension, and early and accurate diagnosis is still facing challenges. A case of subclinical paraganglioma (PGL) complicated with essential hypertension was analyzed retrospectively. A typical and subclinical pheochromocytoma and PGL should be paid more attention due to the lack of clinical features. At the same time, standardized etiological investigation of secondary hypertension is also an indispensable part of an accurate diagnosis. Clinical practice has proven that subclinical PGL and essential hypertension are two independent diseases that can coexist. After reviewing the literature, it is considered that genetic susceptibility is the same pathogenic factor.

**INTRODUCTION**

Paraganglioma (PGL) is a rare cause of secondary hypertension that is manifested as a hypertensive crisis and easily leads to target organ damage. The reported prevalence of pheochromocytoma and paraganglioma (PPGL) is 0.2%–0.6% [1], with an incidence closely related to a germline gene mutation [2]. Surgery is the first option after diagnosis, resulting in a generally normal postoperative blood pressure. In this study, we present our findings on a confirmed case of combined postoperative PGL and primary hypertension.

**CASE PRESENTATION**

**Chief complaints**

A 54-year-old male had high blood pressure for 5 mo.

**History of present illness**

The patient’s blood pressure was 186/100 mmHg at a physical examination 5 mo ago without discomfort. However, taking a 20 mg nifedipine sustained-release tablet once daily did not normalize his blood pressure. He had stopped the medication 3 mo prior to the time of admission. Since the disease onset, he had maintained a good diet and slept without snoring.

**History of past illness**

He had a history of PGL resection (Figure 1) and postoperative pathological diagnosis of PGL (Figure 2).

**Personal and family history**

He had a history of passive smoking, and family history of hypertension, but no PPGL.

**Physical examination**

The physical examination at admission revealed a body temperature of 36.4 °C, pulse of 86 beats/min, breathing of 18 breaths/min, blood pressure of 188/108 mmHg, waist circumference of 96 cm, body mass index of 27.8 kg/m², clear mind, good spirit, and no murmur in neck and umbilical blood vessels. No abnormality was detected in the heart, lungs, and abdomen. No edema was found in both lower limbs, and positive nervous system signs were observed.

**Laboratory examinations**

Laboratory examinations revealed normal macrobiochemical parameters, thyroid function, parathyroid
Figure 1 Computed tomography scan of paraganglioma. Performed on September 1, 2016: 64-slice computed tomography plain scan + enhanced scan (arrow). A mass of approximately 84 mm × 61 mm (right and left × back and forth) was observed below the left renal artery and vein, the abdominal aorta, the left psoas major muscle and the front of the left kidney. The edge was smooth, with an uneven density. The plain scan computed tomography value was within 17–41 HU. The arrow indicates the location, shape and size of the mass.

Figure 2 Histopathological features of paraganglioma. The tumor represents characteristic nest-like structure (arrow, hematoxylin and eosin × 40). The physician who completed the pathological diagnosis was the chief physician, who had been engaged in pathological diagnosis for 31 years. The arrow refers to the typical pathological feature of paraganglioma - nest-like structure.

hormone levels, cortisol and adrenocorticotropic hormone levels, and rhythm as well as normal prolactin, antinuclear antibody spectrum, and 24-h urine protein levels. Blood aldosterone and renin were determined by chemiluminescence measurements (11.31). Metanephrine was 31.9 ng/L (reference range < 96.60 ng/L), detected by liquid chromatography-tandem mass spectrometry. Normetanephrine was 68.9 ng/L (reference range < 163.00 ng/L).

Imaging examinations
Adrenal and renal artery computed tomography: Bilateral adrenal hyperplasia and right renal artery stenosis. Brain magnetic resonance imaging and chest, abdomen, and pelvic computed tomography were normal.

FINAL DIAGNOSIS
(1) Postoperative PGL; and (2) Primary hypertension with hypertensive retinopathy stage 2.
TREATMENT
Felodipine sustained-release tablet of 5 mg was administered once daily combined with olmesartan/hydrochlorothiazide tablet of 20 mg/12.5 mg once daily.

OUTCOME AND FOLLOW-UP
The patient had no symptoms. At the last follow-up examination on April 23, 2021, the blood pressure was normal and stable.

DISCUSSION
Hypertension was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic pressure ≥ 90 mmHg measured three times on a different day in the absence of antihypertensive medications. Secondary hypertension refers to hypertension caused by certain diseases or causes, accounting for about 5% of all hypertension, is characterized by endocrine dysfunction, such as primary aldosteronism and PPGL[3]. PGL patients, accounting for 15%–20% of all PPGL cases, have normal blood pressure without symptoms. They are distributed in the abdomen, chest, pelvic, neck, and brain tissue, especially in the retroperitoneum. A malignant tendency of PGL development has been reported, with a malignant transformation rate of 24%–50%[4]. No typical clinical manifestation of PPGL was observed in the present case.

The blood metanephrine was normal, and only the abdominal computed tomography revealed a left retroperitoneal mass. Importantly, postoperative pathological diagnosis of PGL should be differentiated from adrenocortical eosinophilic and low-grade neuroendocrine tumors[5]. The main difference among the three tumors is the intensity of the neuroendocrine markers; hence, we considered it was nonfunctional subclinical PGL, which was consistent with the results of previous studies[6,7]. PGL is curable secondary hypertension in which resection is to be performed after the diagnosis, which results in achieving normal postoperative blood pressure. This case completely differed from PPGL, with symptoms and positive examination results. It had high concealment, with no PPGL triad of headache, palpitation, sweating, and hypertension, and the specific marker of blood metanephrine was normal. The increase in the blood pressure occurred 3 years after the PGL operation.

Differential diagnosis and screening of PGL metastasis were performed based on the specific medical history, clinical manifestations, etiology of secondary hypertension, distribution of PGL, and the site of metastasis. Renal parenchymal hypertension, renovascular hypertension, primary aldosteronism, sleep apnea hypopnea syndrome, hypercortisolism, pituitary tumors, thyroid and parathyroid dysfunction, pharmacogenic hypertension, and connective tissue disorders, such as vasculitis and systemic sclerosis, were excluded[8,9]. No recurrence or metastasis was observed in PGL, and the diagnosis of primary hypertension was clear.

Meanwhile, because of the lack of family history of hypertension, middle age, short course of disease, mild target organ damage, and PGL history, this case was different from the commonly known primary hypertension. High blood pressure occurred after the PGL operation. The diagnosis of the combination of postoperative PGL and primary hypertension was confirmed by recurrence and metastasis screening. After reviewing the literature[9], the diagnosis of postoperative PGL was clear albeit rare in clinical practice. No related report was available of subclinical postoperative PGL and primary hypertension, and thus we had to make the differential diagnosis. This case has deepened the clinician’s understanding that primary hypertension and secondary hypertension can coexist. In the era of precision medicine, holistic thinking is helpful to the diagnosis and treatment of diseases.

CONCLUSION
Despite its rare occurrence, postoperative PGL patients can develop primary hypertension. The screening, diagnosis, and differential diagnosis of PPGL should be performed in cases with adrenal incidentaloma, retroperitoneal mass, or carotid body tumor. Pathological diagnosis is the gold standard for PPGL diagnosis.

FOOTNOTES
Author contributions: Wei JH conceived the idea, designed the experiments, and interpreted the data; Wei JH and Yan HL performed the experiments, analyzed the data, and wrote the manuscript; all authors reviewed and approved the manuscript.
Wei JH et al. Primary hypertension in postoperative paraganglioma patient

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Long-term survival of gastric mixed neuroendocrine-non-neuroendocrine neoplasm: Two case reports

Lun-Tao Woo, Yong-Feng Ding, Chen-Yu Mao, Jiong Qian, Xiu-Ming Zhang, Nong Xu

Abstract

BACKGROUND
Gastric mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN), which consists of neuroendocrine and non-neuroendocrine components, is quite rare. Until now, most data on gastric MiNEN come from clinical cases, without large-scale retrospective studies or controlled clinical trials. Consequently, no consensus regarding the origin, molecular characteristics, or appropriate treatment of MiNEN has been reached so far. We conducted chemotherapy of irinotecan plus cisplatin (IP regimen) and surgery in two patients with gastric MiNEN, which had never been used in treating this kind of tumor, leading to their long-term survival for more than 3 and 7 years, respectively.

CASE SUMMARY
We present two patients (one male and one female) with gastric MiNEN, with the primary manifestation of recurrent upper abdominal pain. After they were referred to our hospital, a diagnosis of gastric MiNEN was defined with the help of CT scan, and histopathological and immunohistochemical examinations on the samples of gastrointestinal endoscopy or radical surgery. The male patient (case 1) were found to have metastases in the reginal lymph nodes and the left liver. He received four cycles of IP regimens first, then the gastrectomy and partial left liver resection, followed by additional two cycles of IP chemotherapy. The female patient (case 2) underwent a laparoscopic gastrectomy, and received six cycles of IP regimen. She was found to have metastatic lesions in the right lung 2 years after that, and underwent video-assisted thoracoscopic surgery (VATS) of the lower lobe of the right lung. The two patients have now survived for more than 3 years and 7 years, respectively, without any evidence of recurrence or metastases.

CONCLUSION
IP regimen, combined with curative-intent surgery if feasible, could be considered as the priority in the choice of front-line chemotherapy for gastric MiNEN.
Key Words: Gastric; Irinotecan plus cisplatin; Long-term survival; Mixed neuroendocrine-non-neuroendocrine neoplasm; Case report

Core Tip: Mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN) is a rare, highly aggressive tumor with a poor prognosis (median overall survival less than 12 mo), and no consensus regarding the appropriate treatment has been reached so far. We conducted chemotherapy of irinotecan plus cisplatin regimen and surgery in two patients with gastric MiNEN, which had not been used to treat this kind of tumor before, leading to their long-term survival for more than 3 and 7 years, respectively. Our reports may provide a reference for other clinicians.

INTRODUCTION
Gastric mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN), which consists of neuroendocrine and non-neuroendocrine components, is quite rare, accounting for about 7% of all gastric neuroendocrine neoplasms and 25% of all gastric poor differentiated neuroendocrine carcinomas, but their prevalence has not been explored specifically so far[1]. Gastrointestinal tumor with an exocrine and a neuroendocrine component was first described by Cordier in 1924[2]. Many different names had been used since then, causing confusion among clinicians, surgeons, and pathologists, such as composite carcinoid, mucin-producing carcinoid argentaffin cell adenocarcinoma, mixed exocrine-endocrine tumors, mixed adenoneuroendocrine carcinomas, and so on[3]. In the 2019 WHO Classification of Tumors of the Digestive System, the term MiNEN has been used when referring to this kind of tumor[4]. Until now, most data on gastric MiNEN come from clinical cases[5-8], without large-scale retrospective studies or controlled clinical trials. Consequently, no consensus regarding the origin, molecular characteristics, or appropriate treatment of MiNEN has been reached so far.

Due to the lack of knowledge of gastric MiNEN, this tumor has a quite poor prognosis, presenting with a short median survival of less than 12 mo[5,9]. The preferred treatment for high-grade MiNENs is currently suggested to be combining etoposide and a platinum salt (EP regimen) or the combinations of 5-fluorouracil and irinotecan or temozolomide or amrubicin[1]. However, we conducted chemotherapy of irinotecan plus cisplatin (IP regimen) and surgery in two patients with gastric MiNEN, leading to their long-term survival for more than 3 and 7 years, respectively. Here, we present the process of diagnosis and treatment and a brief review of the literature to improve our understanding of the tumor.

CASE PRESENTATION
Chief complaints
Case 1: A 63-year-old man was admitted to the hospital because of frequent upper abdominal pain for over 1 mo.

Case 2: A 54-year-old female patient was admitted to the hospital with recurrent epigastric pain for more than 7 years.

History of present illness
Case 1: The patient felt frequent upper abdominal pain for over 1 mo, so he underwent upper gastrointestinal endoscopy and magnetic resonance imaging at a local hospital. Then he was diagnosed as having gastric MiNEN with metastases in the regional lymph nodes and the left liver. He came to our hospital soon after, and was admitted because of “gastric cancer”.

Case 2: The patient had recurrent epigastric pain for 7 years, and the pain got worse on an empty stomach. She took omeprazole herself without obvious relief. Then she underwent upper gastrointestinal endoscopy at a local hospital and was diagnosed as having gastric cancer. So the patient came to our hospital for surgery and was admitted because of “gastric cancer”.
History of past illness
Case 1: This patient had a history of hypertension for more than 10 years and herniorrhaphy surgery 5 years ago.

Case 2: The patient was diagnosed with chronic nasosinusitis, thyroiditis, cholecystolithiasis, hepatic cyst, and hepatic haemangioma.

Personal and family history
Case 1: The patient's father was dead, and his mother was healthy.

Case 2: The patient's father was dead; her mother and little brother were alive.

Physical examination
Case 1: The physical examination revealed the following: Temperature: 36.5 °C; pulse: 86/min; respiration rate: 14/min; blood pressure: 122/82mmHg. In the upper gastrointestinal endoscopy, no enlarged superficial lymph nodes, no abdominal wall varicosis, and no gastrointestinal peristalsis (Figure 1A).

Case 2: The physical examination revealed the following: Temperature: 37.1 °C; pulse: 80/min; respiration rate: 16/min; blood pressure: 118/76mmHg. Upper gastrointestinal endoscopy confirmed the gastric cancer (Figure 1B).

Laboratory examinations
Case 1: Laboratory examinations revealed the following: Red blood cell count (RBC) 4.2 × 10^12/L; hemoglobin (Hb) 110 g/L; white blood cell count (WBC) 6.8 × 10^9/L; platelet count (PLT) 126 × 10^9/L. The pathological examination and immunohistochemistry (IHC) confirmed the gastric MiNEN and the tumor was composed of two different components. The adenocarcinoma component was positive for cytokeratin 18 (CK18), and the neuroendocrine carcinoma component was positive for chromogranin A (CgA) and synaptophysin (Syn) (Ki67 index 80%) (Figure 2A1-A5). A high mitotic activity was seen (> 20 mitoses/10 high power fields [HPFs]).

Case 2: Laboratory examinations revealed the following: RBC 3.8 × 10^12/L; Hb 102g/L; WBC 8.4 × 10^9/L; PLT 208 × 10^9/L. The histopathological examination revealed tumor infiltration into the subserosal layer, with 11 regional lymph node metastases (pT4aN3aM0 stage). The tumor was composed of two different components, of which the adenocarcinoma component (positive for CKpan and CK18) accounted for 20% and neuroendocrine carcinoma component (positive for CKpan, CK18, CgA, and Syn; Ki67 index 60%) accounted for 80% (Figure 2C1-3). The mitotic activity was high (about 40 mitoses/10 HPFs).

Imaging examinations
Case 1: CT revealed the tumor infiltration into the omentum majus, with metastases to regional lymph nodes and the left liver (stage IV). Subsequently, the patient received four cycles of IP regimen as first-line chemotherapy. CT after the second and third cycles of chemotherapy revealed that the lesion in the left liver and regional nodes decreased markedly (Figure 3). Then, gastrectomy and partial left liver resection were performed and the histopathological examination confirmed that the neuroendocrine component of those lesions basically disappeared, only with adenocarcinoma component remaining in one regional lymph node (Figure 2B1 and B2). Metastases in the left liver totally disappeared (pT1aN1M0 stage). Two cycles of IP chemotherapy ensued after the operation.

Case 2: CT showed that the tumor infiltrated into the stomach wall and metastasized to regional lymph nodes.

FINAL DIAGNOSIS
Case 1: Gastric MiNEN (metastases to the left liver).

Case 2: Gastric MiNEN.

TREATMENT
Case 1: The patient received four cycles of IP regimen as first-line chemotherapy, then gastrectomy and partial left liver resection were performed.
Figure 1 Upper gastrointestinal endoscopy. A: There was a large mass in the greater curvature of the stomach with unclear borders, accompanied by ulcers (case 1); B: There was a pitted ulcer in the corner of the stomach, and the surrounding gastric mucosa was markedly congested and edematous (case 2).

Case 2: This patient underwent a total of six cycles of IP regimens without serious adverse effects.

OUTCOME AND FOLLOW-UP

Case 1: The patient has survived for more than 3 years without any evidence of recurrence or metastases.

Case 2: Two years after treatment, CT re-examination revealed metastatic lesions in the lower lobe of the right lung and video-assisted thoracoscopic surgery (VATS) was performed. Histopathological examination confirmed the neuroendocrine carcinoma (positive for CK7, CgA, and Syn; Ki67 index 30%) infiltration, with no metastases in regional lymph nodes. After the surgery, the patient did not undergo any further chemotherapy or radiotherapy and has survived for more than 7 years without any evidence of recurrence or metastases.

DISCUSSION

MiNEN is rare, especially in the stomach. To date, there is no consensus on the definition of MiNEN, especially the minimum proportion of each component. According to the WHO classification of digestive system tumors, MiNEN should contain both adenocarcinoma and neuroendocrine carcinoma components and each component is not less than 30%. However, this cutoff value has not been universally accepted, as it is defined arbitrarily rather than on proven clinical evidence and a minor (i.e., < 30%) poorly differentiated neuroendocrine carcinoma (PDNEC) component can impair prognosis[1,9,10]. Pham et al[5] once reported a case in which the adenocarcinoma component accounted for 10%-20% of the tumor, just as the case in our two patients. Park et al[11] found that a minor proportion (10%-30%) of PDNEC component would negatively influence the prognosis of patients with gastric MiNENs in a study including 88 patients. Consequently, the current 30% threshold, without sufficient prognostic value, may be not mandatory for defining MiNEN.

Most gastrointestinal MiNENs are highly aggressive, with a poor prognosis and median survival of less than 12 mo[5,9]. At present, the diagnosis mainly relies on pathological examination and IHC of surgical specimen[5,10]. CK, carcinoembryonic antigen, and caudal type homeobox 2 are used as markers for adenocarcinoma components, and Syn, CgA, and CD56 for neuroendocrine components[12]. In our two cases, the adenocarcinoma components were positive for CK18 or CKpan, and neuroendocrine component positive for CgA and Syn.

Until now, most studies suggest that surgical resection should be the main treatment for gastrointestinal MiNENs. Pham et al[5] argued that palliative surgery remains essential even if the patients have developed distant metastases. Our two patients underwent resection of the primary lesion and metastatic lesion, respectively, and both of them achieved long-term survival, being in good condition, without any evidence of recurrence to date. Therefore, we believe that curative-intent surgery if feasible, is crucial for the treatment of MiNEN, as recommended by other authors[12-14].
There is still no consensus regarding the standard front-line chemotherapy against MiNENs[5]. Platinum combined with etoposide (EP) regimen is found to be the most recommended first-line therapy for gastroenteropancreatic neuroendocrine carcinomas (GEPNECs)[5,15,16]. The preferred treatment for high-grade MiNENs is also suggested to be EP regimen or the combinations of 5-fluorouracil and irinotecan or temozolomide or amrubicin[1]. Yamaguchi et al.[17] compared IP regimen and EP regimen in treating GEPNECs, discovering that the IP group had a higher response rate (50% vs 28%, respectively; P = 0.001). When it comes to irinotecan and etoposide, there were some studies demonstrating a lower incidence of grade 4 adverse events and treatment-related deaths in the irinotecan group than in the etoposide group when treating digestive neuroendocrine carcinoma[15,17]. IP regimen is also better than irinotecan monotherapy when comparing progression-free survival and disease control rate[18]. Therefore, we thought that IP regimen could be used for our two patients. Surprisingly, both of them achieved long-time survival for more than 3 years and 7 years, respectively,
which are much longer than those in other studies\cite{5}. It may suggest that IP regimen could be considered as the priority in the choice of front-line chemotherapy for gastric MiNEN. To the best of our knowledge, we were the first to use IP regimen along with surgical resection for patients with gastric MiNENs.

To date, the effect of Ki67 proliferation index variation on prognosis remains unclear. Shi et al\cite{19} discovered that the Ki67 index would rise in 40% (n = 30) patients and decline in 13.3% patients with gastroenteropancreatic NEC during the treatment. In addition, Panzuto, Botling, and their colleagues\cite{20,21} found that the Ki67 index of patients tends to rise at time of disease progression, and median OS was significantly shorter in patients with rising Ki67 index (50.2 vs 115.1 m, hazard ratio = 3.89, 95% confidence interval [CI]: 1.91-7.94, \(P < 0.001\)). The Ki67 index of the patient in case 2 declined from 60% to 30% after IP regimen treatment, which was associated with a long-term survival. This, to some extent, may indicate that the decrease of Ki67 index is related to a better prognosis, which still needs further study.

At present, the most common genetic changes found in MiNENs include \(TP53\), \(KRAS\), \(BRAF\), \(APC\), \(PIK3CA\), \(MYC\), etc\cite{22-25}. We wonder if our two patients share some common genetic changes, which could be part of the reason for their long-term survival. Next-generation sequencing tests were performed on the surgical specimens of them, revealing that they were all proved to be microsatellite stable (MSS), and the tumor mutation burden (TMB) was 4.06 mut/Mb and 2.03 mut/Mb, respectively. \(TP53\) mutation was found in patient 1, and \(BRCA2\) mutation, along with copy number increase in nine genes (\(MET\), \(FGFR1\), \(FGFR4\), \(CDK4\), \(CDK6\), \(CDKN2A\), \(ERBB3\), \(RIT1\), and \(VEGFA\)) in patient 2. We may assume that MSS and TMB fewer than 10 mut/Mb could be associated with improved response to IP regimen from the tests result. It still needs further studies to explore which genetic changes may indicate a better prognosis in patients with MiNEN receiving IP regimen treatment.
CONCLUSION

Gastric MiNEN is a rare malignant tumor without specific clinical symptoms. Histopathological and immunohistochemical examinations are requisite for pathologists and physicians to make diagnosis. Palliative surgery remains essential even when patients have undergone distant metastases. In the choice of front-line chemotherapy, we believe that IP regimen could be considered as the priority. More prospective studies are urgently needed to explore better treatment options for patients with gastric MiNEN.

FOOTNOTES

Author contributions: Woo LT performed the bibliographic retrieval and wrote the paper; Ding YF contributed to the paper revision; Mao CY and Qian J provided the data and detailed information of the patients; Zhang XM performed the pathological examination and immunohistochemistry of the specimens; Xu N conceived the whole idea and contributed to the manuscript revision.

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Percutaneous transforaminal endoscopic decompression combined with percutaneous vertebroplasty in treatment of lumbar vertebral body metastases: A case report

Qiang Ran, Tong Li, Zhi-Ping Kuang, Xiao-Hong Guo

Abstract

BACKGROUND

Percutaneous endoscopic lumbar discectomy (PTED) is a procedure that is commonly used to treat lumbar disc herniation and spinal stenosis. Despite its less invasiveness, this surgery is rarely used to treat spinal metastases. Percutaneous vertebroplasty (PVP) has been utilized to treat lumbar vertebral body metastases but it has not proven useful in treating sciatic patients.

CASE SUMMARY

A 68-year-old woman presented with low back pain and radicular symptoms. She couldn't straighten her legs because of severe pain. Computed tomography (CT) showed a mass lesion in the lung and bone destruction in the L4 vertebrae. The biopsy of the lung lesion revealed adenocarcinoma and the biopsy for L4 vertebrae revealed metastatic adenocarcinoma. PTED paired with PVP was performed on the patient due to the patient's poor overall physical state and short survival time. Transcatheter arterial embolization of vertebral tumors was performed before surgical resection to reduce excessive blood loss during the operation. The incision was scaled up with the TESSY technology. The pain was obviously relieved following the operation and no serious complications occurred. Postoperative CT showed that the decompression around the nerve root was successful, polymethyl methacrylate filling was satisfactory and the tumor...
tissue around the nerve root was obviously removed. During the 1-year follow-up period, the patient was in a stable condition.

**CONCLUSION**
PTED in combination with PVP is an effective and safe treatment for Lumbar single-level Spinal Column metastases with radicular symptoms. Because of the small sample size and short follow-up time, the long-term clinical efficacy of this method needs to be further confirmed.

**Key Words:** Minimally invasive surgery; Nerve root; Percutaneous; Spinal metastases; Transforaminal endoscopic decompression; Case report

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**Core Tip:** Spinal metastatic tumor is a common clinical disease. Because of the poor general condition of patients, minimally invasive treatment is widely used. We present a case of metastatic adenocarcinoma in the L4 vertebrae treated with percutaneous endoscopic lumbar discectomy (PTED) combined with percutaneous vertebroplasty (PVP), with transcatheter arterial embolization of vertebral tumors performed before surgical resection. The therapeutic results were satisfactory. PTED combined with PVP is a safe and effective method for treating Lumbar single-level Spinal Column metastases with radicular symptoms.

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**INTRODUCTION**
As the number of cancer cases increases, the incidence of spinal metastases also increases year by year. Patients suffer from severe low back pain and lower extremity radiating pain due to metastases in the vertebral body[1,2]. Some patients with single vertebral metastases can be treated with open surgery in addition to total bed immobilization and symptomatic pain management. Percutaneous vertebroplasty (PVP) has been widely used in patients who suffer from pain without spinal cord compression and radicular symptoms[3-5]. Percutaneous Transforaminal Endoscopic Decompression (PTED) is rarely reported to be used in spinal metastatic disease. In this report, we introduced and described the surgical technique using PTED combined with PVP in lumbar vertebral body metastases[6,7].

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**CASE PRESENTATION**

**Chief complaints**
A 68-year-old woman with low back pain and radicular symptoms was unable to straighten her leg due to severe pain.

**History of present illness**
Low back pain and radicular symptoms first appeared 2 wk ago. The Lumbar computed tomography (CT) scan showed a mass lesion in the lung. Lumbar CT and magnetic resonance imaging (MRI) showed metastases in the lumbar vertebral body. The severe radicular symptom could not be relieved by painkillers. Furthermore, this patient could not receive an invasive surgery due to poor general conditions.

**History of past illness**
Previous medical history revealed no significant illnesses.

**Personal and family history**
Previous medical history revealed no significant illnesses.

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**Physical examination**
Low back tenderness, percussion pain and the straight leg raising test all yielded positive results.

**Laboratory examinations**
According to cell blood count results, the white blood cell count was increased \(10.8 \times 10^9/L\) and the hemoglobin level was 157 g/L.

**Imaging examinations**
Lumbar CT and MRI showed bone destruction in the L4 vertebrae. MRI revealed that the tumor had invaded the L4 vertebral body and was compressing the nerve root (Figure 1).

**Further diagnostic work-up**
Biopsy and histopathological examination of the L4 vertebrae revealed metastatic adenocarcinoma which probably originated from the lung (Figure 2).

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**FINAL DIAGNOSIS**
The diagnosis of the presented case was lung cancer with lumbar vertebrae metastasis.

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**TREATMENT**
Given the patient's poor general physical condition, a minimally invasive technique was chosen after a multidisciplinary medical staff discussion. The operation plan was PTED combined with PVP under local anesthesia. Transcatheter arterial embolization of vertebral tumors was performed before surgical resection in order to minimize excessive blood loss during the operation (Figure 3A). PVP and PTED were conducted prone on a radiolucent table under local anesthetic. PVP was conducted on both sides of the vertebral body using standard procedures. Because there was no cement leakage, it was confirmed that the patient's radicular symptoms did not worsen after the treatment. The point of entry was 8 cm from the midline. TESSY technology was used to scale up the incision and no obvious bleeding occurred. Endoscopy could observe pathologic fracture fragments and tumor tissue at the rear of the intervertebral space. The tumor invaded the posterior border of the L4 vertebrae and paravertebral tissue compressing the L4 nerve root. The tissues compressing the nerve root were removed carefully with endoscopic forceps and bleeding was coagulated by radiofrequency electrode (Figure 3B).

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**OUTCOME AND FOLLOW-UP**
We have completed sufficient decompression of the intervertebral foramen, partial resection of the vertebral body and pedicle of the vertebral arch and exposure of polymethyl methacrylate injected into the vertebral body (Figure 4). The patient's low back pain and radicular symptoms were clearly relieved after the operation. Postoperative CT showed that the decompression around the nerve root was successful. During the 1-year follow-up period, the patient was in a stable condition.

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**DISCUSSION**
The vertebral body is the most common site among bone metastases accounting for 5.00%-10.00% of patients with malignant tumors[8]. Spinal metastases often present as lesions, site pain and limited mobility[9]. Further progression to spinal canal metastases might result in myeloid or radicular symptoms in some patients. The current treatment options include radiotherapy, chemotherapy and surgery with radiotherapy being the first choice for the majority of patients with spinal metastases[8]. Most patients and their families are hesitant to accept traditional surgical treatment due to the short survival time. In recent years, with the development and maturity of minimally invasive techniques, PVP and PTED have been gradually applied in treating vertebral column metastases[10]. However, PVP is ineffective in treating sciatica patients and decompression of the compressed nerve root is required [11]. In order to remove the tumor thoroughly and reconstruct the stability of the column, total spinal resection should be performed under the condition of ensuring the safety of the spinal cord. In this case, these two procedures were operated alternately. The criterion of complete decompression was that the nerve root could move freely with the changes in irrigation pressure.
Palliative decompression, intralesional resection or marginal resection of the tumor are ineffective when the vertebral body, appendages or the entire column are involved. Compared with traditional open surgery, PTED has the following advantages: (1) The survival time for patients with metastatic tumors in the column is short and their general physical condition is poor. The combined minimally invasive technique is safe and effective so it is easy to be accepted by patients and their families; (2) The symptoms of nerve root compression can be relieved with less trauma, bleeding and operation time; (3)
It has a significant impact on vertebral body stability. The incidence of wound infection and complications (e.g., thrombus, infection caused by post-operative incapacitation) were reduced; and (4) This technique will not cause severe damage to the column’s normal bone and soft tissue structure while removing the tumor. The pain caused by internal fixation can be relieved.

Because the tumor invaded the nerve root, causing accumulated necrotic bone tissue and crucial adhesion in the nerve root, partial nerve root decompression occurred. Meanwhile, the nerve might be drawn at the same time, resulting in nerve root injury. Even a tiny amount of blood oozing might easily cause an unclear view in the surgical field due to the invaded tumor tissue. In this case, the nerve root could not be completely separated from the surrounding tissue and easily recognized. Because of the complicated anatomic structure and abundant blood supply, the tumors in the vertebral body are often accompanied by unclear views in the surgical field, difficulties in separating surrounding tissue, a large amount of bleeding and a long operation time. Before surgery, arterial embolization can drastically limit the tumor’s blood supply, reduce blood loss during the operation, allow for complete resection of the tumor, and increase the operation’s success rate. Recent research and advances in technique have reported that preoperative embolization is a safe and effective method of decreasing intraoperative blood loss[12]. However, the authors consider that this procedure is unsuitable for patients with multiple segmental metastases or tumor’s that are spinal canal space-occupying[13].

**CONCLUSION**

PTED combined with PVP is a safe and effective method for treating Lumbar single-level Spinal Column metastases with radicular symptoms. Because of the small sample size and short follow-up time, the long-term clinical efficacy of this method needs to be further confirmed.

**FOOTNOTES**

**Author contributions:** Ran Q conceived the central idea, analyzed clinical data and wrote the initial draft; All authors participated in clinical diagnosis and revised the manuscript.

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**Country/Territory of origin:** China
REFERENCES


Atypical imaging features of the primary spinal cord glioblastoma: A case report

Xin-Yu Liang, Yao-Ping Chen, Qiao Li, Ze-Wang Zhou

Abstract

BACKGROUND
Primary spinal cord (PSC) glioblastoma (GB) is an extremely rare but fatal primary tumor of the central nervous system and associated with a poor prognosis. While typical tumor imaging features are generally easy to recognize, glioblastoma multiforme can have a wide range of imaging findings. Atypical GB is often misdiagnosed, which usually delays the optimal time for treatment. In this article, we discuss a clinical case of pathologically confirmed PSC GB under the guise of benign tumor imaging findings, as well as the most recent literature pertaining to PSC GB.

CASE SUMMARY
A 70-year-old female complained of limb weakness lasting more than 20 d. Irregular masses were observed inside and outside the left foramina of the spinal canal at C7-T1 on medical imaging. Based on the imaging features, radiologists diagnosed the patient with schwannoma. Tumor resection was performed under general anesthesia. The final histopathological findings revealed a final diagnosis of PSC GB, world health organization Grade IV. The patient subsequently underwent a 4-wk course of radiotherapy (60 Gy in 20 fractions) combined with temozolomide chemotherapy. The patient was alive at the time of submission of this manuscript.

CONCLUSION
Atypical GB presented unusual imaging findings, which led to misdiagnosis. Therefore, a complete recognition of imaging signs may facilitate early accurate diagnosis.
INTRODUCTION

Glioblastoma (GB) is the most common malignancy of the nervous system. Primary spinal cord (PSC) GB is a fairly rare tumor, accounting for 1% to 5% of all GB and 1.5% of all spinal cord neoplasms[1]. Due to its rare occurrence, most reported studies are either case reports or focused on its treatment and prognosis. Apart from histopathological findings, a precise imaging diagnosis also plays an essential role in the prognosis of GB. Furthermore, as it presents a variety of imaging features, it is difficult to differentiate this tumor from ependymoma and astrocytoma as well as neurogenic neoplasms[2,3].

To the best of our knowledge, this is the first literature review to summarize the imaging findings of this rare disease. Due to a misdiagnosed case of pathologically confirmed PSC GB with atypical imaging features in our clinical practice (Figure 1), we reviewed and summarized the imaging and clinical features of PSC GB from 2011 to 2021. By aggregating these data, we intend to improve the diagnostic accuracy of PSC GB for radiologists and clinicians.

CASE PRESENTATION

Chief complaints
A 70-year-old female, with no history of previous illnesses, complained of limb weakness and an inability to walk lasting more than 20 d.

History of present illness
The patient reported feeling weak in her limbs, especially her left arm and leg. She described that, in the previous 2 wk, she had been unable to walk as before.

History of past illness
The patient had no chronic illnesses or history of surgery.

Personal and family history
The patient did not have any significant family history.

Physical examination
Physical examination revealed no deformity in the spine and limbs, with a normal cranial nerve sensation detected. However, there was decreased needling reflection below the bilateral nipples and a muscle strength score of Grade 0 in both lower limbs. Additionally, bilateral abdominal reflexes, anal sphincter reflex, bilateral knee tendon, and Achilles tendon reflexes were absent.

Imaging examination
In the cervical computed tomography and magnetic resonance imaging (MRI) scans (Figures 2 and 3), irregular masses were observed inside and outside of the left foramina of the spinal canal, at C7-T1.
Atypical imaging features lead to misdiagnosis

**CT and MRI**
- Decreased reflection and muscle strength

**Physiological exam**
- Limb muscle strength was Grade 0

**Symptoms**
- Limbs weakness and incontinence for 20 d

**Preoperative imaging diagnosis with schwannoma**
- Tumor growth across and beyond the spinal canal like a benign tumor

**Postoperative pathology**
- WHO Grade IV
- Primary spinal cord glioblastoma

**One week after surgery**
- CT and MRI

**Physical exam**
- Limb muscle strength was Grade II

**Symptoms**
- No relief in incontinence

**Follow-up**
- Still alive

### Figure 1 Timeline of this case report.
CT: Computed tomography; MRI: Magnetic resonance imaging; WHO: World Health Organization.

<table>
<thead>
<tr>
<th>Event</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previously healthy 70 year-old female</td>
<td>November 2019</td>
</tr>
<tr>
<td>Symptoms</td>
<td>November 2019</td>
</tr>
<tr>
<td>Physical exam</td>
<td>December 2019</td>
</tr>
<tr>
<td>CT and MRI</td>
<td>January 2020</td>
</tr>
<tr>
<td>One week after surgery</td>
<td>July 2020</td>
</tr>
<tr>
<td>Physical exam</td>
<td>November 2021</td>
</tr>
</tbody>
</table>

Margins between the medial part and the spinal cord were not clear, whereas the lateral margin was rough, and the foramina was enlarged, with a significantly heterogeneous enhancement.

**MULTIDISCIPLINARY EXPERT CONSULTATION**

According to the results of physical examinations and imaging features, the physicians and radiologists made an initial diagnosis of a benign tumor, like schwannoma. A section surgery was recommended.

**FINAL DIAGNOSIS**

Based on the imaging features, radiologists, and multidisciplinary expert conclusion, the final diagnosis was schwannoma.
Figure 2 Computed tomography images of lesions of the present case. A and B: The tumor was irregular in shape, growing across and beyond the left foramina; C: The left intervertebral foramina was enlarged with inhomogeneous enhancement; D: The lesion was intramedullary and indistinctly demarcated from the surrounding spinal cord.

Figure 3 Magnetic resonance images of the present case. A-C: The tumor was irregular in shape with a rough margin, and having slightly lower signal intensity on T1-weighted imaging and slightly higher signal intensity on T2-weighted imaging; D: The mass had heterogeneous enhancement.

TREATMENT
After the primary diagnosis, C7-T1 spinal canal tumor resection was performed under general anesthesia. During the procedure, the surgeons noticed edema from the C7-T1 spinal cord, with the residing tumor on the left side, which was obscuring the boundary of the spinal cord. The tumor crossed the foramina and was in proximity to the vertebral and internal carotid arteries and left lung tip. The C7 nerve root was observed passing through it, with a visible small amount of subarachnoid hemorrhage. After resection of the tumor (Figure 4A), histopathological findings revealed a primary spinal cord glioblastoma, World Health Organization (WHO) Grade IV (Figure 4B and C).

The patient underwent MRI re-examination 1 wk after surgery (Figure 5). She subsequently underwent a 4-wk course of radiotherapy (60 Gy in 20 fractions) combined with temozolomide chemotherapy.

OUTCOME AND FOLLOW-UP
For the next 6 mo, the patient’s upper limb muscle strength was Grade II, although lower limb muscle strength was Grade 0, with no relief in incontinence. However, the patient is still alive at this time (day of submission of this manuscript).

DISCUSSION
Significance
This is one of the rare cases of PSC GB that was characterized by tumor growth across and beyond the
Figure 4 Diagnosis of World Health Organization Grade IV primary spinal cord glioblastoma was made. A: Resected gross tissue; B and C: Histopathology imaging (magnification × 200). Pleomorphic astrocytic cells with marked nuclear atypia and brisk mitotic activity were observed along with necrosis and microvascular proliferation. Immunohistochemically, the cells were slightly positive for glial fibrillary acidic protein, p53, and vimentin and negative for S-100, isocitrate dehydrogenase, and H3K27M. The proliferation index (measured by Ki67) was found to be at 30%.

Figure 5 Magnetic resonance imaging re-examination 1 wk after tumor resection. A: Axial view; B: Coronal view; C: Sagittal view.

spinal canal, like a benign tumor, which led to the misdiagnosis of neurogenic tumors. To the best of our knowledge, an intramedullary glioma that extends beyond the spinal canal has not been reported before. Also, lesions reported previously were located in the spinal canal exclusively.

Literature review
For conducting the extensive literature review, articles were selected in PubMed and Google Scholar for the most recent 10 years (2011-2021) by using search terms of “spinal cord glioblastoma,” “spinal cord malignant glioma,” and “spinal cord malignant neoplasm.” The search resulted in 79 publications, which were carefully screened by two authors (Liang XY and Zhou ZW) based on the following criteria: (1) Patients with surgically and pathologically confirmed PSC GB; (2) Patients with whole clinical information and high-quality preoperative computed tomography/MR images; and (3) Only literature available in English language. However, publications were excluded from the study if they reported: (1) PSC GB with other malignant or benign tumors; (2) Patients with secondary spinal cord GB who had previously undergone low-grade glioma resection; or (3) Patients who had been diagnosed with primary cerebral GB secondary metastases. The publications were also examined for patient clinical details and reported department to rule out duplicates. After the screening, 8 studies (involving 11 patients) fulfilled our requirements and were included in the analysis. The clinical and imaging characteristics of these 11 lesions are listed in Table 1. The detailed screening flow chart is shown in Figure 6.

Imaging features
Generally, the typical imaging features of GB can be easily recognized by most radiologists. However, benign-looking masses, cystic lesions, multifocal/multicentric tumors, and spinal cord abnormalities may all represent features of GB[2]. Therefore, a precise preoperative neuroimaging diagnosis is much more difficult, owing to the high variability of PSC GB. MRI is widely used in early diagnosis and preoperative evaluation of PSC GBs as a non-destructive and high-qualified imaging modality[2,3]. Usually, PSC GBs appear as infiltrative and expansile intramedullary lesions, with T2 hyperintensity and T1 isointensity or hypointensity with different heterogeneous enhancement post-contrast on T1[2,3]. Both the location and shape of the tumor play significant roles in the radiological differential
Table 1  Review of the literature on primary spinal cord glioblastoma with qualified magnetic resonance images

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Ref.</th>
<th>Age/sex</th>
<th>Symptoms</th>
<th>Lesion location</th>
<th>Imaging findings</th>
<th>Surgery/therapy</th>
<th>Survival in month</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ferrante et al[3], 2021</td>
<td>34 yr/F</td>
<td>MW, SD</td>
<td>Nearly entire cervical spinal cord and medulla oblongata</td>
<td>Isointense to hypointense on T1WI, isointense to hyperintense on T2WI, homogeneous enhancement</td>
<td>None</td>
<td>NR</td>
</tr>
<tr>
<td>2</td>
<td>Shen et al[4], 2020</td>
<td>47 yr/M</td>
<td>MW, SD</td>
<td>Conus medullaris</td>
<td>Hyperintense on T2WI, peripheral enhancement, necrosis enhancing nodule</td>
<td>STR, radio/chemotherapy</td>
<td>33</td>
</tr>
<tr>
<td>3</td>
<td>Delgado et al[5], 2019</td>
<td>21 yr/F</td>
<td>MW, SD</td>
<td>Paresthesia, pain, MW, SD</td>
<td>Multifocal lesion (C5-C7) and (T3-T5), peripheral enhancement, necrotic center</td>
<td>Biopsy, radio/chemotherapy</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>Chanchotisatien et al[6], 2019</td>
<td>27 yr/F</td>
<td>MW, SD</td>
<td>Paresthesia, paralysis</td>
<td>T12 nodular, isointense to hyperintense on T2WI, central significant enhancement</td>
<td>Surgical resection, NR</td>
<td>NR</td>
</tr>
<tr>
<td>5</td>
<td>Caro-Osorio et al[7], 2018</td>
<td>48 yr/F</td>
<td>MW, SD</td>
<td>Hyperintense on T2WI, spinal cord expanding, heterogeneous enhancement</td>
<td>Hypointense on T1WI, hyperintense on T2WI, heterogeneous enhancement</td>
<td>STR, radio/chemotherapy</td>
<td>8</td>
</tr>
<tr>
<td>6</td>
<td>Shen et al[1], 2017</td>
<td>15 yr/F</td>
<td>MW, SD</td>
<td>Paraplegia, urinary incontinence, SD</td>
<td>Hyperintense on T2WI, inhomogeneous enhancement</td>
<td>NTR, radio/chemotherapy</td>
<td>13</td>
</tr>
<tr>
<td>7</td>
<td>Nunn et al[12], 2017</td>
<td>31 yr/M</td>
<td>MW, SD</td>
<td>T11-L1</td>
<td>Hyperintense on T2WI, spinal cord expanding, heterogeneous enhancement</td>
<td>Surgical resection, radio/chemotherapy</td>
<td>14</td>
</tr>
<tr>
<td>8</td>
<td>Prasad et al[13], 2012</td>
<td>15 yr/F</td>
<td>MW, SD</td>
<td>Paraplegia, urinary incontinence, SD</td>
<td>Enlargement of cord, heterogeneously enhancing</td>
<td>STR, radio/chemotherapy</td>
<td>6</td>
</tr>
<tr>
<td>9</td>
<td>Prasad et al[13], 2012</td>
<td>35 yr/M</td>
<td>MW, SD</td>
<td>C6-T7</td>
<td>Enlargement of cord, heterogeneously enhancing</td>
<td>NTR, radio/chemotherapy</td>
<td>15</td>
</tr>
</tbody>
</table>

F: Female; M: Male; MW: Motor weakness; NR: No relief; NTR: Near total resection; SD: Sensory disturbances; STR: Subtotal resection; WI: Weighted imaging.

diagnosis of intramedullary lesions.

In our case, the tumor was detected as a dumbbell mass, spanning the intramedullary and extramedullary region through the foramina. This disguised appearance led us to an erroneous diagnosis of the neurogenic tumor. However, in the reviewed publications, the tumor had an appearance of nodular[3,4], elongated lesions, growing along the spinal cord and confined to the intramedullary area[1,5-7].

The distinction of PSC GB from pathologies like myelitis or other types of intramedullary tumors, such as astrocytomas or ependymomas, are most difficult due to its nonspecific and often very similar
manifestations. The majority of ependymomas are often hyperintense on T2-weighted imaging with inhomogeneous enhancement after injection of gadolinium. Usually, ependymomas show high uptake of 18F-fluorodeoxyglucose, while myxopapillary ependymomas have low uptake of fluorodeoxyglucose [4]. Pilocytic astrocytomas often appear as a well-circumscribed mass with a highly enhanced T2 signal. Nonconventional MRI sequences, such as diffusion tensor images and dynamic susceptibility contrast perfusion weighted imaging, may provide more comprehensive information, which can be useful to differentiate and grade the lesion [8].

A normalized (referenced to brain region of interest) relative cerebral blood volume threshold of 1.75 has been used to predict GB progression. An increase in normalized relative cerebral blood volume (> 1.75) with a decrease in fractional anisotropy of the corresponding region of the tumor might suggest a high-grade glioma [8]. In our case, the tumor demonstrated atypical MRI and computed tomography appearances of PSC GB, although prior familiarity with these imaging features may help to differentiate from other intramedullary tumors.

Clinical characteristics
PSC GB is extremely rare, reported in about 1.5% of all the spinal cord tumors [3]. Due to its rare occurrence, few studies focus on it. Most of the published literature on PSC GB are case reports. Therefore, due to the lack of properly related literature, the clinical features, optimal therapy, and prognosis of PSC GB remain controversial [10]. This tumor is more prone to grow in the cervical or cervicothoracic region and is associated with severe disability and poor prognosis in most patients [11]. The early symptoms of these patients are usually weakness of unilateral or bilateral limbs [1, 3, 5], sensory-motor disorders, and incontinence [6, 12, 13]. However, when accompanied by metastasis of other parts, the symptoms are usually different.

To the best of our knowledge, the largest sample study involving 190 PSC GB patients was reported by Moinuddin et al [14]. They found that PSC GB had a higher incidence in the younger age group (age < 18). In contrast, our patient’s age (70 years old) contributes to the rarity of the present case. They also reported a better overall survival in the 18-year-old to 65-year-old group (13.2 mo) [14]. Previous studies have also suggested that genetic mutations may be a contributing factor for the onset of the disease. It has been observed that patients with constitutional mismatch repair deficiency are more prone to develop high-grade gliomas in the central nervous system [15].

Pathology diagnosis
Due to its diverse and heterogeneous nature, PSC GB is difficult to diagnose merely by imaging techniques. Most PSC GB are confirmed by histopathological parameters, including nuclear atypia, mitotic activity, vascular proliferation, and necrosis [16, 17], along with immunohistochemical parameters, such as glial fibrillary acidic protein and S-100 protein [100 (S-100) positivity with a high Ki-67 index [16-18].
The tissue section of our patient revealed many pleomorphic astrocytic cells with marked nuclear atypia and brisk mitotic activity, which was accompanied by necrosis and microvascular proliferation. The diagnosis of WHO Grade IV GB is mainly based on the routine histopathological findings[16]. Immunohistochemically, the cells were slightly positive for glial fibrillary acidic protein, p53, and vimentin but were negative for S-100, isocitrate dehydrogenase, and histone H3 lysine 27 methylation (H3K27M). The proliferation index (measured by Ki67) was about 30% in the resected tumor. High-grade glioma with isocitrate dehydrogenase gene mutation and positive for H3K27M is reported to have a significantly better prognosis[17,19,20]. However, H3K27M-positive PSC GBs are also at risk of developing local hemorrhage[18]. Before the submission of the current manuscript, our patient was still alive after surgery and radio-/chemotherapy. The survival of our patient might be attributed to an H3K27M mutation.

**Treatments and prognosis**

Although not implying causation, there is a trend towards improved overall survival with the use of chemotherapy and surgical resection for patients suffering from GB[21]. Despite the advancement in surgical techniques and postoperative adjuvant therapies, PSC GB still has an overall poor prognosis[9,21]. The overall survival in patients with PSC GB is approximately 10-14 mo[9]. The disease often leads to severe neurological deficits and poor quality of life, even after treatment.

In our case, the patient underwent surgical resection with subsequent radiotherapy and chemotherapy. Unfortunately, neither treatment alleviated or improved her symptoms nor improved her quality of life. According to a single-center retrospective study by Cheng et al[22], the extent of surgical resection did not have any significance, but radiotherapy accompanied with postoperative chemotherapy was the major prognostic factor for longer survival in adult GB patients. However, the previous study reported that gross-total resection followed by radiotherapy had beneficial effects on the overall outcome of PSC GB in the pediatric age group[23,24]. More effective and targeted therapies need specific investigation in the future for helping patients with unique gene mutations achieve better prognosis[25,26]. Further, broadening treatment avenues would help improve the efficacy of therapies and help in recovery for these patients.

**Limitations**

Due to the large mass in C7-T1, the conventional cervical MR field of view was not able to cover the whole lesion.

**CONCLUSION**

A definitive PSC GB diagnosis requires histopathological confirmation. However, complete recognition of the imaging signs of the disease may facilitate early accurate diagnosis.

**FOOTNOTES**

**Author contributions:** Liang XY contributed to literature retrieval and screening, data reduction, and drafting of the manuscript; Chen YP contributed to literature retrieval and screening, and data analysis; Li Q contributed to acquisition of data and images, and data analysis; Zhou ZW contributed to study design and revising the manuscript critically for important intellectual content.

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**Country/Territory of origin:** China
REFERENCES


Resection with limb salvage in an Asian male adolescent with Ewing’s sarcoma: A case report

Chien-Ying Lai, Kuan-Ju Chen, Tsung-Yu Ho, Ling-Yi Li, Chien-Chung Kuo, Hsien-Te Chen, Yi-Chin Fong

Abstract

BACKGROUND
Ewing’s sarcoma is a highly malignant primary bone tumor that commonly affects children. For young patients, multidisciplinary treatment and limb salvage are recommended, and surgical plans considering the growth potential and bone activity after tumor resection are essential.

CASE SUMMARY
An 11-year-old Asian boy had a 1-mo history of a right-sided limping gait. Imaging revealed a proximal tumor with bone destruction and physeal involvement over the right femoral neck. He was diagnosed with stage IV (T1N0M1aG3) Ewing’s sarcoma with bilateral lung metastases. Neoadjuvant chemotherapy decreased the tumor size and confined it to the metaphyseal region. The patient underwent four stages of surgery: wide tumor excision plus reconstruction with vascular fibular bone graft plus internal fixation; repeat open reduction and internal fixation; femoral lengthening with orthosis after physeal maturity; and orthosis removal and bone elongation (approximately 6 cm). Following surgery, he could walk without discomfort and had almost equal-sized bilateral femoral heads, indicating physis preservation. The surgery was successful, and normal femoral head growth was achieved after complete remission. The patient was able to resume normal activities with equal length of the bilateral lower limbs.

CONCLUSION
Tumor treatment and reconstruction following resection are important in
skeletally immature patients with Ewing’s sarcoma to improve quality of life.

**Key Words:** Ewing’s sarcoma; Lower limb discrepancy; Orthosis; Vascular fibular graft; Reconstruction; Case report

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**Core Tip:** Ewing’s sarcoma is an uncommon primary malignant bone tumor, and its treatment is a challenge to the orthopedic surgeon. Beyond survival, current treatment also focuses on functional preservation and cosmetic appearance. This 9-year follow-up case illustrates the complete treatment course from resection to reconstruction and rehabilitation for Ewing’s sarcoma, which demonstrates a complete clinical picture for pediatric specialist and pediatric surgeons dealing with complex tumor surgery. The patient not only achieved complete remission, but also had good functional outcomes with limb salvage.

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**INTRODUCTION**

Ewing’s sarcoma is a primary malignant tumor that usually occurs in children. It was first described in 1921 by Ewing J. Ewing’s sarcoma constitutes 17.2% of primary malignant bone tumors in the Caucasian population. In a previous study, the ratio of Ewing’s sarcoma to osteosarcoma was 0.1 in the Chinese group and 0.31 in the American group.

A previous study of primary bone cancer in Taiwan conducted between 2003 and 2010 showed that Ewing’s sarcoma accounted for only approximately 8% of all cases. The tumor most commonly occurs in the long bone diaphysis, and the most common site is the femur (22%), followed by the long bones of the lower extremities, including the femur (30%) and the pelvis (19%).

Ewing’s sarcoma generally has a favorable prognosis. The Cooperative Ewing’s Sarcoma Study Group reported a 10-year event-free survival rate of approximately 53% in 301 patients with a median age of 15 years. This predilection for the pediatric population and good prognosis underlines the importance of quality of life in addition to survival.

Physical function and cosmetic appearance have also become more important in recent years. However, reconstruction after wide resection is difficult in adolescents because of the growth potential and activity.

---

**CASE PRESENTATION**

**Chief complaints**

An 11-year-old boy presented with a 1-mo history of a right-sided limping gait.

**History of present illness**

The patient fell approximately 1 mo prior to admission. Since this accident, he had persistent pain in his right hip and a right-sided limping gait.

**History of past illness**

He had a known diagnosis of bilateral pes planus.
Personal and family history
The patient’s mother was G2P2A0; he was born via normal spontaneous delivery at a gestational age of 39 wk. His birth weight was 3300 gm. His parents did not have any specific medical or cancer history.

Physical examination
Physical examination revealed swelling of the right proximal femur and hip, tenderness over the right hip and lateral thigh, right hip pain with passive range of motion, and a right-sided limping gait due to weight-bearing pain. He had no loss of muscle power and sensation in the right lower limb.

Laboratory examinations
Blood tests revealed the following: lactate dehydrogenase, 401 IU/L; alkaline phosphatase, 158 IU/L; and C-reactive protein, 0.93 mg/dL. Chromosome analysis reported normal male 46,XY karyotype.

Imaging examinations
Radiography showed focal bone destruction and osteolytic change over the right femoral neck (Figure 1A). Magnetic resonance imaging showed an intra-skeletal mass in the metaphyseal region with physeal involvement (Figure 1B). Chest computed tomography also indicated bilateral lung metastases (Figure 2).

MULTIDISCIPLINARY EXPERT CONSULTATION
We discussed the case with an expert pediatric hematologist (Wu KH, MD, Chief Doctor, Professor, at the China Medical University Hospital) after tumor biopsy reported Ewing’s sarcoma. Neoadjuvant chemotherapy was recommended, and adjuvant chemotherapy was also needed after tumor resection.

FINAL DIAGNOSIS
Based on these findings, the patient was diagnosed with stage IV Ewing’s sarcoma (T1N0M1aG3). Histological examination of an incisional biopsy specimen confirmed the diagnosis of Ewing’s sarcoma/primitive neuroectodermal tumor, and the tumor was positive for CD-99 and periodic acid-Schiff staining.

TREATMENT
Neoadjuvant chemotherapy with cisplatin, cyclophosphamide, doxorubicin, etoposide, ifosfamide, and vincristine sulfate decreased the tumor size, with the tumor confined to the metaphyseal region (Figure 3). The patient then underwent four stages of surgery.

Stage 1
Wide excision of the tumor (physeal preservation) plus reconstruction with a vascular fibular bone graft plus fixation with a locking T-plate (Figure 4). The patient was placed in the supine position, and an incision from the lateral aspect of the thigh was made via the standard lateral approach. The tumor was then dissected and subjected to intra-operative frozen section pathology. After complete margin resection was confirmed, the femur and proximal femur were removed to harvest the vascular bone graft from the right fibula via the standard lateral approach. The distal ends of the peroneal artery and vein were divided, and the dissection was carried on toward the cephalic end. The vessel branches were ligated, and the flap was harvested based on the right peroneal artery and vein. The total length of the fibula flap was 17 cm, leaving 5 cm distally and 5 cm proximally. The graft was divided into two parts: proximal (10 cm with main blood supply) and distal (6 cm for augmentation of contact with the femoral head). The vascular fibular graft was transferred to the femur, and a vascular anastomosis of the branch of the lateral femoral circumflex artery and vein was performed. Then, the vascular fibular graft was fixed with an Arbeitsgemeinschaft für Osteosynthesefragen (AO) locking plate at the right hip and the distal tibial and fibular with a screw to ensure ankle stability.

The resected mass obtained after performing stage 1 surgery showed a tumor in the metaphysis and adjacent periosteal soft tissue with patchy myelofibrosis and avascular necrosis, but no residual malignant cells, lymphovascular permeation, or perineural invasion. A bone-destructive lesion measuring 3.5 cm × 1.6 cm was found over the distal metaphyseal site of the femur.

After 5 mo, the patient started with gradual limited weight bearing on the right hip. After 14 mo, partial weight bearing (over 30 kg) and walking with a crutch were achieved. However, the plate deformed with broken screws after an increase in partial weight bearing (Figure 5A).
Figure 1 Radiography and magnetic resonance imaging. A: Initial plain X-ray film of the pelvis (anteroposterior view). The arrow indicates the location of the tumor with cortical reaction at the femoral neck region; B: Initial pelvis coronary T2 STIR image showing involvement of the physis. The arrow and arrowhead indicate the location of the tumor and the femoral physis, respectively.

Figure 2 Initial chest computed tomography and chest computed tomography after neoadjuvant chemotherapy. Full remission of the lung metastases after the neoadjuvant chemotherapy is noted. A: Initial: The metastatic Ewing’s sarcoma over the right middle lobe (arrowhead). Pulmonary artery is not distended (arrow), which implies no obstructive tumor thrombus in this multiple metastasis situation; B: After neoadjuvant chemotherapy: Localized same level chest computed tomography with the pulmonary artery (arrow). The previous tumor had disappeared; C: Initial: The metastatic Ewing’s sarcoma in the right inferior lobe (arrowhead) and left inferior lobe with another metastatic Ewing’s sarcoma (arrowhead); D: After neoadjuvant chemotherapy: Localized same level chest computed tomography with similar pulmonary artery distribution. The previous tumors had disappeared.

Stage 2
After 16 mo, we performed a repeat open reduction and internal fixation for the plate impending failure and malalignment of the vascular fibular bone graft with the AO proximal humeral internal locking system (PHILOS) plate (Figure 5B). The femoral head had enlarged with age, but there was also a limb length discrepancy. After a 7.5-year follow-up period since the tumor excision surgery, a symmetric bilateral hip joint surface and equal femoral head size were noted on radiography. There was also no osteonecrotic change in the right femoral head. The right and left lower limb length were 77 and 83 cm, respectively, with a lower limb discrepancy of 6 cm.

Stage 3
Femoral lengthening with orthosis with a distraction rate of 1 mm/day (Figure 5C).
Figure 3 T2 magnetic resonance image (coronary view) after neoadjuvant chemotherapy. The arrow and arrowhead indicate the location of the tumor and the femoral physis, respectively. Note that the tumor is now confined only to the physis.

Figure 4 Intraoperative sample and postoperative pelvic plain imaging. A: Gross view of the resected tumor and resected femoral neck (arrow: Ewing’s sarcoma extra-bony part); B: Split resected femoral neck; C: Folded autologous fibular graft (arrow: vascular pedicle); D: Pelvic plain imaging (anteroposterior) obtained immediately after the surgery (arrow: locking plate used to fix the fibular graft).

Stage 4
Orthosis removal. The AO less-invasive stabilization system locking compression plate elongated the bone by approximately 6 cm.

OUTCOME AND FOLLOW-UP
Two months postoperatively, plain film radiography showed complete corticalization of the elongated femur (Figure 5D). The last follow-up plain film was obtained 14 mo postoperatively, and it showed good bone formation of the elongated femur (Figure 5E). The Musculoskeletal Tumor Society score was 28, and the Harris hip score was 96, 16 mo postoperatively[9,10].

DISCUSSION
Data on the long-term outcomes of Ewing’s sarcoma are currently lacking[2,11]. In Taiwan, Ewing’s sarcoma accounted for only 8% of all bone cancer cases during 2003-2010[12]. We reported the case of an adolescent patient with Ewing’s sarcoma who underwent three types of surgery. The first was a successful hip joint preservation, with the final imaging during follow-up showing an equal femoral head diameter and joint surface congruity. The second was graft substitution of the femoral neck with vascular autograft for the preservation of growth potential, and the choice of bone and implant for
Figures 5 Radiographic images. A: Plain X-ray film obtained after an increase in partial weight bearing. The plate was deformed (arrow: bending site of the plate); B: Revision and fixation with Arbeitsgemeinschaft für Osteosynthesefragen proximal humeral internal locking system plate; C: Radiographic image of orthosis with complete distraction. The femoral distraction gap is approximately 6.5 cm (arrow: distraction gap); D: Radiographic image showing removal of the orthosis and internal fixation with less-invasive stabilization system complete corticalization (arrow: corticalized bone); E: Radiographic image showing complete consolidation phase (arrow: cordialized bone with increased radiopacity).

augmentation and fixation. The third was femoral lengthening technique selected to enable the patient to regain normal ambulatory capacity.

Despite novel treatment modalities, oncological surgery remains crucial for improving survival. In addition, both patients and their family are concerned about regaining normal function and cosmetic appearance after tumor resection. Given that Ewing’s sarcoma affects the bones and soft tissues, potential functional changes are an important consideration when planning surgery. The three main growth areas in the proximal femur are the physeal plate, the growth plate of the greater trochanter, and the femoral neck isthmus. The proximal femoral physeal plate contributes to approximately 30% of the overall length of the femur, and 13% of the entire lower limb. It is important to preserve joint function and activity if limb preservation can be expected, especially in pediatric patients who still have growth potential.

A malignant tumor in the proximal femur can affect the hip joint. Once we decided to perform limb salvage surgery, age, growth potential, and physis involvement were the first factors to be considered. Tsuchiya et al.[14] used a vascular fibular graft to allow growth of the physis in the fibula in the hip joint, with cadaveric femoral allograft as reinforcement. However, this method has not yet been proven to effectively enable growth. Intra-epiphyseal excision is sometimes an option for long bone tumors.[15] In our case, we selected a hip joint preservation technique. Tumor resection in the proximal femur, particularly the femoral neck, arthroplasty, or vascular bone graft with allograft bone augmentation as a structural graft, can be performed in adult patients[14,16].

Although vascular grafts allow for bony growth in pediatric patients, surgery allows enlargement of the hip joint; thus, hip-preservation surgery is needed. Furthermore, the small diameter of the femoral neck makes it challenging to obtain an appropriate proximal femoral allograft in this patient population.
Re-implantation of the resected proximal femur bone post cryotherapy is another option to reinforce the biomechanical construct\textsuperscript{13}. We used a folded autologous vascular fibula graft reconstructed from the proximal femur, particularly the femoral neck. However, given that the tumor was not resected from the femoral subtrochanteric region and that the patient was only 11 years old, we used a locking plate to stabilize the vascular fibula graft\textsuperscript{17}. The Capanna technique was not suitable in our case, because the literature on pediatric allograft is limited, and the smaller bone diameter makes this technique challenging, as it involves a sandwich-like bone graft. If we performed a reconstruction technique similar to that for adults, hemi-arthroplasty is an option with a low risk of mechanical failure. However, the bony growth of the proximal femur in our patient did not reach the expected length, and thus, the implant failed. Accordingly, we performed another surgery with AO PHILOS after 1.5 years. This allowed for better biomechanical distribution of the head-neck force to the femoral shaft, and the vascular graft successfully combined.

After 8 years, the diameter of the femoral head was equal to that of the other site, indicating that preservation of the physis allowed for enlargement of the hip joint. However, the length discrepancies remained an issue. Similar to those in the tibia, complications, particularly infection, in extra-skeletal fixation are of great concern\textsuperscript{18,19}. Concerning the femoral lengthening device, an extra-skeletal monolateral system, such as orthosis, is an efficient approach that does not require joint involvement. The system avoids broken screws and allows for preservation of the remaining physis\textsuperscript{20}. One study compared limb length discrepancies among elongation devices in 73 patients with Ewing’s sarcoma or osteosarcoma, and found that 10 patients required secondary lengthening. The average length achieved was 8.1 cm, and the final residual discrepancy was 1.5-2.5 cm.

Angulation, torsion, osteoporosis, joint instability, muscular weakness, and patient and family cooperation are factors that must be considered prior to long bone elongation surgery. In general, the patient needs to undergo the following five phases before removing the orthosis: (1) Osteotomy; (2) Latency; (3) Distraction; (4) Neutralization; and (5) Consolidation\textsuperscript{19}. Physical activity is limited during the consolidation phase and the percutaneous pins of orthosis also increase the risk of pin tract infection. An internal fixation with a locking plate prevents these problems. The patient underwent another surgery after the complete distraction phase to change the orthosis to an internal fixator during the consolidation phase.

CONCLUSION

Each surgical modality used to treat Ewing’s sarcoma has its own challenges and risks of failure or complications. In the current case, tumor resection, reconstruction, rehabilitation, elongation, and rehabilitation within 9 years enabled good recovery of the patient. Corticalization was confirmed on the final radiographic follow-up, and the patient is currently doing well, with good physical function.

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FOOTNOTES

Author contributions: Lai CY and Fong YC conceptualized the study; Fong YC supervised the entire study; Lai CY drafted and reviewed the manuscript; all authors have read and approved the final version of the manuscript for submission.

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REFERENCES


Early detection of circulating tumor DNA and successful treatment with osimertinib in thr790met-positive leptomeningeal metastatic lung cancer: A case report

Li-Qing Xu, Ying-Jin Wang, Sheng-Li Shen, Yao Wu, Hong-Zhou Duan

Abstract

BACKGROUND
Patients diagnosed with non-small-cell lung cancer with activated epidermal growth factor receptor mutations are more likely to develop leptomeningeal (LM) metastasis than other types of lung cancers and have a poor prognosis. Early diagnosis and effective treatment of leptomeningeal carcinoma can improve the prognosis.

CASE SUMMARY
A 55-year-old female with a progressive headache and vomiting for one month was admitted to Peking University First Hospital. She was diagnosed with lung adenocarcinoma with osseous metastasis 10 months prior to admittance. Epidermal growth factor receptor (EGFR) mutation was detected by genomic examination, so she was first treated with gefitinib for 10 months before acquiring resistance. Cell-free cerebrospinal fluid (CSF) circulating tumor DNA detection by next-generation sequencing was conducted and indicated the EGFR-Thr790Met mutation, while biopsy and cytology from the patient’s CSF and the first enhanced cranial magnetic resonance imaging (MRI) showed no positive findings. A month later, the enhanced MRI showed linear leptomeningeal enhancement, and the cytology and biochemical examination in CSF remained negative. Therefore, osimertinib (80 mg/d) was initiated as a second-line treatment, resulting in a good response within a month.

CONCLUSION
This report suggests clinical benefit of osimertinib in LM patients with positive detection of the EGFR-Thr790Met mutation in CSF and proposes that the positive findings of CSF circulating tumor DNA as a liquid biopsy technology based on the detection of cancer-associated gene mutations may appear earlier than the imaging and CSF findings and may thus be helpful for therapy. Moreover, the
routine screening of chest CT with the novel coronavirus may provide unexpected benefits.

**Key Words:** Non-small cell lung cancer; Epidermal growth factor receptor mutation; Circulating tumor DNA detection; Leptomeningeal carcinomatosis; Osimertinib; Case report

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**Core Tip:** Examination of circulating tumor DNA in cell-free cell-free cerebrospinal fluid (CSF) has been shown to be useful for detecting the genomic mutations of tumors in the central nervous system, and osimertinib is considered to be a recent standardized treatment for epidermal growth factor receptor (EGFR) Thr790Met-mutant non-small-cell lung cancer (NSCLC). Hence, we report a patient with EGFR Thr790Met-mutant NSCLC with meningeal carcinomatosis and resistance to gefitinib and propose that the positive findings of CSF circulating tumor DNA as a liquid biopsy technology based on the detection of cancer-associated gene mutations that may appear earlier than the imaging and CSF findings and thus be helpful for therapy.

**INTRODUCTION**

Patients diagnosed with non-small-cell lung cancer (NSCLC) with activated epidermal growth factor receptor (EGFR) mutations are more apt to develop leptomeningeal (LM) metastasis than other types of lung cancers[1]. According to previous studies, patients with NSCLC with LM carcinoma have a poor prognosis[2]. Early diagnosis and effective treatment of LM carcinoma can improve the prognosis. Circulating tumor DNA (ctDNA) is composed of short, double-stranded DNA fragments from tumor cells. Examination of ctDNA in cell-free cerebrospinal fluid (CSF) has been shown to be useful in detecting the genomic mutations of tumors in the central nervous system (CNS) and has also been used to monitor tumor progression and evaluate the response to treatments[3-5]. However, it is unclear whether ctDNA detection in CSF can provide valuable clinical guidance for the treatment of meningeal metastases. Molecular targeted drugs such as EGFR tyrosine kinase inhibitors (TKIs) have been shown to be effective for patients with NSCLC and LM carcinoma who carry target oncogenes[6]. Osimertinib, a third-generation EGFR TKI, is considered to be a recent standardized treatment for EGFR Thr790Met-mutant NSCLC because of its good efficacy in both systemic and CNS metastasis[7]. However, relevant information about the effectiveness of osimertinib in EGFR Thr790Met-mutant meningeal carcinomatosis is limited. Here, we report a case of patient with EGFR Thr790Met-mutant NSCLC with meningeal carcinomatosis, which is resistant to gefitinib.

**CASE PRESENTATION**

**Chief complaints**

A 55-year-old female experiencing a progressive headache and vomiting for one month was admitted to our hospital.

**History of present illness**

55-year-old female experiencing a progressive headache and vomiting for one month was admitted to our hospital. She was diagnosed with lung adenocarcinoma (Figure 1A) with osseous metastasis 10 mo prior to admittance. EGFR mutation was detected upon genomic examination, so she was first treated with gefitinib for 10 mo before acquiring resistance. A previous enhanced cerebral magnetic resonance imaging (MRI) and PET-CT one month prior showed that there was no obvious abnormality in the CNS. Lumbar puncture showed an increased intracranial pressure (+ACY-gt+ADs-330 mmH2O) without positive cytology and biochemical examination findings in the CSF. However, further CSF ctDNA detection by next-generation sequencing showed an EGFR-Thr790Met mutation. After the patient was admitted, a second enhanced MRI was performed and showed comprehensive linear leptomeningeal enhancement in the cerebral sulcus (Figure 1B). A second cytology and biochemical examination of the...
CSF remained negative.

**History of past illness**
The patient had no special history of past illness other than a hysterectomy procedure for fibroids 10 years prior.

**Personal and family history**
The patient had no special history of past illness other than a hysterectomy procedure for fibroids 10 years prior.

**Physical examination**
Neurological and pulmonary examination of the patient showed no obvious abnormalities.

**Laboratory examinations**
Lumbar puncture showed an increased intracranial pressure (> 330 mmH2O) without positive cytology and biochemical examination findings in CSF. However, further CSF ctDNA detection by next-generation sequencing showed an EGFR-Thr790Met mutation, and the variation frequency was 11.7%.

**Imaging examinations**
(1) Chest CT image at admission shows a lesion in the lingual segment of the upper lobe of the left lung (arrows); and (2) A follow-up cerebral contrast-enhanced MRI shows diffuse and linear enhancement along the surface of the cerebrum (arrows).

**FINAL DIAGNOSIS**
Based on these findings, a diagnosis of LM carcinomatosis of EGFR-Thr790Met-positive lung adenocarcinoma (cT3N3M1b: stage IVA) was established.

**TREATMENT**
Neither surgery nor chemotherapy was applied to the patient due to osseous metastasis. In addition, surgery could not achieve a radical cure. Hence, osimertinib (80 mg/d) was given as a second-line treatment.

**OUTCOME AND FOLLOW-UP**
The patient showed a good response within a month. What’s more, the patient’s headache and symptoms of intracranial hypertension disappeared rapidly after 3 days of osimertinib treatment. After discharge, osimertinib (80 mg/d) was continued, and the patient was closely followed-up. There were no obvious toxic or adverse side effects except for diarrhea and leukopenia. The lung lesion continued to
shrink by the 6-month follow-up CT, and the intracranial pressure returned to normal without the patient experiencing a headache.

**DISCUSSION**

Patients with NSCLC and LM carcinoma have a poor prognosis. Early diagnosis and an appropriate treatment regimen are important to improve the prognosis. The analysis of ctDNA in CSF can be used to detect nervous system tumors and their drug resistance mechanism[^8]. According to previous studies, EGFR-TKIs are effective in patients diagnosed with NSCLC and LM carcinoma with positive EGFR mutations[^9]. Osimertinib has been reported to be more effective due to its better blood-brain barrier permeability[^7]. This report shows a great clinical benefit of osimertinib in LM patients with positive detection of the EGFR-Thr790Met mutation in their CSF. Interestingly, the cytology in CSF and neuroimaging were all negative at the beginning, and when the patient's imaging turned positive, the result of CSF cytology examination was still negative one month after the EGFR-Thr790Met mutation was detected in CSF. Hence, we propose that the positive findings of CSF ctDNA as a liquid biopsy technology based on the detection of cancer-associated gene mutations may appear earlier than the imaging findings and the CSF findings and could thus be more helpful for therapy. Moreover, the character of this report is that headache is the chief complaint of the patient with lung cancer. The patient's initial outpatient cranial MRI and lumbar puncture showed no abnormalities in CSF biochemistry and cytology, except for elevated intracranial pressure. The patient's lung lesion was found due to the routine screening of chest CT with novel coronavirus. Just as the old saying goes, 'there is no great loss without some small gain'.

**CONCLUSION**

This report shows a great clinical benefit of osimertinib in LM patients with positive detection of the EGFR-Thr790Met mutation in CSF and proposes that the positive findings of CSF circulating tumor DNA as a liquid biopsy technology based on the detection of cancer-associated gene mutations may appear earlier than the imaging findings, and the CSF findings and could thus be helpful for therapy. Moreover, the routine screening of chest CT with the novel coronavirus may provide unexpected results.

**FOOTNOTES**

**Author contributions:** Xu LQ conceived the article; Xu LQ and Wang YJ collected the data; Wang YJ assembled the data; Xu LQ, Wang YJ, Shen SL, Wu Y and Duan HZ provided the study materials, write the manuscript and approved the manuscript.

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Delayed arterial symptomatic epidural hematoma on the 14th day after posterior lumbar interbody fusion: A case report

Shen-Shen Hao, Zhen-Fu Gao, Hong-Ke Li, Shuai Liu, Sheng-Li Dong, Hong-Lei Chen, Zhi-Fang Zhang

**Abstract**

**BACKGROUND**

Delayed arterial symptomatic epidural hematoma (SEH) on the 14th day after posterior lumbar interbody fusion (PLIF) is rare but it may lead to severe complications if not identified and treated in a timely manner. After diagnosis of the current case, early surgical removal of the hematoma and strict hemostasis treatment was accomplished. This case report highlights the importance of swift diagnosis and treatment in SEH patients.

**CASE SUMMARY**

A 41-year-old male patient with a single-segment lumbar disc herniation underwent left-side PLIF. On the 14th post-operative day, the patient complained of lumbar incision pain with sudden onset accompanied by left limb radiation pain and aggravated cauda equina symptoms. Magnetic resonance imaging examination and a puncture blood draw at the incision site confirmed a delayed arterial SEH. Emergency surgical removal of the hematoma and hemostasis was performed. About 70 mL of hematoma was found in the left incision. Continuous bleeding was found in the anterior branch of the transverse process of the 4th lumbar artery in the muscle area about 2 cm below the transverse process of the 4th lumbar vertebra. A blood jet of about 10 cm in height was observed and bipolar electrocoagulation was used to stop the bleeding. Post-operative lumbar incision pain and left lower limb pain were relieved immediately and gradually disappeared. There was no recurrence during the 12-mo follow-up.

**CONCLUSION**

For delayed arterial SEH on the 14th day after PLIF, preventive measures including pre-, intra- and post-operative prevention should be implemented.

**Key Words:** Delayed arterial symptomatic epidural hematoma; Treatment methods; Preventive measures; Posterior lumbar interbody fusion; Case report
Core Tip: Posterior lumbar interbody fusion (PLIF) is a standard surgical method for the treatment of lumbar disc herniation. Delayed arterial symptomatic epidural hematoma is an infrequent complication after lumbar spine surgery, occurring with extreme rarity as late as the 14th day after PLIF. Without timely diagnosis and treatment, clinical consequences could be severe. Once the complication had been found in the present case, early surgical hematoma removal and strict hemostasis treatment were required.

INTRODUCTION

Epidural hematoma (EH) is a common complication following posterior lumbar surgery. It has been reported that EH could be detected by imaging in approximately 33%-100% of patient's post-operation [1] with most showing no clinical symptoms. Indeed, the incidence of asymptomatic EH may be as high as 58%[2]. Clinical symptoms of lumbar symptomatic epidural hematoma (SEH) include sudden severe spontaneous waist pain following lumbar spine surgery with compression symptoms after a few minutes to a few days and sphincter dysfunction below the site of the pain. In extreme cases, paraplegia may develop. The aforementioned are the typical clinical features of EH usually occurring within 72 h of surgery and SEH occurring 5 to 16 h after surgery. When SEH occurs more than 72 h post-surgery, it can be defined as a delayed SEH[3] which has an incidence rate of 0.17%[4]. Posterior lumbar interbody fusion (PLIF) is a surgical treatment for lumbar disc herniation, and delayed arterial SEH after PLIF is an infrequent and severe complication. Cases of delayed arterial SEH occurring on the 14th day after PLIF are extremely rare, highlighting the importance of raising clinicians’ awareness about their diagnosis and treatment.

The current report describes the treatment of a sporadic rare patient with delayed arterial SEH on the 14th day after PLIF. This case represents the first patient with SEH following PLIF observed by orthopedic doctors and anesthesiologists in our hospital for decades. Given the rarity of this condition, a comprehensive review and analysis of the existing literature was conducted. The aim of this case report is to analyze the possible causes of delayed arterial SEH, introduce treatment methods and explore preventive measures. Meanwhile, we hope to encourage other clinicians to increase their vigilance against delayed arterial SEH after PLIF and provide some references for the diagnosis and treatment of this serious complication.

CASE PRESENTATION

Chief complaints
A 41-year-old male patient, 174 cm tall and weighing 85 kg, was admitted to our hospital with the chief complaint of “left lower limb pain for more than 7 mo and worsening over the previous 20 d”.

History of present illness
The patient developed left calf pain due to fatigue for more than 7 mo with numbness of his left hip and foot and limited mobility. The symptoms gradually worsened. Bed rest, physical therapy and drug therapy brought no relief. The above symptoms had worsened during the 20 d prior to admission.

History of past illness
The patient had a 2-year history of hypertension for which he usually received “amlodipine besylate tablets” (5 mg po. qd.).

Personal and family history
The patient was a 41-year-old Chinese man, non-smoker with a blood type O and rhesus positive.
Physical examination
Oral history revealed poor spirit, poor sleep, average diet, stool dysfunction and regular urination. Physiological curvature of the lumbar spine was present without kyphosis, scoliosis or lordosis and with a reduced degree of motion. Left lower limb muscle strength was a level 4, and right was a level 5. The muscle tension of both lower limbs was normal. The patient reported feeling weakness in the left hip, left calf and left foot while the right limb was normal. The left knee-tendon reflex was weaker while the right was normal. The left Bragard sign was positive while the right was negative. Babinski’s sign was negative on both sides. There was no edema in either lower limb and normal blood supply.

Laboratory examinations
Coagulation function test: Prothrombin time (PT): 11.30 s; PT%: 93.00%; international normalized ratio (INR): 1.04; fibrinogen C (FC): 3.5 g/L; activated partial thromboplastin time (APTT): 39.80 s; thrombin time (TT): 15.69 s and fibrin (original) degradation product (FDP): 1.04 μg/mL. These results were all within normal ranges.

Imaging examinations
X-ray examination showed that the intervertebral space of the 4th/5th lumbar vertebrae had shrunk (Figure 1). Computed tomography (CT) scan indicated a herniated disc of the 4th/5th lumbar vertebrae (Figure 2). Magnetic resonance imaging (MRI) revealed a herniated disc of the 4th/5th lumbar vertebrae (Figure 3).

FINAL DIAGNOSIS
Patient diagnosis: (1) Lumbar disc herniation with cauda equina injury; and (2) Hypertension.

TREATMENT
After pre-operative preparation, the patient underwent a successful surgery of "left-side PLIF" on the 4th day after admission. The operation time was 120 min with an intra-operative blood loss of 600 mL, placement of 2 drainage tubes and no blood transfusion. The patient’s left calf pain and left hip and foot numbness were significantly reduced post-operatively. Within the 24 h post-operative period, low-molecular-weight heparin was used for anti-coagulation to prevent deep vein thrombosis (DVT). Coagulation function test on the 1st post-operative day showed PT: 12.80 s; PT%: 76.00%; INR: 1.18; FC: 3.48 g/L; APTT: 33.40 s; TT: 15.13 s and FDP: 1.04 μg/mL. These results were similar to those of the pre-operative coagulation function test. After the operation, the drainage tube was unobstructed and drainage volume gradually decreased: 1st post-operative day: 120 mL; 2nd post-operative day: 80 mL; and 3rd post-operative day: 40 mL before drainage tube removal on the 3rd post-operative day. After pulling out the drainage tube, the pain and numbness of the left lower limb were gradually alleviated. Re-examination of lumbar spine X-rays on the 4th post-operative day indicated satisfactory positions of the lumbar spine fixation and fusion cage (Figure 4).

On the 14th post-operative day, the patient reported sudden incision pain. Physical examination revealed no noticeable swelling and redness at the waist incision but evident tenderness. The pain was partially relieved by applying analgesics. On the 15th post-operative day, the patient experienced increased pain at the waist incision, accompanied by symptoms similar to those before the operation including left calf pain, left hip and foot numbness and stool dysfunction. Physical examination revealed a slight swelling of the skin at the incision with pain and aggravation of lower limb pain on pressure. The left Bragard sign was positive while the right was negative. The MRI scan revealed abnormal signals in the left area of the 4th/5th lumbar vertebral body with possible hematoma formation (Figure 5). After departmental consultation, the possibility of a delayed post-operative SEH was indicated. It was considered that the patient experienced symptoms of spinal cord and nerve compression due to possible hematoma formation in the lumbar incision. Immediate puncture of the hematoma with tube placement for drainage was scheduled. This minimally invasive operation was designed to allow the hematoma to be drained and the patient’s symptoms to be relieved without significant impact on the incision. Puncture treatment was performed under C-arm X-ray machine fluoroscopy. When the puncture needle broke through the muscle tissue, bright red blood could be seen gushing out of the puncture needle core with continuous pulsation (Figure 6). The diagnosis of delayed arterial SEH after PLIF was confirmed.

Emergency surgery was performed to stop the bleeding and remove the hematoma. During the 2nd operation, a large hematoma in the left incision with compression around the nerve root became apparent. After the removal of about 70 mL of blood clot (Figure 7), a small artery, an anterior branch of the transverse process of the 4th lumbar artery, was found to be the source of continuous bleeding. The artery location was in the muscle tissue area about 2 cm below the transverse process of the 4th lumbar
Figure 1 Pre-operative radiographs. The intervertebral space of the 4\textsuperscript{th}/5\textsuperscript{th} lumbar vertebrae became smaller. A: The pre-operative anterior position radiograph; B: The pre-operative lateral position radiograph. R: Right direction.

Figure 2 Pre-operative computed tomography scans. The position (horizontal line) of the computed tomography scan shown that there is a herniated disc of the 4\textsuperscript{th}/5\textsuperscript{th} lumbar vertebrae. A: The level of the 4\textsuperscript{th}/5\textsuperscript{th} lumbar vertebrae; B: The herniated disc of the 4\textsuperscript{th}/5\textsuperscript{th} lumbar vertebrae.

Figure 3 Pre-operative magnetic resonance imaging scans. The position (horizontal line) of the magnetic resonance imaging scan shown that there is a herniated disc of the 4\textsuperscript{th}/5\textsuperscript{th} lumbar vertebrae. A: The level of the 4\textsuperscript{th}/5\textsuperscript{th} lumbar vertebrae; B: The herniated disc of the 4\textsuperscript{th}/5\textsuperscript{th} lumbar vertebrae.

The pressure of the gushing blood was high and the height of the bleeding jet reached about 10 cm. Careful bipolar coagulation was used to stop the bleeding and hemostatic gelatin sponge was packed to enhance the hemostatic effect. After flushing of the surgical incision and ensuring of no bleeding point in the incision, it was sutured with placement of a drainage tube. The outcome of the operation was very successful. The operation time was 75 min with intra-operative blood loss of 100 mL. The patient’s pain and numbness were significantly reduced after the operation. Within 24 h, low-molecular-weight heparin was used for anti-coagulation to prevent DVT.
**Figure 4 Post-operative radiographs.** The satisfactory positions of the lumbar spine internal fixation and fusion cage on post-operative 4-d. A: The post-operative 4-d anterior position radiograph; B: The post-operative 4-d lateral position radiograph. R: Right direction.

**Figure 5 Post-operative magnetic resonance imaging films.** The position (horizontal line) of the magnetic resonance imaging scan shown that there is an abnormal signal in the left area of the 4\(^{th}\)/5\(^{th}\) lumbar vertebral body. The white arrow indicates the hematoma. A: The level of the 4\(^{th}\)/5\(^{th}\) lumbar vertebrae; B: The abnormal signal in the left area of the 4\(^{th}\)/5\(^{th}\) lumbar vertebrae.

**Figure 6 The puncture treatment films.** Under C-arm X-ray machine fluoroscopy, the puncture needle in the left-side of 4\(^{th}\)/5\(^{th}\) lumbar vertebrae, bright red blood gushing out of the puncture needle core with continuous pulsation. A: The anterior position under C-arm X-ray machine fluoroscopy; B: The lateral position under C-arm X-ray machine fluoroscopy; C: The bright red blood gushing out of the puncture needle core with continuous pulsation.

### OUTCOME AND FOLLOW-UP

A coagulation function test on the 1\(^{st}\) day after the 2\(^{nd}\) operation showed PT: 11.60 s; PT%: 89.00%; INR: 1.07; FC: 3.41 g/L; APTT: 38.30 s and TT: 16.97 s, which were similar to those of the previous two laboratory tests. The drainage tube was unobstructed and drainage volume gradually decreased: (1) Post-operative day: 90 mL; (2) Post-operative day: 60 mL; and (3) Post-operative day: 30 mL before drainage tube removal on the 3\(^{rd}\) post-operative day. Waist incision and left lower limb pain continued
Figure 7 Surgery for hematoma removal. The incision filled with hematoma that the removed hematoma is about 70 mL. White arrows indicate the hematoma. A: The incision filled with hematoma; B: The removed hematoma.

to decline, and reached zero at the 12th day after the 2nd operation, when the patient was discharged. Only mild left foot and left hip numbness and mild symptoms of stool dysfunction remained. Stool dysfunction was relieved 2 mo after discharge and left foot and hip numbness vanished after 6 mo. There was no recurrence of symptoms on 9 and 12 mo follow-ups (Figures 8 and 9). The patient expressed satisfaction with his treatment.

DISCUSSION

PLIF is a standard surgical method for the treatment of lumbar disc herniation. Bleeding was inevitable at the post-operative decompression site and EH was estimated to form at the decompression or adjacent segment[5]. As the localized space is enlarged after PLIF, nerve compression symptoms generally do not occur. However, SEH represents a particular type of EH accompanied by symptoms of spinal cord or nerve compression. Clinical manifestations include severe swelling and pain at the waist incision, inability to lie flat, pain not wholly responsive to analgesics and irritability. In addition, some patients experience radicular pain, low muscle strength and reduced sensation in the lower limbs with severe cases being complicated by cauda equina syndrome and even paraplegia. SEH after PLIF is an infrequent and severe complication with severe consequences contingent on failure to diagnose and treat the condition in a timely manner. Therefore, early diagnosis and surgery are critical for the treatment of SEH[6]. Delayed arterial SEH on the 14th day after PLIF is a very rare and severe complication. The current case report is designed to raise awareness of this complication among other spinal doctors and provide references for diagnosis, treatment and prevention.

A literature review revealed diverse views on the causes of post-operative EH or SEH. Kao et al[7] believed that the use of an intra-operative gelatin sponge was a risk factor for EH. Kou et al[3] reported that multi-segment spinal surgery increased the risk of epidural venous plexus injury, leading to the formation of EH. Post-operative blockage of the wound drainage tube has also been proposed as a contributory factor[8], as have multi-segment decompression, improper use of hemostatic materials, abnormal drainage, use of anti-coagulants and incomplete hemostasis and spinal revision surgery[9]. Sokolowski et al[5] suggested that the use of low-molecular-weight heparin after surgery might increase the risk of EH, albeit that most examples of EH were asymptomatic and required no treatment. However, it has also been reported that early administration of low-molecular-weight heparin does not increase the risk of EH if lumbar spine surgery was accompanied by hemostasis and adequate drainage[10]. An EH multiple regression model analysis showed that the pre-surgery risk factors were age > 65 years and revision surgery, and the risk factors during surgery were surgery time > 120 min, blood loss > 600 mL and intra-operative infusion of frozen plasma[11]. It is clear that further research is required to fully identify the specific causes of EH or SEH. However, each of the reasons mentioned above is a possible factor, indicating the need for vigilance in clinical work.

Both veins and arteries can contribute to bleeding during SEH. Rupture of the epidural venous plexus (Batson venous plexus) has been suggested as a cause of bleeding[12], as has local arterial rupture since the speed and quantity of blood produced are commensurate with the rapid clinical progression of SEH[13]. Hu et al[14] reported a case of delayed arterial SEH caused by delayed lumbar perforating arterial bleeding in the 2nd week after PLIF. The patient experienced unbearable soreness and discomfort in the lumbosacral area and a burning sensation on urination. After 5 h, he experienced increased numbness in both lower limbs, and was unable to move below the ankles and control urination. Emergency surgery was performed to remove the hematoma and stop the bleeding, after which the patient’s lower limb muscle strength gradually recovered after the 2nd post-operative week, stool function recovered after the
1st month and urine function recovered after the 7th month.

The current case involved bleeding from the anterior branch of the transverse process of the 4th lumbar artery. The vessel issued close to the lower edge of the root of the upper transverse process and ran slightly to the ventral side from the inside to the outside, passed through the transverse process and travelled outward and downward to enter the muscle fascia tissue. This was consistent with the bleeding site we found during the 2nd operation. Intra-operative exposure of the transverse process beyond the boundary of its lower edge might damage the artery. Moreover, when using intra-operative bipolar coagulation to stop bleeding, it should be administered close to the root of the lower edge of the transverse process to avoid damaging the nerve roots in the exit area of the deep intervertebral foramina [15]. Our patient's pain and neurological symptoms were alleviated immediately after the operation and had disappeared completely by the 12th post-operative day. The patient's stool dysfunction disappeared after the 2nd month and the left foot and hip numbness disappeared after the 6th month. There was no recurrence by the 12 mo of follow-up. It can be seen that the symptoms of delayed arterial SEH caused by the rupture of lumbar arteries were severe and the recovery process prolonged.

We consider that there are three main reasons why this severe complication might have affected the present case. Firstly, post-operative administration of anti-coagulant drugs to reduce the incidence of DVT in patients after lumbar surgery may be a factor. Low-molecular-weight heparin is a drug of choice which reduces the incidence of DVT after spinal surgery but also carries a low risk of EH and other bleeding events [16]. Generally, post-operative application of anti-coagulant drugs does not increase the risk of EH and SEH in our clinical experience, but which drugs produce the most favorable outcomes and whether the use of such drugs can confer an increased risk of SEH remain unclear. Secondly, hypertension may contribute to the increased fragility of blood vessels. The current patient had a 2-year history of hypertension and fluctuations of blood pressure may have caused rupture and hemorrhage of local arterioles. Thirdly, an increase in abdominal pressure due to constipation and cough after surgery may cause fluctuations in arterial pressure contributing to the likelihood of rupture and bleeding. All of the above factors may have interacted to cause SEH or one factor may predominate due to the changes in local tissue structure and vertebral body mechanics after PLIF. The mobility of the lumbar spine was
reduced and restrictions in the range of motion might cause damage and rupture of the small artery vessels. Initial local accumulation of blood was cleared by the body on spontaneous cessation of bleeding but changes in biomechanics and long-term stress damage might cause repeated rupture of small blood vessels, forming hematoma and eventually SEH[17].

Delayed arterial SEH is a rare and severe complication which requires prompt diagnosis and emergency surgical treatment. We identify three main items for diagnosis. Firstly, sudden onset of clinical symptoms, such as sudden lumbar incision pain and progressive aggravation accompanied by symptoms of compression of lower limb nerve function and impaired cauda equina nerve function. Secondly, MRI scans reveal the location, scope, size of the hematoma and changes following compression of the dural sac. A preliminary prognosis could be made by analyzing the size of the hematoma and the degree of nerve displacement. Thirdly, a punctured blood draw from the surgical incision site not only confirms the diagnosis but if bright red blood with continuous pulsation from the needle core is found, it will help to reduce the patient's symptoms of nerve involvement. Therefore, we recommend the uses of MRI scanning and puncture blood operation, although the patient's clinical symptoms remain the most valuable diagnosis. On presentation of the symptoms, the operation should be performed quickly following discussion with the patient. Surgical treatment aims to remove the hematoma and stop the bleeding but also relieves the patient's lumbar incision pain and nerve involvement symptoms.

Early detection, diagnosis and treatment are essential for preventing delayed arterial SEH. Further measures are required to prevent its recurrence. We have combined our clinical experience with our survey of the literature to summarize pre-, intra- and post-operative preventive methods[18].

Firstly, pre-operative prevention includes improved laboratory tests, imaging and control of primary diseases. Secondly, intra-operative prevention includes strict hemostasis[19]. For example, bone wax could be used to stop bleeding during bone oozing, bipolar coagulation or gauze compression during venous bleeding and bipolar coagulation during arterial bleeding. Thirdly, post-operative prevention includes placement of a drainage tube through the incision which must remain unobstructed, monitoring and control of blood pressure, anti-tussive action, avoidance of frequent changes in body position, prevention of constipation and the rational use of anti-coagulant drugs.

CONCLUSION

In summary, delayed arterial SEH is an infrequent complication after lumbar spine surgery and is extremely rare as late as the 14th day after PLIF. Serious consequences are likely in the absence if there is timely discovery and treatment. We hope, by our research regarding this case, to increase clinicians' understanding and vigilance regarding this condition and also to provide some reference material for diagnosis, treatment and prevention.

FOOTNOTES

Author contributions: Hao SS was a major contributor and wrote the first draft of the article; Gao ZF critically reviewed and edited drafts; Dong SL diagnosed the patient; Gao ZF and Li HK treated the patient; Liu S made substantial contributions to the conception and designed of the manuscript; Chen HL and Zhang ZF followed up the patients; All authors read and approved the final manuscript.

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Clinical and genetic analysis of nonketotic hyperglycinemia: A case report

Jun-Jie Ning, Feng Li, Sheng-Qiu Li

BACKGROUND
Nonketotic hyperglycinemia (NKH) is a rare autosomal recessive genetic disorder of abnormal glycine metabolism caused by insufficient activity of the glycine cleavage enzyme system. Glycine is believed to function mainly as an inhibitory neurotransmitter, but it can also act as a co-agonist of the N-methyl-D-aspartate (NMDA) receptor. The accumulation of a large amount of glycine in the brain leads to neuronal and axonal injury via overactivation of NMDA receptors located in the hippocampus, cerebral cortex, olfactory bulb, and cerebellum and to stimulation of the inhibitory function of glycine receptors located in the spinal cord and brain stem, resulting in central apnea, hiccups, and hypotonia in the early stage of the disease.

CASE SUMMARY
The child described in this report had typical clinical manifestations of NKH, such as hiccups, disturbance of consciousness, hypotonia, and convulsions, within the first week after birth. Whole-exome genetic testing revealed that the child had a compound heterozygous mutation, namely, c.395C>A (p.S132X) and c.2182G>A (p.G728R), in the GLDC gene, and he was diagnosed with NKH. For treatment, we administered an oral levetiracetam solution and added topiramate and prednisone for epilepsy control, but the epilepsy remained uncontrollable. Ketogenic diet therapy was started at 6 mo of age, his seizures were significantly reduced, and there were no obvious adverse reactions during ketogenic treatment. Furthermore, we found that with the development of the disease, high levels of serum glycine decreased or even disappeared without intervention, and as the disease progressed, the corpus callosum became dysplastic.

CONCLUSION
This case shows that plasma glycine levels cannot be used to evaluate the prognosis of NKH, that the development of the corpus callosum can be affected by NKH, and that a ketogenic diet may be effective for seizure control in NKH.
patients.

Key Words: Nonketotic hyperglycinemia; Compound heterozygosity; GLDC gene; Case report

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Core Tip: Herein, we present the case of a child who had typical clinical manifestations of nonketotic hyperglycinemia (NKH), such as hiccups, disturbance of consciousness, hypotonia, and convulsions within the first week after birth. These symptoms combined with the results of gene testing led to a diagnosis of classical nonketotic hyperglycinemia caused by compound heterozygous variants in the GLDC gene. Plasma glycine levels cannot be used to evaluate the prognosis of NKH, and the corpus callosum can be affected by NKH. A ketogenic diet may be effective for seizure control in NKH patients.

INTRODUCTION
Nonketotic hyperglycinemia (NKH), also known as glycine encephalopathy, is an autosomal recessive genetic disease with abnormal glycine metabolism caused by insufficient activity of the glycine cleavage enzyme system (GCS), and NKH is clinically characterized by the abnormal accumulation of glycine in all tissues of the human body, especially in the serum and cerebrospinal fluid[1]. According to an epidemiological survey of 55000 newborns, the incidence of NKH is approximately 1/63000[2]. The GCS is composed of glycine decarboxylase (P protein), aminomethyl transferase (T protein), hydrogen carrier protein (H protein), and dihydroamide dehydrogenase (L protein). The P, T, and H proteins are encoded by the GLDC (OMIM 238300), AMT (OMIM 238310), and GCSH (OMIM 238330) genes, respectively. Variations in these genes can cause a decrease in GCS activity and lead to glycine accumulation, and 70%-75% of NKH patients carry GLDC variations[3]. Here, we present the case of a young boy who presented with clinical features of NKH and was ultimately diagnosed by whole-exome genetic testing.

CASE PRESENTATION

Chief complaints
A 7-day-old male child was admitted to the neonatology department of our hospital on December 30, 2020 due to "eating less, crying less, and moving less for 7 d".

History of present illness
The patient was the firstborn child and was delivered vaginally at full term, with a birth weight of 3.75 kg. The Apgar scores at 1, 5, and 10 min after birth were all 10 points. He was provided a reasonable amount of food after birth but had low sucking power, hiccups, and occasional apnea. The mother denied a history of exposure to poisons, chemicals, or radiation and had regular prenatal examinations during pregnancy; no abnormality was found. The parents did not have blood relations.

History of past illness
No history of past illness.

Personal and family history
There was no history of family hereditary diseases.

Physical examination
Upon admission examination, the following was observed: Body temperature, 36.8 °C; heart rate, 128 beats/min; respiratory rate, 34 times/min; arterial blood pressure, 83/46 mmHg; SpO₂, 95%; slightly dry skin; poor elasticity; no rash or ecchymosis on the skin; irregular breathing; no obvious dyspnea; trachea in the middle; no abnormal breath sounds heard in both lungs. Examination of the heart and
abdomen did not reveal any abnormalities. Neurological examination showed the following: No response after stimulation; the anterior fontanelle measuring 1.0 cm × 1.0 cm that was flat and soft; hypotonia; and an inability to elicit primitive reflexes. A few hours after admission, the child was observed to have frequent apnea neonatorum.

**Laboratory examinations**

Arterial blood gas analysis showed the following: pH, 7.16 (reference range: 7.35–7.45); PCO₂, 96 mmHg (reference range: 35–45 mmHg); PO₂, 276 mmHg (reference range: 80–100 mmHg); HCO₃⁻, 34.2 mmol/L (reference range: 21.4–27.3 mmol/L); extracellular fluid base excess, 5.5 mmol/L (reference range: -3–3 mmol/L); lactic acid, 0.9 mmol/L (reference range: 0.5–2.2 mmol/L); and blood ammonia, 100 μmol/L (reference range: 18–72 μmol/L). An electroencephalogram (EEG) showed that diffuse low-amplitude irregular 1–6 Hz δ and θ waves and low-amplitude β waves were mixed in the quiet state, and the external stimulation background did not change. The EEG activity voltage was low, which represented a moderately abnormal neonatal EEG. Serum tandem mass spectrometry showed that the glycine concentration was 850.05 μmol/L (reference range: 130–650 μmol/L), and urine organic acid analysis showed no obvious abnormality. CSF glycine levels were not measured. Routine blood test, routine blood coagulation test, myocardial enzyme, C-reactive protein, procalcitonin, liver and kidney function tests, electrolyte assessment, and cerebrospinal fluid and biochemistry tests did not show obvious abnormalities.

**Imaging examinations**

Head magnetic resonance imaging (MRI) in the neonatal period (aged 7 d old) showed that a myelinated T1 hypersignal was not found in the hind limbs of the bilateral internal capsules or cerebellar dentate nucleus, and no abnormal corpus callosum was found. When the child was 2 mo old, re-examination of head MRI showed that the corpus callosum was smaller than it was on earlier imaging; the bilateral ventricles were full and irregular (more pronounced on the left side); the corticospinal tract, the white matter of bilateral ventricles, and the parietal lobe showed symmetrical high signal intensity on diffusion-weighted imaging; and the apparent diffusion coefficient map showed slightly low signal intensity (Figure 1).

**Whole-exome sequencing**

The proband has a variant on exon 8, position chr9:6620259G>T, NM_000170.3:c.395C>A, p.(Ser132*) and a variant on exon 18, position chr9:6556173C>T, NM_000170.3:c.2182G>A, p.(Gly728Arg). The p.(Ser132*) variant has been described in one individual in the gnomAD database v3.1.1 (entry: 9-6620259-G-T). Its allele frequency is 0.000006573. It is reported in dbSNP (rs386833576). According to the American College of Medical Genetics and Genomics (ACMG) guidelines, this variation was judged to be a pathogenic variation based on the supporting evidence (PVS1 + PM2 + PM3). In the pedigree analysis, the father of the proband has no mutation at this site, while the mother of the proband has a heterozygous mutation at this site. The variant p.(Gly728Arg) has been reported on ClinVar as likely pathogenic (accession number VCV000580932.2), and it has been described in dbSNP (rs386833542). Its allele frequency in gnomAD database v2.1.1 is 0.000003977. According to the ACMG guidelines, this variation was judged to be a pathogenic variation based on the supporting evidence (PSI + PM1 + PM2 + PM5 + PP3). By pedigree analysis, the father of the proband has heterozygous variation at this site, while the mother has no variation at this site. The parents of the child are heterozygous, with a normal phenotype, which is consistent with the pathogenesis of autosomal recessive compound heterozygous genetic diseases.

**FINAL DIAGNOSIS**

The final diagnosis was classical NKH and epilepsy syndrome.

**TREATMENT**

After admission, invasive ventilation, aggressive anti-infective therapy, and symptomatic treatments were given. After 1 wk, the child could obviously breathe spontaneously, the arterial blood gas analysis was basically normal after re-examination, and the ventilator was successfully withdrawn. However, during hospitalization, the child developed convulsions, characterized by loss of consciousness, staring in both eyes, clenching of fists with both hands, and chewing movements of the lips. After demonstrating rigidity of the limbs, the child quickly developed atonic seizures that lasted 15–220 s each time and occurred 3–5 times a day (Video). Re-examination by EEG still showed abnormalities. During the attack, persistent multifocal or extensive irregular sharp waves or sharp slow waves were observed, most of which were in a burst-suppression state, and the inhibition segment lasted 2–66 s (Figure 2).
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Figure 1 Head magnetic resonance imaging of the nonketotic hyperglycinemia child at the age of 2 mo. A: The corpus callosum was small (arrow); B: On diffusion-weighted imaging, the upper corticospinal tract and bilateral paraventricular and parietal white matter showed a symmetrical high signal intensity (arrow); C: Apparent diffusion coefficient diagram showed a slightly lower signal (arrow).

Figure 2 In the abnormal electroencephalogram, persistent multifocal or extensive irregular sharp waves or sharp slow waves could be seen during the interattack, most of which were in a burst-inhibition state, and the inhibition period lasted 2–66 s.

Levetiracetam was added to relieve convulsive treatment.

OUTCOME AND FOLLOW-UP

When the child was 2 months old, he had good suckling and swallowing but still had repeated convulsions, with hypotonia in the extremities. Re-examination by EEG showed a burst-inhibition state. The blood glycine level became normal. For treatment, we continued to administer an oral levetiracetam solution (60 mg/kg/d) and added topiramate (5 mg/kg/d) and prednisone (2 mg/kg/d) for epilepsy control. Unfortunately, the epilepsy of the child remained uncontrollable. Ketogenic diet therapy with a 4:1 (lipid:nonlipid) ketogenic milk formula was started at 6 mo of age, and daily calorie and protein requirements were ensured, and the child's urinary ketones were monitored daily. The number of attacks and adverse reactions were recorded during ketogenic diet treatment. On the 25th day after ketogenic treatment, the child's seizures were completely controlled, and the EEG improved after review. No serious adverse reactions occurred during the ketogenic treatment (Figure 3).
DISCUSSION

NKH is a rare inherited genetic metabolic disease with variable clinical manifestations. Three types of glycine encephalopathy have been identified according to the clinical phenotype and the presence or absence of genetic variation: Classic, atypical, and transient. Most neonatal NKH cases are classified into the classic type, showing a normal phenotype at birth. In most cases, drowsiness, coma, hiccups, hypotension, and myoclonic seizures gradually appear in the first week after birth and develop into central apnea requiring ventilator-assisted breathing, with a mortality rate as high as 50% at this time [4]. These symptoms subside on their own after 1 to 3 wk, but surviving infants experience serious nervous system sequelae within 6 mo, such as epileptic encephalopathy, developmental delay, and growth retardation [5,6]. Atypical NKH is rare and has heterogeneous and nonspecific disease courses, which make the diagnosis more difficult. If hypotonia, developmental delay, and epilepsy occur in infancy and the symptoms are milder than those of classic NKH, it is necessary to pay attention to this type of possibility. Transient NKH is even rarer; although it develops after birth, as the activity of glycine lyase increases, it may heal itself within a few months.

In NKH, serum and cerebrospinal fluid glycine levels are elevated, and the ratio of cerebrospinal fluid to plasma glycine is greater than 0.08. Absence of ketoacidosis and urine organic acid abnormalities indicate the diagnosis of NKH. However, perinatal medication (especially the use of sodium valproate), congenital intrauterine infection, and neonatal asphyxia can cause the level of neonatal glycine to rise; thus, the diagnosis ultimately depends on the pathogenic variant of the GCS genes. Notably, transient NKH has a good prognosis, but its onset is similar to that of the classic type; therefore, it is necessary to distinguish between the two. Our case showed that if the child’s symptoms gradually improve, the serum fluid glycine levels have been repeatedly tested and decrease or become normal, and the genetic test does not show any genetic mutations related to the disease, it may be a temporary type of NKH, but additional data from more cases are needed for further verification.

The child described in this report had typical clinical manifestations of NKH, such as hiccups, disturbance of consciousness, hypotonia, and convulsions, within the first week after birth. Although cerebrospinal fluid glycine was not measured, no organic acid abnormality was found by blood and urine tandem mass spectrometry and gas chromatography. Combined with the gene detection results for the child, a diagnosis of classic NKH caused by compound heterozygous variations in the GLDC gene was made. To date, only four NKH patients with compound heterozygote variations in the GLDC gene have been reported in China [7-9]. In this study, a nonsense mutation (c.395C>A) was found in the GLDC gene, which led to the replacement of serine at position 132 of the coding region by a termination codon (p.S132X), which may lead to the loss of gene function. This is the first time that this mutation has been found in the Chinese population. Compound heterozygosity with another pathogenic mutation may be the basis for the pathogenesis of NKH in this child, which enriches the variation spectrum of the GLDC gene.
A retrospective cross-sectional study showed that a small corpus callosum is the most common structural abnormality of NKH and that this structural abnormality is directly related to the severity of the clinical phenotype[10]. In this case, no abnormal corpus callosum was found on neonatal MRI, but with the development of the disease, the corpus callosum became dysplastic, suggesting that the corpus callosum could be affected by glycine metabolism. Other studies have found that EEG can evaluate the therapeutic effect at each stage and provide a clinical basis for adjusting the administration scheme and its dosage. Plasma glycine levels cannot be used to evaluate the prognosis of NKH, as this study found that a high serum glycine level can decrease or even disappear by itself, but the EEG will still show a burst-inhibition state, which further indicates that NKH is an irreversible brain injury. At present, there is no effective treatment for this rare disease, and the focus of treatment is to rationally use antiepileptic drugs to control epileptic seizures, reduce the plasma concentration of glycine by injecting sodium benzoate, and antagonize N-methyl-D-aspartate receptors by injecting ketamine or oral dextromethorphan. The ketogenic diet is a high-fat, low-carbohydrate, and moderate protein diet that is used mainly for the adjuvant treatment of drug-resistant epilepsy and epileptic encephalopathy[11]. It has been reported that a ketogenic diet has a good effect on infantile spasm, Dravet syndrome, Lennox–Gastaut syndrome, and epileptic encephalopathy caused by gene mutations such as SCN1A, KCNQ2, STXBP1, and SCN2A[12]. This case showed that a ketogenic diet may be a valuable treatment modality for refractory seizure control in classical NKH.

CONCLUSION

This study found that a high serum glycine level can decrease or even disappear on its own, indicating that plasma glycine levels cannot be used to evaluate the prognosis of NKH. With the development of the disease, the corpus callosum can be affected by glycine metabolism. A ketogenic diet may be effective for seizure control in classical NKH patients.

FOOTNOTES

**Author contributions:** Ning JJ and Li F were the patient’s doctors; Ning JJ reviewed the literature, contributed to drafting the manuscript, and provided plans for the treatment; Li SQ was the nurse in charge of the child.

**Informed consent statement:** The patient’s parents provided informed written consent for the publication of this case report.

**Conflict-of-interest statement:** All the authors report no relevant conflicts of interest for this article.

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REFERENCES


Ectopic Cushing's syndrome in a patient with metastatic Merkel cell carcinoma: A case report

Avraham Ishay, Elia Touma, Olga Vornicova, Roni Dodiuk-Gad, Tal Goldman, Naiel Bisharat

Abstract

BACKGROUND
Ectopic Cushing syndrome (ECS) is a rare condition commonly associated with neuroendocrine tumors (NET), mainly bronchial carcinoids. The association of paraneoplastic syndrome with Merkel cell carcinoma (MCC) is limited to individual case reports.

CASE SUMMARY
In this article we report an unusual and striking presentation of ECS in a patient with known metastatic MCC. An elderly patient presented with new onset severe hypertension, hyperglycemia and hypokalemia, muscle wasting, and peripheral edema. A diagnosis of adrenocorticotropic hormone dependent, non-pituitary, Cushing syndrome was established. Medical therapy inhibiting adrenal function was promptly started but unfortunately the patient survived only a few days after diagnosis.

CONCLUSION
The occurrence of an aggressive form of ECS in patients with NET should be recognized as an ominous event. To our knowledge, the association of this complication in a patient with MCC had not been reported.

Key Words: Merkel cell carcinoma; Paraneoplastic syndrome; Ectopic Cushing's
Merkel cell carcinoma (MCC) is an uncommon but highly aggressive skin cancer with neuroendocrine features. Its incidence and mortality are increasing. We describe an elderly patient with a 2-year history of metastatic MCC, with no apparent cutaneous lesion at diagnosis, who presented with uncontrolled hypertension, diabetes mellitus, and hypokalemia. A diagnosis of ectopic Cushing syndrome was established. The occurrence of ectopic Cushing syndrome in patients with neuroendocrine tumor is a major cause of poor prognosis. To our knowledge, this is the first reported case of ectopic Cushing syndrome linked to the rapid progression of a metastatic MCC.

**Core Tip:** Merkel cell carcinoma (MCC) is an uncommon but highly aggressive skin cancer with neuroendocrine features. Its incidence and mortality are increasing. We describe an elderly patient with a 2-year history of metastatic MCC, with no apparent cutaneous lesion at diagnosis, who presented with uncontrolled hypertension, diabetes mellitus, and hypokalemia. A diagnosis of ectopic Cushing syndrome was established. The occurrence of ectopic Cushing syndrome in patients with neuroendocrine tumor is a major cause of poor prognosis. To our knowledge, this is the first reported case of ectopic Cushing syndrome linked to the rapid progression of a metastatic MCC.

**INTRODUCTION**

Merkel cell carcinoma (MCC) is an uncommon but highly aggressive skin cancer with neuroendocrine features[1]. It was first described by Toker in 1972 as "trabecular carcinoma of the skin"[2]. Evidence suggests that its incidence and mortality are increasing across the world[3]. Ectopic Cushing syndrome (ECS) is a rare condition due to ectopic production of adrenocorticotropic hormone by non-pituitary tumors. The adrenocorticotropic hormone producing neoplasms usually originate from neuroendocrine tumors (NET) and can present as benign indolent tumors or aggressive metastatic tumors with a poor prognosis[4]. Although in the past elevated adrenocorticotopic hormone levels in plasma and tumoral tissue were demonstrated in patients with MCC[5,6], there are no reports of adrenocorticotropic hormone producing MCC that fulfill the diagnostic criteria for ECS. We describe a patient with metastatic MCC who developed an aggressive form of ECS.

**CASE PRESENTATION**

**Chief complaints**

An 82-year-old man with a 2-year history of MCC was referred for evaluation and treatment of uncontrolled high blood pressure and new onset hyperglycemia.

**History of present illness**

In 2018, a cervical lymphadenopathy biopsy showed metastatic MCC with no apparent primary cutaneous lesion (Figure 1). Multiple bone metastases were demonstrated by an ¹⁸F (18-fluorodeoxyglucose) PET/CT scan (¹⁸FDG-PET/CT). No pathological uptake was seen in the lungs. The patient achieved good response to avelumab initially as disclosed by a significant reduction of uptake intensity in cervical lymph nodes and in the skeleton on a subsequent ¹⁸FDG-PET/CT scan. But thereafter, the disease progressed despite adjuvant radiotherapy and systemic therapy including etoposide, carboplatin, and topotecan. Indeed, a further ¹⁸FDG-PET/CT scan showed intensification of the uptake in bones, and new metastases in mediastinal lymph nodes and multiple cutaneous lesions. Noticeably, no disease was present in the lungs.

**History of past illness**

The patient’s history was significant for multiple surgical treatments for squamous cell carcinoma and basal cell carcinoma of the skin.

**Personal and family history**

Multiple surgical treatments for squamous cell carcinoma and basal cell carcinoma of the skin.

**Physical examination**

Physical examination revealed high blood pressure (198/100), and a 4 cm-sized purplish-blue tumor in his central chest (Figure 2), bilateral axillary lymphadenopathy, and bilateral lower extremities pitting
edema. The clinical phenotype was dominated by weight loss and muscle wasting.

**Laboratory examinations**

Initial blood work revealed a glucose level of 241 mg/dL with hypokalemia (2.7 mmol/L). The 24-h free urine Cortisol level was 9986 nmol/24 hr (normal values: 57.7-806.8). After high dose (8 mg) overnight
Table 1 Cortisol and adrenocorticotropic hormone (ACTH) levels after stimulation with IV corticotropin releasing hormone 100 µg

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<tr>
<td>ACTH (pmol/mL)</td>
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dexamethasone suppression test (HDST), the 8-am serum cortisol was 44.9 µg/dL (normal values: 4.3-22.4). Serum adrenocorticotropic hormone level was elevated: 106 pg/mL (0.0-46). Testing with intravenous corticotropin releasing hormone (CRH) administration did not affect adrenocorticotropic hormone or cortisol levels, which is typical of ECS (Table 1).

**Imaging examinations**

Magnetic resonance imaging scan of the pituitary gland was normal.

**FINAL DIAGNOSIS**

Ectopic adrenocorticotropic hormone dependent Cushing’s syndrome.

**TREATMENT**

The patient was treated with ketoconazole.

**OUTCOME AND FOLLOW-UP**

The patient’s blood pressure and glucose levels were normalized; however, his general state did not allow additional antineoplastic therapy and he died within few days.

**DISCUSSION**

We present an 82-year patient with a metastatic MCC presenting with an overwhelming form of ECS. ECS is a rare condition which accounts for about 10%-20% cases of adrenocorticotropic hormone dependent Cushing syndrome. Neuroendocrine tumors (NETs), principally bronchial carcinoids, are the most frequent causes of ECS. Less frequent causes are thymic carcinoids and pancreatic NETs. Small cell lung carcinoma is a known cause of ECS, but in our patient imaging studies did not reveal any lung lesions. Recently, a case of metastatic NET of unknown origin presenting with ECS was reported. Several manifestations of MCC-associated paraneoplastic syndromes have been reported, but ECS associated with MCC has not been described, even though a case of metastatic MCC within a cortisol-producing adrenal adenoma has been recently reported. The time elapsed between the first symptoms of hypercortisolism and the diagnosis of ECS may predict the prognosis of the underlying malignancy. The shorter it is, the poorer is the prognosis. In addition to the grade of NET, the severity of cortisol excess is an independent negative prognostic factor. The molecular mechanisms underlying ECS-associated malignant tumors include aberrant processing of the proopiomelanocortin (POMC) gene leading to release in the circulation of high molecular weight adrenocorticotropic hormone precursors like POMC and pro-adrenocorticotropic hormone. It is speculated that the ability of the tumor to express aberrant molecules is related to the progression of the disease. If ectopic adrenocorticotropic hormone producing malignancy is diagnosed early as a localized disease, surgical removal of the primary tumor is the treatment of choice, but it is rarely achievable in patients with aggressive neoplasms. In this ECS group, a prompt control of hypercortisolism should be attempted by medical treatment or alternatively by adrenalectomy.

**CONCLUSION**

MCC and neuroendocrine ECS are both rare conditions. The occurrence of ECS in patients with metastatic NETs is a major cause of poor prognosis. The suspicion of Cushing syndrome should receive adequate attention and prompt evaluation to confirm the diagnosis and initiate rapidly the treatment.
FOOTNOTES

Author contributions: Ishay A and Touma E were the patient's physicians, wrote the manuscript, and reviewed the literature; Vornicova O, Doduìk Gad, and Bisharat N were involved in the patient treatment and contributed to manuscript drafting; Goldman T was the pathologist and prepared and interpreted the pathology images.

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attain a more favorable prognosis.
Occurrence of MYD88L265P and CD79B mutations in diffuse large b cell lymphoma with bone marrow infiltration: A case report

Wen-Ye Huang, Zhi-Yun Weng

Abstract

BACKGROUND
Over the past 20 years, we have gained a deep understanding of the biological heterogeneity of diffuse large B cell lymphoma (DLBCL) and have developed a range of new treatment programs based on the characteristics of the disease, bringing us to the era of immune-chemotherapy. However, the effectiveness and molecular mechanisms of targeted-immunotherapy remain unclear in DLBCL. Targeted-immunotherapy may be beneficial for specific subgroups of patients, thus requiring biomarker assessment.

CASE SUMMARY
Here, we report a case of MCD subtype DLBCL with MYD88L265P and CD79B mutations, considered in the initial stage as lymphoplasmic lymphoma (LPL) or Waldenstrom macroglobulinemia (WM). Flow cytometry supported this view; however, the immunohistochemical results of the lymph nodes overturned the above diagnosis, and the patient was eventually diagnosed with MCD subtype DLBCL. The presence of a monoclonal IgM component in the serum and infiltration of small lymphocytes with a phenotype compatible with WM into the bone marrow led us to propose a hypothesis that the case we report may have transformed from LPL/WM.

CONCLUSION
This highlights the possible transformation from WM to DLBCL, CD79B mutation may be a potential biomarker for predicting this conversion.

Key Words: Bone marrow infiltration; Case report; CD79B; Diffuse large B cell lymphoma; Ibrutinib; MYD88L265P

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Core Tip: This report highlights the possible transformation from Waldenstrom macroglobulinemia (WM) to diffuse large B cell lymphoma (DLBCL). Bone marrow infiltration by small lymphocytes, with an immunophenotype compatible with WM and the presence of MYD88L265P and CD79B mutations, support the hypothesis that the case may have transformed from lymphoplasmic lymphoma/WM. The CD79B mutation may be a potential biomarker for predicting the conversion of WM to DLBCL. Understanding the biology and mechanisms behind this process is important to identify susceptible patients. Frail patients could benefit from personalized low toxicity therapeutic approaches based on their mutational profile.

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URL: https://www.wjgnet.com/2307-8960/full/v10/i22/7994.htm
DOI: https://dx.doi.org/10.12998/wjcc.v10.i22.7994

INTRODUCTION

The cell of origin (COO) is determined by the algorithm of Hans; thus, diffuse large B cell lymphoma (DLBCL) cases can be classified as germinal center B-cell-like (GCB) or non-GCB[1]. With the progression of clinical practice, COO has been found to be insufficient to explain different treatment responses. The biological heterogeneity of DLBCL may be directly due to its various genetic abnormalities related to its pathogenesis. Common genetic abnormalities in DLBCL include MYD88L265P, CD79B, BCL2, BCL6, EZH2, NOTCH2, and NOTCH1[2]. Among them, reports of CD79B and MYD88L265P are not uncommon, which are significantly related to the molecular typing of DLBCL.

CD79 is a transmembrane protein comprising two distinct peptide chains, CD79A and CD79B, which form a molecular complex with B-cell receptor (BCR). The cytoplasmic ends of the two peptide chains of CD79 contain an immunoreceptor tyrosine-based activation motif, which is involved in activating the nuclear factor kappa light chain enhancer of activated B cell (NF-κB) signaling pathway during antigen-mediated BCR activation[3]. Myeloid differentiation primary response 88 (MYD88) is a soluble adaptor protein in the cytoplasm; it belongs to the Toll/interleukin-1 receptor and death domain family members and mediates NF-κB signaling[4]. A mutation in CD79B was detectable in 30% of patients with ABC DLBCL and 3% of those with GCB DLBCL. In addition, MYD88 mutations were detected in 28% of ABC DLBCL[5]. They play an important role in DLBCL evolution. In recent years, with extensive research on multi-platform genomes, DLBCL was divided into seven genetic subtypes[2]; DLBCL with MYD88L265P and CD79B mutations were defined as the MCD genetic subtype, 42% of which had double concomitant mutations, mostly observed in the ABC subtype[2].

Here, we present a rare DLBCL case with mutations positive for MYD88L265P and CD79B, named MCD genetic subtype, characterized by discordant bone marrow (BM) infiltration, which may have transformed from indolent lymphoma.

CASE PRESENTATION

Chief complaints
Fever and fatigue.

History of present illness
An 84-year-old bedridden man presented to the clinic with complaints of fever and fatigue and was hospitalized on January 2021.

History of past illness
He had been taking medication for hypertension and diabetes for more than 10 years and underwent interventional treatment for coronary atherosclerotic heart disease 4 years prior.

Personal and family history
He had no history of viral hepatitis B or family history of cancer.

Physical examination
Rales could be heard in the lungs, and edema was visible in the lower extremities.
Laboratory examinations
A laboratory exam revealed normocytic anemia (hemoglobin 66 g/L), elevated C reactive protein (169 mg/L), and hydrogen hexachloro platinum (III).

Imaging examinations
B mode ultrasonography showed several swollen cervical lymph nodes, with the largest being 1.7 cm × 1.1 cm with an abnormal structure. An abdominal computed tomography scan with contrast revealed pulmonary infection, no evidence of splenomegaly, and multiple enlarged lymph nodes in the mediastinum and abdominal region, with a maximum size of 2.5 cm × 2.5 cm (Figure 1). We completed the routine examination of the BM, and no abnormal cells were detected in the smear. However, using BM as a specimen, flow cytometry identified a group of abnormal monoclonal B cells that showed restricted expression of the intracellular kappa light chain. This group of B cells tested positive for CD19, CD20, and CD79b and were negative for CD5, CD10, CD23, and FMC7 (Figure 2). The morphology of the BM biopsy suggested that small B-cell lymphomas were scattered, indicating that the disease involved the BM (Figure 3).

In the case of monoclonal small B-lymphocyte tumors, chronic lymphocytic leukemia (CLL), lymphoplasmacytic lymphoma (LPL), and Waldenstrom macroglobulinemia (WM) should be considered. However, patients with CLL usually also express CD5 and CD23, and the peripheral blood is involved; this patient did not have these characteristics. Our case was characterized by IgM monoclonal gammopathy without plasmacytoid changes. To further confirm the diagnosis, we performed a biopsy of the patient’s cervical lymph nodes. The immunohistochemical results of the lymph nodes are as follows (Figure 4): Bcl-2(+); Bcl-6(+); CD10(-); CD20(+); CD3(-); CD5(-); CMYC(40%); CyclinD1(-); Ki67(70%); MUM-1(+); P53(60%).

FINAL DIAGNOSIS
The immunohistochemical results support the diagnosis of subtype activated B-cells like that of DLBCL [stage IV B, National Comprehensive Cancer Network International Prognostic Index (IPI) ≥ 6, Eastern Cooperative Oncology Group performance score = 4]. Interestingly, the patient had MYD88L265P and CD79B mutations.

TREATMENT
Ibrutinib is an irreversible small-molecule BTK inhibitor and a B lymphocyte signaling protein, which can effectively inhibit the proliferation and survival of malignant B lymphocytes[6]. Studies have found that compared with GCB subtypes, ibrutinib has a better effect on patients with ABC DLBCL[7]. More importantly, the combined application of ibrutinib and rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone can significantly increase the toxicity of the drug for patients aged ≥60 years, which in turn affects the therapeutic effect[8]. The patient could not tolerate chemotherapy. After a comprehensive assessment, the patient was treated with I-R (ibrutinib 420 mg/d combined with rituxan...
Figure 2 Flow cytometry shows monotypic kappa light chain restricted B cells that tested positive for CD19, CD20, and CD79b, and negative for CD5, CD10, CD23, and FMC7.

Figure 3 B lymphocytes had a scattered distribution (about 10%). A, B: Histomorphology suggests that small B lymphocytes infiltrated the bone marrow (A, 10 x; B, 20 x); C, D: The expression of CD20 can be detected by immunohistochemistry (D, 20 x), and the positive rate of Ki-67 is less than 5% (C, 10 x).
OUTCOME AND FOLLOW-UP
Unfortunately, due to financial pressure and being long-term bedridden, this patient eventually refused to receive further treatment and died two months later.

DISCUSSION
Multiple studies have shown that the MYD88 mutation is present in 90% of patients with LPL/WM; however, it is not specific to LPL/WM and is also present in DLBCL. Further research confirmed that the MYD88L265P mutation is unique to ABC and rarely occurs in GCB or primary mediastinal diffuse large B-cell lymphoma[5]. Studies have reported that continuous excessive activation of the NF-κB signaling pathway is characteristic of ABC-DLBCL. Dubois et al[9] further emphasized that activation of the NF-κB signaling pathway in the ABC subtype is related to the L265P mutation site, whereas non-L265P mutants harbor a mutational profile more similar to GCB-DLBCL. The impact of MYD88L265P and CD79B mutations on the prognosis of the ABC type is worth discussing, and most reports have shown that these two mutations negatively affect patient outcomes. One study showed that MYD88L265P and CD79B increase the risk of recurrence and progression. In addition, detection of the MYD88L265P mutation can effectively improve the predictive performance of the IPI scores[10]. Using next generation sequencing to detect 361 cases of DLBCL, a study showed that CD79B and MYD88L265P synergistically enhance activation of the NF-κB pathway[9]. Wilson et al[7] designed a phase II clinical trial involving 80 patients with relapsed or refractory DLBCL; ibrutinib had a good therapeutic effect on 80% of patients with CD79B and MYD88L265P dual mutations, whereas the seven patients with MYD88L265P mutations/CD79B wild-type cases did not show any response (0/7), suggesting that the MYD88L265P/CD79B dual mutation DLBCL may represent a unique group with stronger sensitivity to BTK inhibitors, which may be related to the CD79B-dependent BCR activation pathway.

The mechanism of the emergence of monoclonal IgM is unclear; it may be related to the differentiation of plasma cells in the BM[11]. Cox et al[12] analyzed 151 patients with DLBCL and found that 17 cases (11.2%) had a serum monoclonal IgM component, although none were associated with...
Table 1 Summary of previously published series of cases

<table>
<thead>
<tr>
<th>Ref.</th>
<th>No. of case</th>
<th>A/G</th>
<th>BM</th>
<th>Extramedullary site</th>
<th>Histological type</th>
<th>Staging</th>
<th>Therapy</th>
<th>Interval (mo)</th>
<th>Ending</th>
<th>Survival (mo)</th>
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</thead>
<tbody>
<tr>
<td>Uchino et al [18]</td>
<td>1</td>
<td>55/M</td>
<td>+</td>
<td>Spleen</td>
<td>Nospecified</td>
<td>IV B</td>
<td>R-CHOP</td>
<td>408</td>
<td>CR</td>
<td>&gt; 17</td>
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<tr>
<td>Owen et al [19]</td>
<td>2</td>
<td>80/M</td>
<td>+</td>
<td>Mesenteric mass</td>
<td>ABC</td>
<td>IV</td>
<td>R-CVP</td>
<td>36</td>
<td>Dead</td>
<td>No specified</td>
</tr>
<tr>
<td>Owen et al [19]</td>
<td>3</td>
<td>63/M</td>
<td>+</td>
<td>Lymphadenopathy</td>
<td>GCB</td>
<td>IV</td>
<td>R-CHOP</td>
<td>84</td>
<td>PR</td>
<td>No specified</td>
</tr>
<tr>
<td>Shiseki et al [20]</td>
<td>4</td>
<td>63/M</td>
<td>+</td>
<td>Lymph node</td>
<td>No specified</td>
<td>IV</td>
<td>THP-COP</td>
<td>36</td>
<td>CR</td>
<td>&gt; 60</td>
</tr>
<tr>
<td>Kikukawa et al [21]</td>
<td>5</td>
<td>60/F</td>
<td>+</td>
<td>Brain</td>
<td>ABC</td>
<td>IV</td>
<td>R-MPV, WBRT+Ara-C</td>
<td>72</td>
<td>PR</td>
<td>&gt; 6</td>
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<tr>
<td>Okolo et al [22]</td>
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<td>69/M</td>
<td>+</td>
<td>Retroperitoneal mass</td>
<td>No specified</td>
<td>IV</td>
<td>R-CHOP, DRC</td>
<td>Unknown</td>
<td>CR</td>
<td>No specified</td>
</tr>
<tr>
<td>Kobayashi et al [23]</td>
<td>7</td>
<td>75/M</td>
<td>+</td>
<td>Liver and ileum</td>
<td>GCB</td>
<td>IV</td>
<td>R-CHOP</td>
<td>120</td>
<td>PR</td>
<td>No specified</td>
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<tr>
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<td>60/M</td>
<td>+</td>
<td>Inguinal lymph node</td>
<td>ABC</td>
<td>IV A</td>
<td>O+CHOP, DHAP</td>
<td>168</td>
<td>Dead</td>
<td>4</td>
</tr>
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1. Interval from the diagnosis of lymphoplasmic lymphoma/Waldenstrom macroglobulinemia to the diagnosis of diffuse large B cell lymphoma.

BM: Bone marrow; CR: Complete response; PR: Partial response; R-CVP: Rituximab, cyclophosphamide, vincristine, prednisone; R-CHOP: Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; THP: Epirubicin; R-MPV: Methotrexate, vincristine, procarbazine; WBRT: Whole-brain radiation; Ara-C: Cytarabine; DRC: Desamethasone, rituximab, cyclophosphamide; O: Obinutuzumab; DHAP: Cisplatin, cytarabine, desamethasone.

MYD88L265P mutations, which indicates there is no necessary connection between monoclonal IgM and MYD88L265P. Cho et al [13] studied the relationship between the clonal status of monoclonal immunoglobulin gene rearrangement and histological B cell aggregation in the BM. The results showed that of the 394 patients with DLBCL, 32 patients had BM invasion, and only two patients with large B cell lymphoma had no gene rearrangement detected [13]. This suggests that patients with BM invasion were more likely to have monoclonal immunoglobulin gene rearrangements. However, there is no correlation with the COO [13]. Although BM infiltration was found in our case, it showed a histological inconsistency compared with the immunohistochemistry of the peripheral lymph nodes. Regarding the biological and clinical impact, discordant BM infiltration was associated with lower progression free survival and a higher incidence of central nervous system relapse independent of the COO and IPI; therefore, the prognostic impact of discordant BM infiltration could be limited to non-CGB cases [14].

The most interesting part of this case is the possible transformation from WM to DLBCL. We support this hypothesis on two pillars: the presence of a monoclonal IgM component in the serum and infiltration of small lymphocytes with a phenotype compatible with WM into the BM. Castillo et al [15] retrospectively analyzed 1446 patients with WM; a total of 20 patients underwent histological transformation. Interestingly, all 20 patients had tissue transformation to DLBCL and had a high IPI score. The median survival time after transformation was not more than 3 years. Among them, 13 patients were tested for Ki67 expression, and it was found that their median value-added index was 90% (range 50%-99%), which suggests that the malignancy in these patients is higher. Two cases in this study were tested for MYD88L265P mutations before and after histological transformation, and the results were positive [15]. This also suggests that ibrutinib may be a potential treatment option for these histological conversion cases. Regarding the biological analysis of patients with diffuse large B lymphoma with BM infiltration, 24% of patients have discordant BM involvement, which manifested as infiltration by small cells forming lymphoid aggregates. This group, classified by flow cytometry (FCM), showed a wide variety of indolent B-cell lymphomas, although only one case showed DLBCL [14]. Genomic analysis technology can further determine whether this group of patients has transformed from indolent lymphoma [16]. As the transformation from WM to DLBCL is very rare, relevant literature on this was collected (Table 1).

The other interesting hypothesis concerns the role of mutations in CD79B in the transformation to DLBCL. A small sample study found that CD79B mutations may be a potential biomarker for predicting the conversion of WM to DLBCL [16]. We propose a transformation hypothesis on the basis of the antiapoptotic NF-kB pathway. The mutation of MYD88 is the most important pathogenic mechanism of LPL/WM. When LPL/WM acquires the mutation of CD79B, the reduced activity of LYN contributes to their increased surface BCR expression and constitutive BCR signaling. Chronically active BCR signaling and MYD88L265P-dependent signaling synergy promotes the conversion of WM to DLBCL (Figure 5). However, the genetic pathogenesis is a complex process that may incorporate other genetic
Figure 5 Nuclear factor-κB activation through the classical pathway is a hallmark of the ABC diffuse large B cell lymphoma subtype. MYD88 is an adapter protein that couples TIR-containing receptors, regulating downstream signaling circuits, including the nuclear factor (NF)-κB. MYD88 coordinates the IRAK family kinases into a helical signaling complex through the interaction with the IRAK kinase. Phosphorylation of IRAK1 by IRAK4 will allow for the recruitment of the ubiquitin ligase TRAF6 and the activation of the downstream pathways. The mutation in MYD88L265P forms a stable, phosphorylated form of IRAK1, which upregulates gene expression signatures of NF-κB. The BCR consists of IgL and IgH chains that are noncovalently coupled to the CD79B (Ig-β) and CD79A (Ig-α) subunits, which regulate BCR surface trafficking, internalization, and expression. Upon antigen encounter, the BCR, CD79A and CD79B transmit signals to multiple downstream signaling pathways. Once BTK is recruited to the BCR signaling complex, LYN or SYK can phosphorylate and activate BTK. In turn activate PKCβ, leading to phosphorylation of CARD11 and activation of NF-κB. CBM complex, a signaling hub consisting of CARD11, BCL10, MALT1, and other proteins, which is required for the activation of classical NF-κB pathway in lymphocytes.

changes to facilitate its transition to DLBCL. Schmitz et al[17] proposed the classification of genetic subtypes that uncovered the interrelationship between this genetic nosology and the oncogenic signaling pathway. MYD88L265P and CD79B played an important role in the evolution of WM to DLBCL, which fits the genetic characteristics of the MCD genetic subtype. It further explains why the MCD genetic subtype responds to ibrutinib[7].

In summary, with the development of genetic testing technology, research has further focused on the classification of DLBCL and its pathogenic mechanism. In the era of immune-chemotherapy, the molecular classification of DLBCL appears to offer greater prognostic interest than IPI. Furthermore, the molecular profile could help us in the choice of the optimal therapy. Ibrutinib appears a good option in patients with MCD molecular subtype DLBCL: MYD88+ CD79B+. Bone marrow infiltration by small lymphocytes, with an immunophenotype compatible with WM and the presence of MYD88L265P and CD79B mutations, supports the hypothesis that the case may have transformed from LPL/WM. Furthermore, frail patients could benefit from personalized low toxicity therapeutic approaches based on their mutational profile.
CONCLUSION

The CD79B mutation may be a potential biomarker for predicting the conversion of WM to DLBCL. Understanding the biology and mechanisms behind this process is important in identifying susceptible patients.

FOOTNOTES

Author contributions: Weng ZY provided direction and guidance throughout the preparation of this manuscript and drafted the paper; Huang WY contributed to data analysis; and all authors have read and approved the final manuscript.

Informed consent statement: Written consent was obtained from the patient’s family to participate in the study.

Conflict-of-interest statement: The authors declare that they have no conflicts of interest to disclose.

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10.1038/nn.3884


[PMID: 30901302 DOI: 10.1200/JCO.18.02403]


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Rare case of compartment syndrome provoked by inhalation of polyurethane agent: A case report

Jun Ho Choi, Hyun Myung Oh, Jae Ha Hwang, Kwang Seog Kim, Sam Yong Lee

BACKGROUND
The most common causes of compartment syndrome in the lower extremities include lower limb fractures, trauma-induced crushing injuries, severe burns, and non-traumatic factors. However, there have been no reports of compartment syndrome secondary to toxic inhalation.

CASE SUMMARY
A 59-year-old man, who lost consciousness after applying polyurethane-based paint on a water tank, was brought to the emergency room. The initial blood test showed apparent rhabdomyolysis. One day later, pain and swelling in both legs were observed, and the physical examination confirmed the presence of compartment syndrome. Double-incision fasciotomy was performed on both legs. Frequent dressings and negative pressure wound treatment were done on both legs, and skin grafting was performed after healthy granulation tissue had been identified. No other complications were observed after treatment. However, symptoms of peroneal neuropathy, particularly limited ankle dorsiflexion and reduced sensation on the lower extremities, were observed.

CONCLUSION
Workers using polyurethane agents should wear gas masks and be evaluated for compartment syndrome and rhabdomyolysis secondary to toxic inhalation.

Key Words: Compartment syndrome; Polyurethanes; Rhabdomyolysis; Hypoxia; Peroneal neuropathies; Case report

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**Core Tip:** Compartment syndrome secondary to non-traumatic etiology is often diagnostically challenging based solely on history taking and may be misdiagnosed in the absence of comprehensive physical evaluation. Moreover, to date, no study has reported compartment syndrome caused by inhalation toxicity. We report a rare case of compartment syndrome secondary to polyurethane inhalation.

**Citation:** Choi JH, Oh HM, Hwang JH, Kim KS, Lee SY. Rare case of compartment syndrome provoked by inhalation of polyurethane agent: A case report. *World J Clin Cases* 2022; 10(22): 8003-8008

**URL:** https://www.wjgnet.com/2307-8960/full/v10/i22/8003.htm

**DOI:** https://dx.doi.org/10.12998/wjcc.v10.i22.8003

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**INTRODUCTION**

According to Matsen, compartment syndrome occurs when increased pressure within a limited space compromises the circulation and function of tissues within that space[1]. It is a medical emergency, that necessitates immediate intervention, to avoid complications, such as muscle ischemia, neuropathy, and necrosis, which may result in limb amputation[2]. Compartment syndrome is a common complication of lower extremity fractures, trauma-induced crush injuries, severe burns, and some non-traumatic conditions[3]. Compartment syndrome secondary to a non-traumatic etiology is difficult to diagnose based on history taking only, and it may be misdiagnosed, based on an incomplete physical evaluation. Moreover, there have been no studies documenting the development of compartment syndrome secondary to inhalation toxicity. This study reports a rare case of compartment syndrome secondary to polyurethane inhalation.

**CASE PRESENTATION**

**Chief complaints**
A 59-year-old man, who lost consciousness after applying polyurethane-based paint to a water tank, was brought to the emergency department.

**History of present illness**
The patient was found lying prone in the tank one hour after he had entered. He did not wear a mask to protect against the inhalation of harmful chemicals while painting the water tank (a closed space of 32000 L).

**History of past illness**
The patient denied a history of diseases that could have triggered such a medical condition such as intense physical activities.

**Personal and family history**
The patient had no previous disease history.

**Physical examination**
There were no noted signs of trauma in the lower extremities and other regions of the body.

**Laboratory examinations**
The initial blood test results suggested rhabdomyolysis with an increased serum creatine kinase of 15250 IU/L and myoglobin greater than 20000 IU/L. The blood urea nitrogen and creatinine values remained within the normal range, but the alanine transaminase and aspartate transaminase reached up to 917 and 3765 IU/L, respectively. The electrocardiogram showed sinus tachycardia with nonspecific T wave abnormalities, which indicated an electrolyte imbalance without significant cardiac injuries.

**Imaging examinations**
No imaging studies were performed.
Final Diagnosis

One day after admission, the patient developed pain and edema of the lower extremities, and the physical examination confirmed the presence of compartment syndrome. It is characterized by pain, pallor, paresthesia, pulselessness, and paralysis, which are typically referred to as the 5Ps of compartment syndrome (Figure 1). The intracompartmental pressure in the lower extremities ranged from 100 to 130 mmHg in all fascial compartments.

Treatment

The patient was admitted to the intensive care unit (ICU), and extensive hydration and hyperbaric oxygen therapy were initiated to manage the acute drug intoxication syndrome, accompanied by rhabdomyolysis. No glucocorticoid or dehydration diuretics were administered during the patient’s course in ICU.
Bilateral lower extremity fasciotomy was performed on the lateral and medial aspects of the extremities to relieve the pressure in the anterior, lateral, superficial posterior, and deep posterior compartments (Figure 2). The pain, pallor, and paresthesia improved in both lower extremities postoperatively. Frequent dressing changes using betadine-soaked gauze and weekly serial debridement were performed for wound management.

One month later, the dressing method was shifted to negative-pressure wound therapy. Growth of healthy granulation tissue within the wound was observed three months later, and meshed split-thickness skin grafting was performed (Figure 3).

OUTCOME AND FOLLOW-UP
The patient showed no other signs of compartment syndrome. However, he developed symptoms of peroneal neuropathy, particularly limited ankle dorsiflexion and sensory loss in areas of the lower extremities innervated by the peroneal nerve. Nerve conduction studies were performed to evaluate the motor and sensory functions of the left and right lower extremities (Table 1). The patient’s symptoms gradually improved, but complete recovery of the nerve functions has not been achieved. Therefore, further physical treatment is required.

DISCUSSION
Polyurethane polymers are highly stable materials that are primarily used in fabrics and paints[4]. Due to its high risk of respiratory toxicity, routine room ventilation or working outside is advised when using polyurethane polymers[5]. Polyurethane inhalation within a closed space without a protective mask possibly resulted in the loss of consciousness and rhabdomyolysis in this patient.

Rhabdomyolysis is associated with traumatic and non-traumatic etiologies, including infections, drugs, and toxin inhalation[6]. Carbon monoxide (CO), one of the most common environmental toxins, has reportedly caused various medical conditions, including muscle injury and consequent rhabdomyolysis[7]. In this case, the rhabdomyolysis was attributed to polyurethane inhalation-induced injury, which was similar to that associated with CO intoxication. However, a similar clinical presentation has not been reported in previous studies. The underlying mechanism behind polyurethane-induced muscle injury remains unknown. Melandri et al[8] presented a case of prolonged hypoxia due to opiate overdose, resulting in rhabdomyolysis and myocardial damage. This was similar to the present case in that toxic inhalation induced hypoxia, rhabdomyolysis, and compartment syndrome. Acute compartment syndrome of the extremities most commonly results from traumatic injuries, such as long bone fractures, severe burns, and crush injuries[9]. Additional risk factors include age, sex, and bleeding tendency[10]. It is difficult to diagnose, particularly in patients with a vague history and no identifiable cause. In the present case, the causal relationship between polyurethane inhalation and compartment syndrome was not established. However, other attributable causes were not identified for the patient’s
Table 1 Electrodiagnostic testing results. Initial test results done right after the fasciotomy suggested that the patient developed both peroneal and tibial neuropathy.

<table>
<thead>
<tr>
<th>Needle electromyography</th>
<th>Initial</th>
<th>After eight months</th>
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<tbody>
<tr>
<td><strong>Right lower limb</strong></td>
<td></td>
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<tr>
<td>Extensor digitorum brevis</td>
<td>Spontaneous activity</td>
<td>Abnormal activity</td>
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<tr>
<td>MUAPs</td>
<td>No MUAPs</td>
<td>No MUAPs</td>
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<tr>
<td>Abductor hallucis</td>
<td>Spontaneous activity</td>
<td>Abnormal activity</td>
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<td>MUAPs</td>
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<tr>
<td>Tibialis anterior</td>
<td>Spontaneous activity</td>
<td>-</td>
</tr>
<tr>
<td>MUAPs</td>
<td>-</td>
<td>DIP, normal MUAPs</td>
</tr>
<tr>
<td>Peroneus longus</td>
<td>Spontaneous activity</td>
<td>-</td>
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<tr>
<td>MUAPs</td>
<td>-</td>
<td>PIP, normal MUAPs</td>
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<tr>
<td>Gastrocnemius (medial head)</td>
<td>Spontaneous activity</td>
<td>-</td>
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<tr>
<td>MUAPs</td>
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<td>DIP, normal MUAPs</td>
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<tr>
<td><strong>Left lower limb</strong></td>
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<tr>
<td>Extensor digitorum brevis</td>
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<td>Peroneus longus</td>
<td>Spontaneous activity</td>
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<td>MUAPs</td>
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<td>PIP, normal MUAPs</td>
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<tr>
<td>Gastrocnemius (medial head)</td>
<td>Spontaneous activity</td>
<td>-</td>
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<tr>
<td>MUAPs</td>
<td>-</td>
<td>DIP, polyphasic MUAPs</td>
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</table>

MUAP: Motor unit action potential; DIP: Discrete interference pattern; PIP: Partial interference pattern. The full test was not completed due to the wound status. Electromyography done eight months after suggested that the patient developed both incomplete peroneal and tibial neuropathy. Motor unit action potential and conduction study indicated that the left lower limb had some regeneration evidence, but no significant changes were observed compared to the previous test.

disease. Therefore, toxic inhalation was likely involved in the development of rhabdomyolysis and compartment syndrome[11]. Polyurethane-induced asphyxiation likely induced prolonged hypoxia and consequent muscle injury[12].

The accurate diagnosis and prompt management of acute compartment syndrome are important to avoid permanent neurological and functional injuries of the extremities, fatal necrosis, and even amputation. Eliminating the probable cause by performing an emergency reduction of the long bone fractures, followed by immediate fasciotomy (the only available treatment for compartment syndrome), is indicated in patients suspected of acute compartment syndrome[13,14]. Double-incision fasciotomy is the most frequently used technique because it allows access to all four compartments of the lower extremities[15]. In the present case, an immediate fasciotomy was performed at the time of consultation for surgical intervention. Although nerve injury was not observed intraoperatively, the patient developed peroneal neuropathy later in the course of treatment.

**CONCLUSION**

Workers, using polyurethane agents in confined spaces, must wear protective gear, including a gas mask. A thorough physical evaluation is essential to avoid a missed diagnosis and to exclude toxic inhalation-induced rhabdomyolysis in patients, presenting with compartment syndrome. Considering other diagnoses and radiological evaluation findings is an appealing option, but the subsequent delay results in unwanted complications. Therefore, rhabdomyolysis and compartment syndrome should be considered in the differential diagnosis, and fasciotomy should be the preferred treatment option in patients with the aforementioned clinical presentation.
Choi JH et al. Rare case of compartment syndrome

FOOTNOTES

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Acute ischemic Stroke combined with Stanford type A aortic dissection: A case report and literature review

Zhi-Yang He, Lin-Peng Yao, Xiao-Ke Wang, Nai-Yun Chen, Jun-Jie Zhao, Qian Zhou, Xiao-Feng Yang

BACKGROUND
Acute aortic dissection (AAD) is a high mortality disease that can lead to acute ischemic strokes (AIS). Some of the patients with AAD combined with AIS initially present with neurological symptoms, which can easily lead to missed or delayed AAD diagnosis. This is attributed to the lack of physician awareness or the urgency of patient thrombolysis. Intravenous administration of thrombolytic therapy (IVT) for AAD is associated with poor prognostic outcomes. We report a patient with AIS combined with AAD who developed a massive cerebral infarction after receiving IVT for a missed AAD diagnosis.

CASE SUMMARY
A 49-year-old man was admitted to a local hospital with an acute onset of left-sided limb weakness accompanied by slurred speech. The patient had a history of hypertension that was not regularly treated with medication. Physical examination revealed incomplete mixed aphasia and left limb hemiparesis. Cranial computed tomography (CT) scan showed bilateral basal ganglia and lateral ventricular paraventricular infarct lesions. The patient was diagnosed with AIS and was administered with IVT. After IVT, patient’s muscle strength and consciousness deteriorated. From the local hospital, he was referred to our hospital for further treatment. Emergency head and neck CT angiography (CTA) scans were performed. Results showed multiple cerebral infarctions, and aortic dissection in the ascending aorta, innominate artery, as well as in the right common carotid artery. Then, the CTA of thoracoabdominal aorta was performed, which revealed a Stanford type A aortic dissection and aortic dissection extending...
from the aortic root to the left external iliac artery. Laceration was located in the lesser curvature of the aortic arch. AAD complicated with AIS was considered, and the patient was immediately subjected to cardiovascular surgery for treatment. The next day, the patient underwent aortic arch and ascending aortic replacement and aortic valvuloplasty.

CONCLUSION
Clinical manifestations for AAD combined with AIS are diverse. Some patients may not exhibit typical chest or back pains. Therefore, patients should be carefully evaluated to exclude AAD before administering IVT in order to avoid adverse consequences.

Key Words: Acute aortic dissection; Acute ischemic stroke; Intravenous thrombolysis; Ultrasound evaluation; Case report

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Core Tip: Acute aortic dissection (AAD) is a high mortality condition that can lead to acute ischemic stroke (AIS). A patient was treated with thrombolytic therapy in a local hospital for AIS but his symptoms did not improve and progressed to a large cerebral infarction. The patient was eventually diagnosed with AAD. This is a rare case and we should rule out AAD before thrombolysis in patients with cerebral infarction.

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DOI: https://dx.doi.org/10.12998/wjcc.v10.i22.8009

INTRODUCTION
For patients with acute ischemic stroke (AIS) presenting with moderate to severe neurological deficits, intravenous rt-PA within 4.5 h of symptom onset remains the standard treatment option in the absence of contraindications to thrombolytic therapy[1]. Some patients with acute ischemic cerebral infarction present themselves to hospitals with little time left for thrombolysis, however, patient care should involve ruling out conditions associated with increased risks of hemorrhagic complications, such as acute aortic dissection (AAD), before administering thrombolytic therapy.

Because of the extension of the dissection into the common carotid artery, the prevalence of cerebral infarction in patients with Stanford type A aortic dissection cases is approximately 6%[2]. The most common presentation of AAD is a sudden onset of severe chest or back pains, without evidence of myocardial ischemia. However, a subset of AAD patients initially present with neurologic symptoms, including transient or permanent central neurologic symptoms (such as syncope) and various spinal symptoms (such as paralysis or paraplegia)[3]. The AAD patients that present with neurological symptoms can easily be misdiagnosed. Because of the high risk of aortic arch or ascending aortic rupture, AAD is a contraindication for thrombolytic therapy[4].

A patient with AAD combined with cerebral infarction was diagnosed with cerebral infarction at a local hospital and administered with thrombolytic therapy. Then, the patient was referred to our hospital for further treatment. He was found to have cerebral infarction combined with AAD, and was surgically treated. We intend to use this case report and literature review to provide basis for clinical practice.

CASE PRESENTATION
Chief complaints
The main complaint was left-sided limb weakness and slurred speech.

History of present illness
A 49-year-old middle-aged man was admitted to a local hospital with a sudden onset of left-sided limb weakness and slurred speech for 1 h. The patient was conscious upon admission and had no discomforts, such as headaches or chest pain.
History of past illness
He had a previous history of hypertension and was not on any oral medications to control blood pressure.

Personal and family history
He denied any family history of brain diseases.

Physical examination
Clinical examination upon admission revealed consciousness, incomplete mixed aphasia, grade 2 muscle strength in the left upper extremity, grade 0 muscle strength in the left lower extremity, and normal muscle strength in the right limb.

Laboratory examinations
Blood tests were performed. Routine blood tests: leukocyte counts, 15.8 × 10^9/L; platelet counts, 119 × 10^9/L; erythrocytes, 4.95 × 10^12/L; and calcitoninogen, 4.49 ng/mL. Cardiac enzyme profiling revealed: lactate dehydrogenase, 768 U/L; creatine kinase, 1743 U/L; creatine kinase isoenzyme, 74 U/L. Blood gas analysis revealed: lactate, 2.5 mmol/L. With regards to coagulation function, prothrombin time was 15.2 s, with an international standardized ratio of 1.27, prothrombin time was 18.4 s, fibrinogen was 1.07 g/L, and D-dimer was 7.190 mg/L.

Imaging examinations
Cranial computed tomography (CT) scan revealed bilateral basal ganglia and lateral ventricular paraventricular infarct lesions (Figure 1). This patient had a National Institute of Health Stroke Scale score of 9. In this patient, recombinant tissue fibrinogen activator was used to perform intravenous thrombolysis (IVT). The patient became less conscious and had grade 0 muscle strength in the left limb. On the next day, he was transferred from the local hospital to our hospital for further treatment. He was examined at our hospital and found to have a D-dimer greater than 100000 mg/L. Cranial CT was performed, which revealed multiple cerebral infarctions in the right basal ganglia (Figure 2A) and right frontotemporoparietal (Figure 2B). CT perfusion showed multiple ischemic cores in the right frontotemporoparietal lobe as well as relatively extensive hypoperfusion areas (Figure 3). Emergency head and neck CT angiography (CTA) revealed aortic dissection in the ascending aorta, innominate artery, and right common carotid artery. Then, CTA of thoracoabdominal aorta was performed, which revealed aortic dissection in the ascending aorta, innominate artery, right common carotid artery, abdominal trunk, common hepatic artery, splenic artery, superior mesenteric artery, left common iliac artery, and left external iliac aorta (Figure 4). CTA revealed a Stanford type A aortic dissection that extended from aortic root to the left external iliac artery.

FINAL DIAGNOSIS
Stanford type A AAD complicated by AIS was considered.

TREATMENT
The patient was immediately scheduled for cardiovascular surgery. On the next day, he was subjected to aortic arch and ascending aortic replacement and aortic valvuloplasty. Laceration of AAD was intraoperatively found in the lesser curvature of the aortic arch. Postoperatively, CTA at 19 d revealed reconstructed and remodeled aortic arch and thoracic aorta with periaortic hematoma (Figure 5).

OUTCOME AND FOLLOW-UP
The patient had grade 1 muscle strength in the left limb and was transferred to a rehabilitation facility for further care and management. Six months after discharge, the patient still has hemiparesis of the left limb. The patient’s modified Rankin Scale score was 4.

DISCUSSION
We report a patient with a case of cerebral infarction as the first presentation who received intravenous thrombolytic therapy after a missed AAD diagnosis, and who ultimately had a poor prognostic
He ZY et al. stroke combined with aortic dissection

Figure 1 Cranial computed tomography within 2 h of the onset of illness. Cranial computed tomography revealed small lacunar lesions next to the basal ganglia and lateral ventricles (red arrows).

Figure 2 Cranial computed tomography on the second day of intravenous thrombolytic therapy. Computed tomography shows right basal ganglia (A) and right frontotemporoparietal (B) brain tissue infarction (the red arrows).

outcome. A limited number of studies have reported cases with cerebral infarction as the first symptom with concomitant AAD[4-10]. Clinical management of these patients is below optimal thresholds. We report this case and review the relevant literature to provide a reference for clinicians.

AAD is a high mortality disease, and its incidence is about 3 cases per 100000 people per year[11]. Risk factors for AAD include long-term arterial hypertension, smoking, dyslipidemia, drug abuse (cocaine, crack cocaine, or amphetamine), connective tissue disorders, vascular inflammation, deceleration trauma and iatrogenic factors (catheter or instrument intervention as well as valvular or aortic surgery)[3]. Hypertension is a common risk factor for aortic coarctation, with up to 75% of AAD patients suffering from hypertension[12]. The patient in this article had no obvious history of trauma, surgery, or drugs use, but had a history of untreated hypertension. Therefore, hypertension may be the main cause of AAD in this patient. Through various mechanisms, including extension of the dissection to common carotid artery, to intracranial carotid artery[13], thromboembolism and cerebral hypoperfusion[14], Stanford A AAD can be complicated by stroke[15]. Studies have reported that AAD often involves the right common carotid artery. Therefore, patients often present with pulse weakness and left-sided hemiparesis[6]. Consistent with previous reports, the patient in this report had a right-sided common carotid artery dissection and first presented with left-sided hemiplegia. We hypothesize that the patient had an unstable embolus in the right common carotid artery dissection, which dislodged and led to an acute stroke.

Chest or back pains comprise the most common AAD symptoms. Most patients with AAD combined with neurological symptoms present with initial pain, but one third of patients have no pain symptoms [16]. Patients with neurological symptoms only, and without pain, may be missed for AAD at the time of diagnosis. This was the case with our reported patient. He initially presented with painless neurological symptoms and eventually, the disease. Aortic dissection was missed upon first admission at the local hospital. In addition, some patients have aphasia or a reduced level of consciousness, and...
are unable to report chest and back pain, leading to undiagnosed or delayed diagnosis of AAD[8]. About 1% of patients with acute ischemic stroke have AAD[6]. Therefore, for patients with cerebral infarction, in addition to focusing on patient’s chest and back pains, physicians should pay attention to any unexplained hypotension, mild dyspnea, asymmetry in blood pressure between the arms (differences in systolic pressure over 20 mmHg), loss of consciousness, electrocardiogram changes, heart murmurs and cold extremities[17].

In addition to clinical symptoms, some ancillary tests can provide some assistance in the diagnosis of AAD. Yoshimuta et al[18] reported that D-dimer levels are significantly elevated in patients with ischemic stroke and AAD than in those without AAD. They concluded that D-dimer is a potential early diagnostic marker for AAD with isolated neurological symptoms in ischemic stroke patients. Our reported patient had elevated D-dimer levels (7.190 mg/L) in blood at the time of presentation, implying that he was at risk of AAD. It has also been reported that chest x-ray can provide valuable diagnostic information by detecting widened mediastinum and abnormally shaped aorta in 80% of AAD patients[16]. Although abnormal chest radiography may be helpful in evaluation of suspected AAD, it may be normal in a subset of patients[2]. Ordinary CT can detect a certain proportion of AAD patients, but it is also negative in a significant proportion of AAD patients. CTA plays a central role in the diagnosis of AAD, but some patients with cerebral infarction cannot be routinely subjected to CTA to determine whether they have a combined AAD and whether they are eligible for thrombolytic therapy because of the urgent time window. Magnetic resonance imaging (MRI) can be used to comprehensively evaluate aortic dissection, but it is slower than CT imaging. Moreover, some AIS patients do not have sufficient time to perfect MRI. In addition, MRI is difficult for unstable AAD patients during imaging.

Ultrasound is a non-invasive, bedside, real-time diagnostic tool that can be used to detect AAD in patients with cerebral infarction in a timely manner[8]. Carotid ultrasound is an effective method for the diagnosis of AAD-associated carotid artery dissection[4,8,19]. Tsivgoulis et al[4] emphasized that simultaneous ultra-early ultrasound evaluation and clinical assessment of acute stroke patients can help in the early diagnosis of AAD and prevent inadvertent use of intravenous thrombolytic agents in such patients.

Figure 3 Axial computed tomography perfusion images on the second day of intravenous thrombolysis. Cerebral blood flow (A), cerebral blood volume (B), mean transit time (C), PS (D), Tmax (E) and Time to peak (F) show multiple ischemic cores in the right frontotemporoparietal lobe as well as relatively extensive hypoperfusion area.
Failure of physicians to take an adequate history or/and physical examination, failure to identify atypical symptoms, failure to arrange or interpret diagnostic tests, and failure to arrange appropriate specialized consultation were the main factors contributing to misdiagnosis of AAD in the emergency department\[20\]. Due to the high mortality rate of AAD, reducing missed diagnoses of AAD can prevent potential medical disputes.

IVT is an effective treatment for AIS within 4.5 h of symptom onset. However, IVT is contraindicated in patients with AIS combined with AAD, as it may lead to aortic dissection\[21\], or delay life-saving surgery\[22\]. IVT in patients with acute stroke caused by AAD has been associated with poor prognosis \[16,23\]. The patient in this article presented with worse muscle strength and consciousness after IVT. This outcome could be attributed to various reasons. When alteplase was used for IVT, more thrombus disintegrated and were dislodged from the intima of the right common carotid artery, leading to
excessive embolization of the right cerebral hemisphere and, ultimately, to a more severe cerebral infarction in the patient.

For some patients with AIS due to large-vessel occlusion, mechanical thrombectomy within 24 h after symptom onset may improve functional outcomes[24]. In patients with severe functional impairment possibly caused by large vessel occlusion, a CTA or magnetic resonance angiogram of the head and neck should be performed to determine the occlusion location and the eligibility for mechanical thrombectomy[24]. The patient in this article did not perform a CTA examination at the initial visit because the local hospital was only equipped to do non-enhanced CT. The patient was transferred to our hospital more than 24 h after the onset of the disease and beyond the time window for mechanical thrombectomy.

Acute Type A AAD has a mortality rate of 50% within the first 48 h without surgery, and surgery remains the best therapy for reducing the risk of mortality[25]. However, it has not been conclusively determined whether surgery should be performed in patients with Type A AAD presenting with neurological deficits or coma. Coma, shock secondary to pericardial tamponade, malperfusion of coronary or peripheral arteries, and stroke are significant predictors of postoperative mortality[25]. Although AAD patients with coma or cerebral malperfusion have a poor postoperative prognosis, some patients have been reported to recover if rapid cerebral reperfusion is achieved[26,27], especially if the time between symptom onset and arrival at the operating room is less than 5 h[28]. Ueyama et al[29] successfully treated a patient with Stanford type A AAD combined with cerebral malperfusion through urgent surgical therapy. Surgery can also provide IVT opportunities for patients with cerebral infarction after AAD treatment. Intravenous recombinant tissue-type plasminogen activator therapy for ischemic stroke has been shown to be effective and safe several days after surgical treatment of AAD[30].

CONCLUSION

AAD is a serious and lethal disease. Some AAD patients with acute stroke present atypical symptoms, with only neurological deficits as first symptoms, making it easy to miss or delay AAD diagnosis. When
He ZY et al. stroke combined with aortic dissection

FOOTNOTES

Author contributions: He ZY and Yao LP contributed equally to this case, both wrote and revised the text; Zhou Q and Yang XF contributed equally in this case report; all were part of the clinical team that treated the patient, and all contributed to the text.

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Compound-honeysuckle-induced drug eruption with special manifestations: A case report

Li-Feng Zhou, Rong Lu

**Abstract**

**BACKGROUND**
The clinical manifestations of drug eruption are complex and diverse, which can lead to missed diagnosis or misdiagnosis. The clinical manifestations of drug eruption caused by compound honeysuckle have not been reported.

**CASE SUMMARY**
A 20-year-old man was admitted to our department of dermatology due to erythema and papules on the chest and abdomen with pruritus for 3 d. The next day after taking compound honeysuckle granules, the patient suddenly developed a rash and intense itching on his chest and abdomen. Physical examination revealed diffuse red needle-cap size macules and papules with well-defined borders on the chest and abdomen, and discoloration after finger pressure. No abnormality was observed in other areas of the skin. Back skin scratch was positive. White blood cells, eosinophil count and eosinophil ratio were higher than normal. Histopathological examination of the skin lesions on the left abdomen revealed intercellular edema, blurred focal basal cell layers, and focal lymphocyte infiltration in the superficial dermis and perivascular areas. Immunohistochemistry showed CD3⁺ CD4⁺ and CD8⁺ T lymphocytes. The diagnosis was drug eruption with special manifestations induced by compound honeysuckle. The skin lesions completely subsided without pruritus after 2 wk of antihistamine and hormone therapy. Follow-up for > 1 mo showed no recurrence.

**CONCLUSION**
Chinese patent medicine compound honeysuckle granules can induce allergic reaction and rare skin damage.
Key Words: Drug eruption; Drug dermatitis; Blaschko line; Compound honeysuckle; Allergic reaction; Case report

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Core Tip: Drug eruption is a common disease in dermatology. The severity of the disease varies, and it can endanger life. The clinical manifestations of drug eruption are complex and varied, and it can imitate any skin disease. Here, we report a case of drug eruption caused by oral administration of Chinese patent medicine compound honeysuckle granules. The clinical manifestations of drug eruption are unique, and the drug eruption is distributed along the Blaschko line on both sides of the chest and abdomen, which is rare clinically.

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INTRODUCTION

Drug eruption, also known as drug dermatitis, is an inflammatory reaction occurring in the skin and mucous membranes when drugs enter the body through oral administration, intravenous injection and other routes. The severity of the disease varies, and the liver, kidneys, bone marrow and other organs may be involved in severe cases, and may even endanger life[1]. Drug eruption is a common dermatological disease. Drug allergy accounts for 15% of adverse drug reactions, and the incidence of drug eruption in inpatients is 2%–3%[2]. The incidence of drug eruption in the general population is estimated to be between 0.3% and 8%[3,4]. There are many kinds of drugs causing eruptions, and the clinical manifestations of drug eruption are complex and diverse, which can imitate any skin disease[5]. Therefore, it is important to know the clinical manifestations of drug eruption for the diagnosis of skin diseases. We here report a case of drug eruption in a 20-year-old man with specific manifestations induced by oral compound honeysuckle granules.

CASE PRESENTATION

Chief complaints
A 20-year-old man was admitted to our department of dermatology due to erythema and papules on the chest and abdomen with pruritus for 3 d.

History of present illness
The patient felt fatigue and discomfort without headache, pharyngeal pain or fever 5 d ago. Therefore, the patient took compound honeysuckle granules orally, three times a day, 10 g each time. The next day after taking the drug, red rash and severe itching appeared on the chest and abdomen. The patient stopped taking the drug and did not receive diagnosis and treatment. The original rash did not change and pruritus was more obvious after 1 d. There was no fever during the course of the disease.

History of past illness
The patient was previously healthy and denied any history of allergic disease or other diseases.

Personal and family history
The patient denied a family history of genetic disease, and there were no family members with similar disease.

Physical examination
Vital signs were normal. Heart, lung and abdomen examination showed no abnormalities. There was no hyperemia or edema in the pharynx, no hyperplasia in pharyngeal lymphatic follicles, no swelling or hyperemia in the tonsils, no secretions, normal tongue coating, or no oral mucosal spots. No enlarged lymph nodes were palpable behind the ears, in the neck or under the jaw, and the tourniquet test was negative. Dermatological findings showed diffuse distribution of bright red needle-cap size macules and
papules with well-defined borders on the chest and abdomen. The rash was discolored after finger pressure (Figure 1A and B). No abnormality was observed on the skin of the face, neck, limbs, axilla and behind the bilateral axillary front. Skin laceration was positive (Figure 1C).

**Laboratory examinations**

Blood routine examination showed increased white blood cell count (9.82 × 10⁹/L), eosinophil count (0.65 × 10⁹/L) and eosinophil ratio (0.07), and all other indicators were normal. Routine tests of urine, liver and kidney function, blood lipids and electrolytes were all within the normal range. The antinuclear antibody profile and anti-double-stranded DNA were negative. IgA (0.17 g/L) was slightly increased and the remaining immune indexes were normal. Histopathological examination of the skin lesion on the left abdomen showed intercellular edema of the epidermis, blurred focal basal cell layers, and focal lymphocyte infiltration in the superficial dermis and perivascular layers (Figure 2A and B). Immunohistochemistry showed CD3⁺, CD4⁺ and CD8⁺ T lymphocytes.

**Imaging examinations**

Chest X-ray and abdominal color ultrasound showed no abnormalities.

**FINAL DIAGNOSIS**

The patient was diagnosed with compound-honeysuckle-induced drug eruption with specific appearance.

**TREATMENT**

We asked the patient to drink plenty of water daily. He was treated with oral desloratadine dry suspension granule 1 g daily, oral prednisone acetate tablets 20 mg daily, and oral compound glycyrrhizin tablets 225 mg daily. Seven days after maintenance treatment, the rash was significantly relieved, and itching was also relieved. Desloratadine dry suspension granules 1 g per day were added, prednisone acetate tablets were tapered to 15 mg per day, compound glycyrrhizin tablets were stopped, and calcium carbonate D3 granules 6 g per day were taken orally for another 1 wk. Subsequently, the skin lesions and itching completely disappeared, and no scale or pigmented spots were found. All drugs were then withdrawn.

**OUTCOME AND FOLLOW-UP**

After 2 wk of antihistamine and glucocorticoid treatment, the thoracic and abdominal rash and the itching disappeared completely. The patient was followed up for > 1 mo and no recurrence was found.

**DISCUSSION**

Drug eruption is a common dermatological disease. Most patients have acute onset and severe symptoms. Some cases may involve the liver, kidneys, and gastrointestinal and other visceral systems, and severe cases may endanger life. The occurrence of drug eruption is related to genetic factors, functional conditions and enzyme defects.

The pathogenesis of drug eruption is complex. Studies have found that T-cell-mediated immune response is involved in the occurrence of drug eruption, and the dominant subsets of T lymphocytes vary in different types of drug eruption[6]. CD4⁺ T cells play a predominant role in drug eruption[7]. Activated CD4⁺ T cells mainly secrete a variety of cytokines and inflammatory mediators, such as interferon-A, tumor necrosis factor receptor, interleukin-2 and other Th1 cytokines, which play a role in drug eruption[8]. Hari et al.[6] reported maculopapular exanthema drug eruption with almost only CD4⁺ T cell infiltration. Yawalkar et al.[9] demonstrated that maculopapular exanthema drug eruption was mainly infiltrated by CD3⁺ T cells and also marked by CD4⁺ T cells. In our case, the rash was mainly infiltrated by CD4⁺ T cells, with more CD3⁺ T cells and a small number of CD8⁺ T cells, which was similar to the previous studies on T lymphocyte infiltration with drug eruption.

In recent years, new discoveries have been made about the pathogenesis of drug eruption. Studies have shown that HLA polymorphism is the main genetic factor of drug sensitization[10]. HLA-B alleles may activate T cells by expressing peptides that bind to drugs or drug metabolites[11]. The main chemical components of compound Honeysuckle are phenolic acids, including chlorogenic acid, neochlorogenic acid and cryptochlorogenic acid. Both chlorogenic acid and cryptochlorogenic acid can
Drug eruption with special manifestations

Figure 1 Skin lesions of the patient with drug eruption caused by compound Honeysuckle. A and B: Macules with well-defined borders on the chest and abdomen; C: Positive for skin scratch on the back.

Figure 2 Histopathology of the abdominal skin lesion. A: Epidermal spongiform dermatitis, interfacial dermatitis, focal lymphocyte infiltration in the superficial dermis and perivascular layer (hematoxylin and eosin staining, 20×); B: CD4+ (immunohistochemical staining, 20×); C: CD3+ (immunohistochemical staining, 20×); D: CD8+ (immunohistochemical staining, 20×).

Cause allergic reactions, but neochlorogenic acid cannot[12]. In our case, skin rash appeared on the chest and abdomen after oral administration of compound Honeysuckle granules, which was probably related to genetic polymorphism. The peptide expressed by specific alleles was combined with drugs or drug metabolites to activate CD4+ T cells, resulting in allergic reaction and drug eruption.

Drug eruption needs to be distinguished from eruptive skin diseases caused by infectious diseases such as measles, rubella and scarlet fever. In our patient, there was no fever, cough, runny nose or other symptoms before the eruption, no congestion in the pharynx, no Koplik spot in the buccal mucosa, and no skin rash on the face and neck. The itching was severe, and the rash subsided slowly after drug withdrawal. No desquamation or pigmentation was observed at the subsided area, so measles were ruled out. There was no fever, runny nose, cough, pharyngeal pain or other symptoms of upper respiratory tract infection, no skin rash on the face and neck, no lymph node enlargement behind the occiput, behind the ears and on the neck, and there was no abnormal lymphocyte count before the eruption, so rubella was excluded. Before the eruption, the patient had no fever, no pharyngeal congestion, no tonsil enlargement, no cervical lymph node enlargement, no pallor around the mouth, normal lingual papilla, negative tourniquet test, severe itching, and no abnormal neutrophil count, which excluded scarlet fever. One day after the patient took compound Honeysuckle granules orally, diffuse red macules suddenly appeared on the chest and abdominal wall, and the rash distribution was symmetrical. The color disappeared after finger pressing, and the itching was obvious. The rash did not
increase after withdrawal of compound Honeysuckle granules. Skin scratch was positive, the number and ratio of eosinophils were higher than normal, and the rash was infiltrated with CD4+ T lymphocytes. Skin diseases with similar rashes and exanthem infectious skin diseases were excluded, and drug eruption was finally diagnosed.

Blaschko line was described by Alfred Blaschko in 1901 and refers to the linear distribution of various nevi and acquired skin diseases on human skin mucosa[13]. Later, Happle et al[14] gave a supplementary description of the distribution of skin lesions on the head and neck. Its distribution pattern is S-shaped on the side and front of the trunk, V-shaped in the middle of the back, spiral on the head and occiput, arc-shaped on the side of the head and neck, and linear on the limbs. The Blaschko line represents the pathway of epidermal cell migration and proliferation during fetal development, reflecting the existence of skin mosaicism[15]. Skin lesions along the Blaschko line are clinical manifestations caused by skin chimerism[16]. Many congenital skin diseases as well as some acquired skin diseases can be distributed along the Blaschko line, which may be the rapid response of the chimera of skin susceptibility genes to systemic immune factors[17]. Munro et al[18] believe that mutated cells arranged along the Blaschko line could cause disease under the excitation of some epigenetic factors. Gene mosaicism may play an important role in the occurrence of diseases distributed along the Blaschko line. Under some external stimuli, the mosaicism and cloning expression of genes encoding skin antigen determinants caused the loss of immune tolerance, which leads to skin inflammation at the T-cell stage distributed along the Blaschko line. This results in dermatitis distributed along the Blaschko line[19]. In our case, the rash only appeared on the chest and abdomen. The rash boundary was unusually clear, and the rash distribution was consistent with the Blaschko-line pattern of mosaicism described by Happle et al[14]. The pathogenesis may be mosaicism of genes encoding this skin region, loss of immune tolerance, and inflammatory response in this region under the stimulation of drugs or drug metabolites.

The histopathology of Blaschko line dermatitis is mainly characterized by spongiform dermatitis[20-22], and there are also reports of interfacial dermatitis[23]. The histopathology of our patient showed changes in spongiform dermatitis, as well as interfacial dermatitis.

Some lesions distributed along the Blaschko line can spontaneously resolve, which is difficult to explain by genetic pathogenesis, and some scholars believe that it may be related to the enhanced peripheral nerve response to foreign stimuli caused by neurological dysfunction[24]. In our case, the rash did not increase after discontinuing the sensitizing drugs, indicating that the external stimulant drugs play an important role in the occurrence of inflammation. The patient was treated with antihistamines and glucocorticoids, and the rash subsided completely, indicating that the rash was caused by an allergic reaction to drugs rather than by pathogenic microorganisms.

Drug eruption along the Blaschko line caused by drugs is rare. Sigal-nahum et al[25] reported linear fixed drug eruption in the left lower limb after intramuscular injection of cefazoline. Ozkaya-Bayazit et al[26] found that trimethoprim induced linear fixed drug eruption on the right arm. Coskun et al[27] found that calcium acetate induced Blaschko line drug eruption, extending from the right shoulder to the flexor surface of the right forearm. Das et al[28] reported that azithromycin induced linear fixed drug eruption over the midline of lower back. Brinkmeier et al[29] showed that metronidazole induced Blaschko line drug eruption on the right chest and abdomen and right upper limb. Couderc et al[30] showed that cestuzumab induced Blaschko line drug eruption on the left lower limb. In our case, drug eruption occurred after oral administration of Chinese patent medicine compound Honeysuckle granules, and the rash was distributed along the Blaschko line on the chest and abdomen, with no separation at the midline. No clinical reports on the similar case have been reported.

CONCLUSION

There are few drug-induced eruptions along the Blaschko line. A rash along the Blaschko line has been reported mainly on one side of the trunk or limb and is induced by western medicine. The rash in the present case was caused by oral Chinese patent medicine compound Honeysuckle granules and appeared on both sides of the thorax and abdomen along the Blaschko line. To our knowledge, this is the first report of drug eruption along the Blaschko line caused by Chinese patent medicine compound Honeysuckle.

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FOOTNOTES

Author contributions: Zhou LF and Lu R contributed equally to this work; Zhou LF contributed to the manuscript by
tracing the history, reviewing the literature, collecting and analyzing clinical data and figures, and writing the manuscript; Lu R contributed to conception of the article, literature retrieval, photography and editing, and manuscript revision and polishing.

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Spontaneous internal carotid artery pseudoaneurysm complicated with ischemic stroke in a young man: A case report and review of literature

Yu-Lin Zhong, Jia-Ping Feng, Hui Luo, Xue-Hao Gong, Zhang-Hong Wei

Abstract

BACKGROUND
Carotid artery pseudoaneurysm (PSA) is infrequently encountered in clinical settings. Internal carotid artery (ICA) PSA complicated with ischemic stroke is rare. PSAs are typically caused by iatrogenic injury, trauma, or infection. The underlying mechanisms of spontaneous PSA formation are not well characterized. We report a healthy young man who presented with stroke as a complication of spontaneous PSA of the left ICA.

CASE SUMMARY
A 30-year-old man working as a ceiling decoration worker was hospitalized due to sudden-onset speech disorder and right lower extremity weakness. Medical history was unremarkable. Brain computed tomography revealed ischemic stroke. Digital subtraction angiography showed a left ICA PSA with mild stenosis. The patient was conservatively managed with oral anticoagulation and antiplatelet therapy. He recovered well and was discharged. The patient was in good condition during follow-up.
CONCLUSION
The occupational history of patient should be taken into consideration while evaluating the etiology of spontaneous ICA PSA in young people with stroke.

Key Words: Pseudoaneurysm; Carotid artery injury; Ischemic stroke; Case report

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Core Tip: In a previously healthy youngster with stroke, it is counterintuitive to make a connection between stroke and pseudoaneurysm (PSA), especially if there is no obvious cause. To best of our knowledge, this is the first report of spontaneous carotid artery PSA with stroke in a young adult. This case report may provide insights for diagnosis of carotid artery PSA in youngsters. Conservative therapy is a viable alternative for young patients with small carotid PSA.

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DOI: https://dx.doi.org/10.12998/wjcc.v10.i22.8025

INTRODUCTION
Arterial wall has a three-layered structure comprising of intima, media, and adventitia[1]. Rupture of the arterial wall may occur due to several reasons, such as iatrogenic injury, trauma, infection, or tumor invasion[2]. Disruption of the arterial wall following injury leads to formation of hematoma adjacent to the artery; subsequent proliferation of peripheral fibroblasts may result in encapsulation and organization of the hematoma leading to the formation of pseudoaneurysm (PSA)[3]. A previous study has shown that PSA formation is the most common complication of endovascular intervention with the incidence rates ranging from 0.7% to 6.25%. Femoral arteries and cardiovascular is the most common site of formation of PSA[4]. Traumatic internal carotid artery (ICA) PSA is a rare entity, with an incidence of approximately 9% in cases with head and neck trauma[5]. The clinical manifestations depend on the size, site, and etiology of the PSAs; however, the development of PSA can cause severe complications such as rupture, stroke, or asphyxia[6,7]. Digital subtraction angiography (DSA) has a high sensitivity and specificity for the diagnosis of ICA PSA and is considered as the diagnostic gold standard of PSA[8].

In this case report, we describe a case of a 30-year-old male who suffered speech disorders and right lower extremity weakness and review the previously reported cases.

CASE PRESENTATION

Chief complaints
A 30-year-old man was admitted to the Neurology department of our hospital because of the chief complaints of speech disorder and right lower extremity weakness five days ago.

History of present illness
Five days ago, the patient developed sudden-onset speech disorder and right lower extremity weakness at work and was admitted to a local hospital. The condition of the patient showed gradual improvement after administration of thrombolytic treatment. The etiology of stroke was still unknown. In order to seek more comprehensive diagnosis and treatment, the patient was referred to the Neurology department of our hospital.

History of past illness
The patient had no history of hypertension, diabetes, or coronary artery disease. Furthermore, there was no history of acute trauma or iatrogenic injury.

Personal and family history
The patient was a ceiling decoration worker. He had no history of smoking and alcohol consumption.
Personal and family history was unremarkable. There was no family history of connective tissue disease, such as Marfan syndrome.

**Physical examination**

On physical examination, the patient was found to have a hemiparetic gait. The muscle strength of right upper and lower limbs was grade 4 and the light touch sensation was attenuated on the right side. Babinski sign was found in the sole of his right foot. Other physical findings were unremarkable.

**Laboratory examinations**

Routine blood parameters were as follows: Leukocyte count $11.37 \times 10^9/L$; platelet count $344 \times 10^9/L$; neutrophils 84.9%; plasma fibrinogen 4.12 g/L; lactic dehydrogenase 287 U/L. Renal function and liver function tests were normal.

**Imaging examinations**

Cerebral computed tomography showed low-density foci in the left frontotemporal and centroparietal regions, which were indicative of left ischemic stroke. Ultrasonography of the carotid arteries exhibited a mixed echogenic mass at the origin of the left ICA (Figure 1). Computed tomography angiography (CTA) revealed a nodular mass with mural thrombus in continuity with the adjacent left ICA lumen; the size of the mass was approximately $10 \times 7$ mm (Figure 2). DSA indicated a PSA at the origin of the left ICA with mild stenosis.

**FINAL DIAGNOSIS**

Left ICA PSA complicated with ischemic stroke.

**TREATMENT**

Low-dose alteplase and oral anticoagulation and antiplatelet therapy. For ischemic stroke, the local hospital evaluated the condition of patient and opted for low-dose alteplase to maintain the benefits of treatment while reducing the risk of systemic or intracerebral hemorrhage[9]. As for carotid PSA, the patient failed the ICA temporary occlusion test, which implied that his cerebral arteries could not develop sufficient cerebral collateral circulation. Therefore, we intended to use a combination of endovascular stent placement and coil embolization to treat the PSA. However, the patient refused this treatment option because of the costs and the associated risks. Therefore, he was conservatively managed with oral anticoagulation and antiplatelet therapy.

**OUTCOME AND FOLLOW-UP**

The patient recovered satisfactorily and was discharged from hospital on day 8. In order to prevent recurrence of ischemic stroke, he was prescribed oral aspirin for one month[9]. The patient was found to be in a good condition on follow-up evaluation performed at 3 and 6 months. Cerebral computed tomography (CTA) showed a large encephalomalacia focus in the left temporal-basal region, which indicated that the patient was at the convalescent stage of ischemic stroke. On cervical CTA, the size of PSA at the origin of the left carotid artery was significantly smaller than before, which was consistent with the results of DSA (Figure 3). However, we did not obtain further follow-up data for patients beyond 6 months.

**DISCUSSION**

The incidence of stroke in young people has increased over the past decades, reaching 221 per 100000 by the end of 2019. Underlying cardiovascular disease is the main cause of stroke in this population, while aneurysms or PSA are not common causes of stroke[10,11]. PSA typically occurs due to iatrogenic injury, trauma, infection, and tumor invasion[3,12]. Spontaneous PSA are rare entities. Spontaneous PSA associated with stroke are exceedingly rare[13]. A comprehensive search of the literature was performed using the PubMed, Embase, Cochran Library and Web of Science databases to retrieve studies published before December 2021 (Supplementary material). In the 16 cases reviewed by us, the etiology of 5 cases (31%) was trauma[14-18] and 4 cases (25%) had iatrogenic injury[19-22], while only 2 cases (13%) were spontaneous; however, both spontaneous cases had a history of hypertension and hyperlipidemia[23,24] (Table 1). Our patient was a young adult with no personal or family history of
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Table 1 Literature review of pseudoaneurysm with the clinical presentation of stroke

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Ref.</th>
<th>Year</th>
<th>Age</th>
<th>Sex</th>
<th>Site</th>
<th>Etiology</th>
<th>Imaging modality</th>
<th>Treatments</th>
<th>Outcome</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>[35]</td>
<td>2005</td>
<td>62</td>
<td>M</td>
<td>L INA</td>
<td>Infectious</td>
<td>US, MRI</td>
<td>Surgical resection</td>
<td>REC</td>
<td>1 mo</td>
</tr>
<tr>
<td>3</td>
<td>[19]</td>
<td>2007</td>
<td>60</td>
<td>M</td>
<td>R ICA</td>
<td>Iatrogenic</td>
<td>MRI, DSA</td>
<td>Endovascular stenting</td>
<td>REC</td>
<td>NA</td>
</tr>
<tr>
<td>4</td>
<td>[15]</td>
<td>2007</td>
<td>31</td>
<td>M</td>
<td>R ICA</td>
<td>Traumatic</td>
<td>MRI, CT, DSA</td>
<td>Endovascular stenting</td>
<td>REC</td>
<td>NA</td>
</tr>
<tr>
<td>5</td>
<td>[24]</td>
<td>2008</td>
<td>51</td>
<td>M</td>
<td>L ICA</td>
<td>Spontaneous</td>
<td>MRI, CT, DSA</td>
<td>Endovascular stenting</td>
<td>REC</td>
<td>NA</td>
</tr>
<tr>
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<td>71</td>
<td>M</td>
<td>L ICA</td>
<td>Radioactive</td>
<td>US, CT, MRI, DSA</td>
<td>Endovascular occlusion</td>
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<td>L ICA</td>
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<td>Endovascular stenting</td>
<td>REC</td>
<td>14 mo</td>
</tr>
<tr>
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<td>2017</td>
<td>2</td>
<td>M</td>
<td>L ICA</td>
<td>Infectious</td>
<td>MRI, CT, DSA</td>
<td>Endovascular occlusion</td>
<td>REC</td>
<td>1 mo</td>
</tr>
<tr>
<td>9</td>
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<td>2018</td>
<td>85</td>
<td>M</td>
<td>L ECA</td>
<td>Spontaneous</td>
<td>US, CT, MRI, DSA</td>
<td>Conservative therapy</td>
<td>Death</td>
<td>7 mo</td>
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<td>10</td>
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<td>60</td>
<td>F</td>
<td>L ECA</td>
<td>Congenital</td>
<td>MRI, CT, DSA</td>
<td>Endovascular stenting</td>
<td>REC</td>
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<td>2019</td>
<td>45</td>
<td>M</td>
<td>L CCA</td>
<td>Iatrogenic</td>
<td>CT, CTA</td>
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<td>REC</td>
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<td>12</td>
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<td>2019</td>
<td>57</td>
<td>F</td>
<td>L CCA</td>
<td>Iatrogenic</td>
<td>CT, CTA</td>
<td>Endovascular occlusion</td>
<td>REC</td>
<td>6 mo</td>
</tr>
<tr>
<td>13</td>
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<td>2019</td>
<td>79</td>
<td>M</td>
<td>R FA</td>
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<td>CT, MRI, CTA</td>
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</tr>
<tr>
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<td>2020</td>
<td>53</td>
<td>M</td>
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<td>Infectious</td>
<td>CT, DSA</td>
<td>Conservative therapy</td>
<td>REC</td>
<td>NA</td>
</tr>
<tr>
<td>15</td>
<td>[17]</td>
<td>2020</td>
<td>31</td>
<td>F</td>
<td>L VA</td>
<td>Traumatic</td>
<td>CT, CTA, DSA</td>
<td>Conservative therapy</td>
<td>REC</td>
<td>6 mo</td>
</tr>
<tr>
<td>16</td>
<td>[18]</td>
<td>2021</td>
<td>35</td>
<td>M</td>
<td>L ICA</td>
<td>Traumatic</td>
<td>US, MRI, MRA</td>
<td>Endovascular occlusion</td>
<td>REC</td>
<td>3 mo</td>
</tr>
<tr>
<td>Present case</td>
<td>2022</td>
<td>30</td>
<td>M</td>
<td>L ICA</td>
<td>Spontaneous</td>
<td>US, CT, CTA, DSA</td>
<td>Conservative therapy</td>
<td>REC</td>
<td>6 mo</td>
<td></td>
</tr>
</tbody>
</table>

CCA: Common carotid artery; CT: Computed tomography; CTA: Computed tomography angiography; DSA: Digital subtraction angiography; ECA: External carotid artery; F: Female; FA: Femoral artery; ICA: Internal carotid artery; INA: Innominate artery; L: Left; M: Male; MRA: Magnetic resonance angiography; MRI: Magnetic resonance imaging; NA: Not available; R: Right; REC: Recovery; SA: Splenic artery; US: Ultrasound; VA: Vertebral artery.

cardiovascular disease. Moreover, there was no history of neck trauma or surgery on the neck. We speculated that the etiology was related to the nature of the patient’s job. The patient worked as a ceiling decorator, whose daily work entailed prolonged extension of the neck for working on the ceiling. The prolonged neck extension may have caused damage to the wall of the ICA, which contributed to the formation of PSA. Moreover, PSAs are more prone to thrombosis due to vortex in the PSAs[25]. The patient developed sudden weakness of the right lower limb and speech disorder at work, which may be due to the hemodynamic changes at the thrombus site caused by the change in head posture. Subsequently, the thrombus embolized to the M1 segment of the left middle cerebral artery, resulting in ischemic stroke of the temporoparietal lobe[26]. Our experience suggests that carotid PSA should be considered when evaluating a patient presenting with stroke. what’s more, it is necessary to perfect the relevant examinations.

Carotid ultrasonography, a noninvasive, cost-effective, and radiation-free method, is currently the first-line imaging modality for screening carotid artery PSA. Doppler sonography can help distinguish a PSA from an aneurysm and/or other cervical mass[27]. It typically shows a neck mass with the typical features of PSA, including spontaneously echogenic swirling flow in the lumen and “to-and-fro” waveforms at the neck[28]. However, the “to-and-fro” waveforms were not observed in our patient, probably because of the relatively small tumor size. Furthermore, it is difficult to directly detect an ICA PSA that is located about 20 mm above the bifurcation of the common carotid artery[29]. In our patient,
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Figure 1 Ultrasonography and contrast-enhanced ultrasound of the carotid artery. A: Conventional carotid artery ultrasonography showing a connection of the mass with the left internal carotid artery (ICA); B: Contrast-enhanced ultrasound of the carotid artery showing contrast agent filling in the distended area of the left ICA, but no enhancement in the low echo area of the mural.

Figure 2 Left internal carotid artery pseudoaneurysm with acute ischemic stroke. A: Computed tomography (CT) angiography reconstruction shows a nodular mass with mural thrombus in continuity with the adjacent left internal carotid artery lumen; B: Digital subtraction angiography indicates a pseudoaneurysm at the origin of the left internal carotid artery with mild stenosis; C: Cerebral CT showing an area of low-density foci in the left frontotemporal and centroparietal regions, which indicates left ischemic stroke.

although this PSA was located 17 mm above the common carotid artery bifurcation, when we found a mass in the initial part of the ICA, we performed contrast-enhanced ultrasound (CEUS) of the carotid artery. CEUS showed contrast agent filling in the distended area of the left ICA, but no enhancement in the low echo area of the mural (Video 1). This finding suggests that the combination of ultrasonography and CEUS of the carotid artery may facilitate the diagnosis of PSA located at a relatively high position. CTA can effectively depict the localization, size, and mural thrombus of PSA[30]; furthermore, CTA with 3D reconstruction maps can delineate the outer wall of PSA and its relationship with peri-PSA vascular structures, which can provide surgeons with intuitive 3D image guidance[8]. In our case, CTA reconstruction revealed a nodular mass with mural thrombus in continuity with the adjacent left ICA lumen, which was an important anatomical information. The gold standard for the diagnosis of PSA is DSA with > 99% sensitivity and 100% specificity[8,31]. Out of the 16 reported cases, DSA was used as a diagnostic method in 11 cases (69%). In the present case, angiography showed the contrast agent entering the tumor cavity along with changes in eddy currents, which indicated rupture of the left ICA wall and the formation of PSA. Furthermore, the parent artery was localized with delayed distal development, which indicated compression of ICA. Although the diagnostic performance of DSA is pretty good, it is difficult to detect PSA that is filled with thrombus at the early stage[32].

Surgery and endovascular therapy are two main treatment modalities for carotid PSA[33]. Because of the severe complications of surgery and the rapid advances in the field of endovascular intervention, endovascular therapy has emerged as the preferred treatment for carotid PSA, especially for patients with PSA who present with stroke[34]. Surgical resection is used as an alternative to endovascular treatment. In addition, the choice of endovascular therapy depends on the lesion site and the performance status of patient[14]. Out of the 16 reviewed cases, only 3 patients (13%) were treated with surgical resection[14,35]. Endovascular therapy mainly includes use of covered stent grafts, micro-coil embolization, and detachable balloon embolization[36]. Choice of endovascular treatment depends on
Multiple factors, mainly the site of PSA, age of patient, and intracranial collateral circulation[37]. ICA temporary occlusion test should be performed first for PSAs occurring in the extracranial ICA[38]. If the test is successful, the ICA can be permanently occluded using a detachable balloon. If the test fails, the patient can be treated with covered stent grafts and accessory micro-coil embolization[39]. Our patient failed the ICA temporary occlusion test, which indicated the lack of adequate cerebral collateral circulation. Therefore, we intended to combine endovascular stent placement and coil embolization to treat the PSA; however, the patient opted for conservative management owing to the high cost of treatment and the associated risks. At 6-mo follow-up, the patient was in a relatively good condition and cervical CTA showed significant reduction in the size of PSA. Anticoagulant and antiplatelet agents may decrease mortality related to carotid PSA; however, such conservative management alone is not recommended owing to the risk of delayed rupture of PSA of the carotid artery, which is a life-threatening condition[40]. Out of the 16 cases reviewed, only 3 patients (19%) were conservatively managed. Budincevic et al[25] reported an 85-year-old man who died after receiving conservative therapy. However, Xue et al[17] reported a 31-year-old woman who showed satisfactory outcome with conservative treatment, which is consistent with our present case. Our patient may have shown better efficacy of conservative treatment owing to the relatively small size of the aneurysm. In addition, previous studies have shown that the choice of endovascular therapy should depend on the etiology of PSAs and that endovascular therapy is not necessary for all types of PSAs[41,42]. Thus, it is important to select appropriate treatment according to the etiology. Our report may provide an alternative therapy for young patients with small carotid PSA, nevertheless, the length of follow-up in our report was relatively short, which is its limitation.

CONCLUSION
We report a young man with clinical presentation of ischemic stroke that was triggered by thrombosis of PSA. The etiology of spontaneous ICA PSA in this case remains unknown. We inferred that the etiology may be related to the characteristics of the patient's occupation. Therefore, history of trauma, infection, and occupational history should be carefully elicited in young patients with acute ischemic stroke who have no history of cardiovascular disease. DSA is the gold standard for the diagnosis of carotid PSA; however, the combination of CEUS and conventional ultrasonography of the carotid artery may facilitate the diagnosis of PSA that is located at a relatively high position. Last but not least, although endovascular therapy is the recommended treatment for carotid PSA, the treatment strategy should be personalized based on the patient characteristics. Conservative therapy may be a viable alternative for young patients with small carotid PSA.

FOOTNOTES
Author contributions: Zhong YL and Feng JP contributed equally to this manuscript; Zhong YL and Feng JP were responsible for collecting the medical history of the patient and drafting the report; Luo H reviewed the literature; Gong XH revised the manuscript; Wei ZH reviewed and edited the manuscript; all authors issued final approval for the version to be submitted.
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Microcystic adnexal carcinoma misdiagnosed as a “recurrent epidermal cyst”: A case report

Si-Xuan Yang, Yan Mou, Shu Wang, Xin Hu, Fu-Qiu Li

BACKGROUND

Microcystic adnexal carcinoma (MAC) is a rare malignant cutaneous adnexal neoplasm, often presenting as a flesh-colored and slow-growing indurated plaque or cystic nodule in the mid-facial region. Its characteristic indolent presentation usually leads to initial misdiagnosis, resulting in tumor mismanagement and added morbidity due to increased propensity for local invasion.

CASE SUMMARY

A 63-year-old Chinese male patient with a long-term history of excessive ultraviolet irradiation had received two surgeries for an “epidermal cyst” on his glabella and was presented to our hospital’s Dermatology Department for further diagnosis and therapy of the lesion on his glabella. One month ago, his two 7 mm × 7 mm subcutaneous nodules were diagnosed as "recurrent epidermal cysts", and he underwent local excision surgery. Additionally, he has post medical history of surgery for right clear cell renal carcinoma. According to his biopsy, the patient was diagnosed as MAC in our hospital, and a tumor remnant was found on his wound. He then underwent wide local excision to achieve negative margins and reconstruction of full-thickness flap transplantation for tissue coverage. He remained tumor-free after six months of follow-up.

CONCLUSION

This case highlights the importance of MAC’s possible pathogenic factor of excessive ultraviolet exposure, its differential diagnosis to avoid misdiagnosis and mismanagement to adverse prognosis, the patient’s particular medical history of clear cell renal carcinoma, the alert for any tumor recurrence in older patients, and
his uncommon multiple nodules mess consisting of two 7 mm × 7 mm subcutaneous nodules, that will enrich the existing knowledge of MAC’s clinical features.

**Key Words:** Microcystic adnexal carcinoma; Recurrent epidermal cyst; Differential diagnosis; Clear cell renal carcinoma; Excessive ultraviolet radiation; Case report

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**Core Tip:** Microcystic adnexal carcinoma is an uncommon skin malignant tumor with a high misdiagnosis rate. We present a rare case of multiple nodules of microcystic adnexal carcinoma misdiagnosed as a “recurrent epidermal cyst.” The patient has a long-term history of excessive ultraviolet irradiation.

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**INTRODUCTION**

Microcystic adnexal carcinoma (MAC) is a rare cutaneous adnexal neoplasm that typically manifests as a single lesion in the mid-facial region[1,2]. It was first described by Goldstein et al[1] in 1982. Highly recurrent MAC often has deep, local infiltration and perineural invasion; however, regional lymph node or distant metastasis rarely occurs[3]. MAC has a high rate of misdiagnosis as an epidermal cyst due to its indolent features and lack of dermatologists’ familiarity[1,2]. We report a case of MAC misdiagnosed as a recurrent epidermal cyst occurring in a sun-exposed area, which was a mess consisting of two 7 mm × 7 mm subcutaneous nodules, rarely reported before. This study highlights the significance of the MAC’s differential diagnosis, its possible pathogenic factor of excessive ultraviolet exposure, and the patient’s particular medical history of right clear cell renal carcinoma. Besides, this case can help improve our wariness of seemingly innocent lesions that may suddenly appear in the head and neck region, especially with a history of excessive ultraviolet exposure or other malignant tumors[4].

**CASE PRESENTATION**

**Chief complaints**

A 63-year-old Chinese male patient was presented with complaints of a slowly growing mass on his glabella for 20 years. He had two excision surgeries, one ten years ago and one a month ago. The histopathological slice made in the local hospital a month ago reveals deep local infiltration and intramuscular invasion.

**History of present illness**

This lesion first appeared 20 years ago as a painless, skin-colored nodule on the glabella, with no signs of pruritus or numbness. Ten years ago, the lesion was diagnosed as an “epidermal cyst” and was removed in the local hospital without histopathological examination. Two new flesh-colored nodules emerged in the same place as the first lesion nine years ago. One month ago, the patient was diagnosed with a “recurrent epidermal cyst” in a local hospital (Figure 1). Its lesion was presented as a skin-colored mass on his glabella that was progressively growing, immovable and firm and comprised two 7 mm × 7 mm subcutaneous nodules. Subsequently, he underwent a local excision surgery. Biopsy revealed deep local infiltration and intramuscular invasion. He was then presented to our hospital for further diagnosis and therapy.

**History of past illness**

The patient had a medical history of right clear cell renal carcinoma, was surgically treated nine years ago, had not recurred, and denied any history of postoperative radiotherapy or chemotherapy.

**Personal and family history**

The patient had a long-term history of excessive ultraviolet irradiation. He reported an occupational history of working as a truck driver for more than 40 years, frequently working in a sun-exposed
Initial clinical examination of the microcystic adnexal carcinoma in the local hospital. The lesion revealed a skin-colored mass consisting of two 7 mm × 7 mm subcutaneous nodules on the glabella.

Physical examination
Physical examination on admission showed an approximately 10 mm × 10 mm red papule on his glabella. No paresthesia of neck nodes was noted.

Laboratory examinations
The histological and immunohistochemical patterns of the patient were consistent with MAC.

Imaging examinations
None of the imaging examinations revealed anomaly.

FINAL DIAGNOSIS
This patient was diagnosed as MAC on glabella with positive margins.

TREATMENT
The patient underwent wide local excision to achieve negative margins and reconstruction of full-thickness flap transplantation for tissue coverage. Perineural invasion, regional lymph node, and distant metastasis were not discussed.

OUTCOME AND FOLLOW-UP
The operation and postoperative clinical course went uneventful, and the patient was discharged. Postoperative histological and immunohistochemical results confirmed MAC diagnosis and showed negative resection margins. Three months after the surgery, an examination in our hospital showed that the 30 mm × 35 mm surgical incision healed well without recurrence (Figure 2). Patient satisfaction with reconstruction was noted after three months on his next visit.

DISCUSSION
The MAC etiopathology remains unclear. Ultraviolet and therapeutic radiations have been implicated in their possible pathogenic factors[5-7]. The patient's occupation is unique to our case, coupled with his medical history of clear cell renal carcinoma[4]. He reported a history of excessive sun exposure, averaging no less than six hours a day for more than 40 years, without any extra protection. This
resulted in dramatically elevated UV exposure levels, potentially posing an extra risk for MAC development[5]. Avoiding excessive UV irradiation may be one of the MAC’s precautionary measures. Patients with predisposing factors such as irradiation may develop double cancers, including MAC[4].

The relation of MAC with renal cell carcinoma is still unclear. A thorough patient history, including occupation, malignant neoplasm illnesses, and heightened suspicion of this pathology, can aid in early identification and reduced morbidity[8].

MAC is a rare cutaneous malignancy that often occurs in the mid-facial area, presenting as a slow-growing, flesh-colored, or whitish nodule[1]. Its characteristic indolent presentation usually leads to initial misdiagnosis, resulting in tumor mismanagement and added morbidity due to increased propensity for local invasion[3]. Its differential diagnoses include epidermal cyst, desmoplastic trichoepithelioma (DTE), morphoeform basal cell carcinoma (MBCC), squamous cell carcinoma, syringoma, and syringoid eccrine carcinoma (SEC)[1-3,6,9]. MAC’s typical microscopic features are located inside the dermis in the histopathology examination. They are defined by a diffusely infiltrative growth with the invasion of the subcutis and deeper tissues. In a desmoplastic stroma, they develop in cords and strands. Keratocysts and dystrophic calcifications are common on the surface. Duct distinction is a bonus feature that comes in variable degrees. There is very little cytologic atypia. Perineural nerve and skeletal muscle invasion are almost always present (Figure 3A and B)[1,3,10]. The ductal differentiation of MAC can help distinguish it from other benign adnexal neoplasms such as epidermal cyst, DTE, and syringoma, which often require no treatment[11]; for example, the small keratin-filled cysts structure of MAC can help differentiate this from SEC[11]. A full-thickness biopsy, including incisional biopsies, punch biopsies, and excisional biopsies, is required to avoid missing its deep infiltrative nature[7,9,11]. We must appreciate the value of a prompt histological evaluation. A medical facility’s standard practice is to perform histology on all biological materials (including benign skin lesions). The patient could have received better therapy if the skin samples had been evaluated histologically years ago.

Immunohistochemistry can serve as a supplement for distinguishing MAC from other neoplasms. However, none by itself is sensitive and specific enough for the diagnosis of MAC (Figure 3C-F)[7,11]. Carcinoembryonic antigen is a marker used to demonstrate ductal differentiation of MAC[3,9]. CK20 positivity has proven to be strongly predictive of DTE, whereas it is usually negative in MBCC and MAC[3,7]. CK19 positivity suggests MAC and not DTE. CD34 reveals focal stromal cell positivity in DTE, while the stromal cells in MAC and MBCC are often negative[3]. BerEP4 can be used to differentiate MAC (BerEP4 negative) from MBCC and DTE (both BerEP4 positive)[3,7,11]. Surgery is still the first-line treatment for this neoplasm, which mainly includes Mohs micrographic surgery (MMS) and wide local excision (WLE)[5,8,9,11]. MMS has been compared to routine surgical excision due to poorly defined clinical margins and a tendency for perineural invasion[7,8]. Although wide local excision was first accepted, recurrence rates have been found to be greater in patients who received MMS[9]. Our patient opted for WLE due to financial constraints, as MMS was much more expensive than WLE. Postoperative histological analysis showed he obtained negative margins. However, we will continue to follow up with our patient to observe his prognosis due to the indolent course of this tumor, with cases of recurrence reported up to 30 years after initial treatment[2,9,12].

Recently, some research indicated that distinct molecular markers for MAC might be potential diagnostic and therapeutic targets for the disease. Chen et al. discovered TP53 mutations as well as chromosomal deletions of CDKN2A and CDKN2B in a 68-year-old man’s metastatic MAC. CDK4 and CDK6 inhibitors have been discovered and are being researched for cancers that display these molecular markers. The Food and Drug Administration has authorized one for subgroups of breast cancer patients[13,14]. Yu et al.[13] investigated four calcium signaling pathway genes, including CACNA1S, RYR1,
ATP2A1, and MYLK3, that were elevated in MAC at the RNA level and expressed more in MAC than in normal sweat glands and histologic mimics of MAC at the protein level. C-kit has been found in a subgroup of MAC patients, boosting the prospect of future use of imatinib mesylate. The use of the anti-epidermal growth factor receptor (EGFR) antibody cetuximab and the multi-targeted tyrosine receptor kinase (MTRK) inhibitor sorafenib in the evidence-based clinical practice recommendations for MAC published in JAMA Dermatology[16].

CONCLUSION

MAC is an uncommon cutaneous adnexal malignancy, often showing as a flesh-colored and indolent lesion in the mid-facial area, leading to initial misdiagnosis and mismanagement to add morbidity. Dermatologists should raise the awareness of MAC and its differential diagnoses and be alert for any tumor recurrence or double cancers in elderly patients with predisposing factors. The link between renal cell carcinoma and MAC might be a coincidence that needs further investigation. Moreover, this study of rare multiple nodule lesions can enrich the knowledge of MAC's clinical features.

FOOTNOTES

Author contributions: Yang SX performed research and wrote the paper; Mou Y, Wang S, Hu X; and Li FQ contributed critical revision of the manuscript for important intellectual content; all authors have read and approve the final manuscript.

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Accidental discovery of appendiceal carcinoma during gynecological surgery: A case report

Lin Wang, Yan Dong, Ya-Hui Chen, Ya-Nan Wang, Lin Sun

BACKGROUND
Malignant tumors of the appendix are extremely rare, constituting about 1% of all gastrointestinal tumors. Generally, pathology identifies these tumors during or after appendectomy because they are difficult to detect at the preoperative stage. This case report aims to introduce the definitive diagnosis and treatment of mucinous adenocarcinoma of the appendix.

CASE SUMMARY
A 49-year-old female patient came to our hospital with right lower abdominal pain, nausea, and vomiting for three days. There was no change in the menstrual cycle. Gynecological ultrasound showed a cystic, solid mass in the right adnexa. Abdominal enhanced computed tomography showed a thick appendix. Cancer was found on exploration of the appendix during gynecological surgery. The right colon was removed. After surgery, the patient received chemotherapy and is recovering well.

CONCLUSION
Appendiceal carcinoma is frequently found during or after surgery, and both preoperative examination and early evaluation of clinical manifestations are extremely important.

Key Words: Abdominal pain; Pelvic mass; Appendix carcinoma; Mucinous adenocarcinoma; Case report
Core Tip: Mucinous adenocarcinoma of the appendix has a low incidence rate and is relatively rare. Increased tumor markers in patients has certain guiding significance. Imaging examination can indicate that the appendix is thickened, and diagnosis depends on histopathology.


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INTRODUCTION

Malignant appendix epithelial tumors can be divided into three categories: mucinous adenocarcinoma of the appendix (MAA)[1], intestinal type of adenocarcinoma, and signet ring cell carcinoma. Of these, MAA is the most prevalent histological form. Its occurrence may be linked to chronic inflammatory infiltration of the appendix. Here, we report a case of appendiceal mucinous adenocarcinoma, accidentally found during surgery for right lower abdominal pain and a pelvic mass. We also reviewed available relevant literature.

CASE PRESENTATION

Chief complaints
A 49-year-old female patient came to our hospital with right lower abdominal pain, nausea, and vomiting.

History of present illness
The patient’s symptoms started three days ago with right lower abdominal pain, nausea, and vomiting.

History of past illness
There was no change in the menstrual cycle. The patient had no previous medical history.

Personal and family history
The patient is in good health and has no family genetic diseases.

Physical examination
Gynecologic examination suggested normal vulvar development, a smooth vagina, little vaginal discharge, a soft cervix, an average size uterus, and no tenderness. There was no abnormality in the left accessories, and a cystic solid tumor approximately 6 cm in size was palpated in the right accessories.

Laboratory examinations
Human epididymal protein 4 (HE4), carcinoembryonic antigen (CEA), and alpha- fetoprotein (AFP) levels were normal on May 14, 2021. The patient’s CA125 level was 392.9 U/mL and CA199 level was 88.27 U/mL on May 14, 2021.

Imaging examinations
Gynecological ultrasound on May 15, 2021, showed a cystic, solid mass in the right adnexa area approximately 6.2 cm × 5.6 cm × 5.8 cm in size, with an unclear right ovary. On May 18, 2021, a complete abdominal computed tomography (CT) scan showed a hypocystic shadow in the right adnexa area with a visible compartment inside and appendiceal thickening with a maximal thickness of around 12 mm (Figure 1). The mass in the pelvic cavity was unidentified.

FINAL DIAGNOSIS

The patient underwent an exploratory laparotomy on May 21, 2021, during which the right accessory and cystic mass were removed, thickening of the appendix (~6 cm in length and ~1 cm in diameter) was noted, with a hard texture and edema, attached to the posterior wall of the ascending colon. Appendix malignancy could not be excluded, and was diagnosed following rapid intraoperative pathology. The final diagnosis of the presented case was MAA.
TREATMENT

Gastrointestinal surgery consisting of a right hemicolectomy and peripheral lymph node dissection was performed. The residual intestine, stomach, liver, greater omentum, and peritoneum surface were examined at the end of surgery, and no abnormalities were found.

OUTCOME AND FOLLOW-UP

Postoperative pathology confirmed mucinous adenocarcinoma of the appendix with partial signet-ring cell carcinoma. Immunohistochemistry was performed using the following markers: CDX-2 (+), CK7 (-), CK20 (+), CA125 (+), CD56 (-), Syn (-), Pax-8 (-), WT-1 (-), and SATB2 (+) (Figure 2). The patient received chemotherapy 45 days after the operation. Six courses of XELOX chemotherapy (Oxaliplatin + Capecitabine) were completed, and there was no evidence of recurrence. MAA with signet-ring cell features is considered more invasive and has a worse prognosis. The patient requires regular follow-up every four months for three years, every six months for the next two years, and then every year for the next 15 years, following initial therapy[2].

DISCUSSION

MAA is a rare disease characterized by elevated CA199 and CEA levels. C. PABLO et al showed that tumor markers CEA and CA199 have high clinical value in diagnosing MAA[3,4]. Moreover, the increasing level of CA125 while maintaining normal HE4 helps discriminate between benign and malignant ovarian tumors. Our patient showed elevated CA199 and CA125 levels, which can help diagnose appendiceal lesions[5]. Moh M used immunohistochemistry to identify SATB (-) in ovarian mucinous tumors. The presence of SATB2 (+) and CDX-2 (+) highly suggests that the tumor originates from the colon or appendix[4]. Imaging is a useful diagnostic tool for MAA. Ultrasound observations revealed a cystic mass in the appendix, heterogeneous echogenicity, hypocoystic or tubular lesions in the appendix, and irregular thickening. CT scans can rule out appendiceal inflammation and abscess, and all the above findings help diagnose mucinous cystadenoma[1,6]. MAA is difficult to diagnose due to the non-specific nature of early symptoms, including lower abdominal pain, weight loss, nausea, vomiting, a palpable mass, and acute appendicitis, and is frequently misdiagnosed as a gynecological condition such as right adnexal mass[7]. The bladder may also be affected, with symptoms of bladder irritation or the formation of hematuria, leading to a misdiagnosis of urinary tract infection or bladder cancer[8-10]. In most cases, appendiceal malignancy is detected accidentally by abdominal CT or surgery for appendicitis due to other reasons. Appendiceal cancer is difficult to identify even by preoperative colonoscopy[11]. In the case of submucosal lesions of the cecum near the mouth of the appendix, mucus flows out of the mouth of the appendix; thus, the treating physician should be highly vigilant against appendiceal lesions. Mucinous adenocarcinoma of the appendix is associated with a high risk of peritoneal seeding along with hematogenous and lymph node metastasis. As a surgical treatment for mucinous adenocarcinoma, simultaneous surgical removal of the appendix and right hemicolectomy with peripheral lymph node dissection is preferred[12]. Laparotomy is superior to laparoscopic surgery as it facilitates identification of the involvement of other organs. It is better to protect against incision, thereby avoiding mass rupture, leading to intra-peritoneal dissemination and affecting prognosis.
Figure 2 Histopathological examination of surgically resected specimens. A: The cavity is filled with mucus, mucinous adenocarcinoma of the appendix, and some signet ring cell carcinoma (200×); B: Immunohistochemistry showed SATB2 (+) (200×); C: Immunohistochemistry showed CK20 (+) (200×); D: Immunohistochemistry showed CDX-2 (+) (200×).

CONCLUSION

MAA is remarkably rare, difficult to diagnose and distinguish from other tumors. Preoperative laboratory and imaging examinations, and a well-planned diagnostic and treatment strategy are essential. In mucinous neoplasms, we believe that a right hemicolectomy should definitely be performed if required for tumor clearance because a complete cytoreduction of mucinous tumors of the appendix is associated with improved survival\(^{[12,13]}\). The patient described here presented with common clinical symptoms of MAA. For patients with the appearance of an abnormal appendix during preoperative examination, it is necessary to examine the appendix at the same time to avoid missed diagnosis and misdiagnosis.

FOOTNOTES

Author contributions: Wang L drafted, reviewed, and revised the manuscript; Sun L was the primary physician during the patient’s inpatient stay; Dong Y, Wang YN and Chen YH provided the images; all authors have read and approved the final manuscript.

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Intra-ampullary papillary-tubular neoplasm combined with ampullary neuroendocrine carcinoma: A case report

Hana Zavrtanik, Boštjan Luzar, Aleš Tomažič

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**Abstract**

**BACKGROUND**

The ampulla of Vater is an anatomic and histologically complex region giving rise to a heterogenous group of tumors. This is, to the best of our knowledge, the first case of intra-ampullary papillary-tubular neoplasm combined with ampullary neuroendocrine carcinoma reported in the literature.

**CASE SUMMARY**

A 61-year-old woman presented to the emergency department for evaluation of painless jaundice. Contrast-enhanced computed tomography (CT) of the abdomen and chest showed a periampullary tumor mass measuring 15 mm × 12 mm × 14 mm, with no evidence of locoregional and distant metastases, for which she underwent pancreatoduodenectomy. Histopathologic examination of a resected specimen revealed an intra-ampullary papillary tubular neoplasm with high-grade dysplasia in combination with poorly differentiated grade 3 neuroendocrine carcinoma with a mitotic count of more than 20 mitoses per 10 high power fields and Ki-67 index of 100%. No positive lymph nodes were identified. Her postoperative course was uneventful. Postoperatively, she remained under close surveillance. Multiple liver metastases were observed on follow-up CT 8 mo after the surgery, so systemic therapy with cisplatin and etoposide was initiated.

**CONCLUSION**

The simultaneous occurrence of neuroendocrine and non-neuroendocrine tumors in the ampulla of Vater is rare and the pathogenesis of such tumors is largely unknown. Due to unpredictable clinical behavior and lack of solid evidence on optimal treatment strategy, close patient surveillance is advised after radical resection of the primary tumor.
Key Words: Ampulla of Vater; Neuroendocrine carcinoma; Mixed tumour; Pancreaticoduodenectomy; Prognosis; Case report

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Core Tip: The ampulla of Vater is a transitional region with various distinctive histomorphologic characteristics, although the simultaneous occurrence of neuroendocrine and non-neuroendocrine tumors in this region is rare. When present, problems arise in differentiation between mixed neuroendocrine–non-neuroendocrine neoplasm and the collision of two distinct tumors. Due to the rarity of such tumors, their clinical behavior remains largely unknown, as do appropriate treatment measures. After radical resection, if feasible, the standard of care for the most aggressive and/or predominant component of the tumor from the same site of origin may be adopted. Newly diagnosed cases should be discussed at multidisciplinary team meetings to tailor postoperative treatment and follow-up appropriately.

INTRODUCTION
The ampulla of Vater is an anatomically and histologically complex region constituting the junction of the biliary, pancreatic, and digestive tracts, giving rise to a heterogenous group of tumors with different growth patterns and histologic types[1]. However, the simultaneous occurrence of exocrine and neuroendocrine tumors is very infrequent.

The term intra-ampullary papillary-tubular neoplasm (IAPN) is relatively new, introduced by Ohike et al[1] in 2010 to describe mass-forming preinvasive neoplasms growing predominantly within the ampullary channel, with minimal or no involvement of the bile duct, pancreatic duct, or duodenal papilla. Due to their papillary and/or tubular growth, and variable cell lineage and spectrum of dysplastic changes (adenoma-carcinoma sequence), these tumors are remarkably analogous to pancreatic and biliary intraductal papillary and tubular neoplasms [i.e., intraductal papillary mucinous neoplasms (IPMNs), intraductal tubular papillary neoplasms (ITPNs), and intraductal papillary neoplasms][1]. IAPNs are relatively rare, constituting 33% of primary ampullary tumors and 5.5% of all pancreato-duodenectomy/ampulectomy species[1]. Most cases of IAPN are associated with high-grade dysplasia (94%) or small parts of invasive carcinoma (78%)[1,2]. In their series of 82 IAPN cases, Ohike et al[1] reported four cases of IAPN-associated mixed adenocarcinomas: Two with mucinous, one squamous, and one with a neuroendocrine component.

Neuroendocrine carcinomas (NECs) are poorly differentiated high-grade epithelial neoplasms showing morphological and immunohistochemical features of neuroendocrine differentiation[2]. Although rare, constituting 0.9%-2% of primary ampullary tumors[3-5], NECs in the small intestine are almost exclusive to the ampullary region[2,6]. However, available data is limited to small case series or retrospective reviews[3-8], with only few reports concerning ampullary tumors with neuroendocrine and non-neuroendocrine components[9].

In the present case, we describe an unusual combination of IAPN with high-grade dysplasia and NEC with a Ki-67 proliferation index of 100% arising within the ampulla of Vater. We discuss its clinical and histopathological features, as well as possible pathogenesis.

CASE PRESENTATION

Chief complaints
A 61-year-old woman presented to the emergency department for evaluation of painless jaundice.

History of present illness
A week before presentation, the patient noticed darker urine and pruritus. Her stools became completely pale and yellowing of her skin appeared. She denied abdominal pain, fever, and chills but reported nausea and loss of appetite, with a loss of 4 kg over the last 4 mo.
**History of past illness**

The patient’s medical history was notable for ankylosing spondylitis and arterial hypertension. She had undergone cholecystectomy due to cholecystolithiasis in the past.

**Personal and family history**

The patient reported an 18 pack-year history of smoking. She had no history of alcohol abuse. Her medications included esomeprazole for ulcer prophylaxis, perindopril/indapamide for arterial hypertension, meloxicam for ankylosing spondylitis, and cholecalciferol for prevention of vitamin D deficiency-related disorders. She had no known allergies. Her family history was unremarkable.

**Physical examination**

The patient’s vital signs were normal on admission. Physical examination revealed jaundice. Her abdomen was nondistended, soft, and nontender with no palpable mass.

**Laboratory examinations**

Initial laboratory findings showed elevated levels of bilirubin (total: 91 µmol/L; direct: 65 µmol/L), and pancreatic (amylase: 3.27 µkat/L; lipase: 3.79 µkat/L) and liver enzymes (aspartate aminotransferase: 3.84 µkat/L; alanine aminotransferase: 9.73 µkat/L; gamma-glutamyltransferase: 27.31 µkat/L; alkaline phosphatase: 10.61 µkat/L). Serum levels of the tumor markers carbohydrate antigen 19-9 (CA 19-9) and carcinoembryonic antigen (CEA) were within the normal range (CA 19-9: 20.8 kU/L; CEA: 3.9 µg/L).

**Imaging examinations**

Abdominal ultrasound showed grossly distended intra- and extra-hepatic bile ducts with a probable level of obstruction at the ampulla of Vater. A contrast-enhanced computed tomography (CT) scan of the abdomen and chest revealed a well-defined homogenously enhancing mass measuring 15 mm × 12 mm × 14 mm in the duodenal ampullary region, causing upstream dilatation of intra- and extra-hepatic bile ducts and the main pancreatic duct (Figure 1). An enlarged lymph node measuring 1 cm in the hepatoduodenal ligament and separate lymph nodes measuring 8 mm in the retroperitoneum were observed. In the laterobasal segment of the left lower pulmonary lobe, a small 4 mm soft tissue nodule of uncertain potential was described. There was no convincing evidence of distant metastases. Following discussion of the patient’s case at a multidisciplinary team meeting, the patient underwent pancreatectoduodenectomy (Whipple procedure) and was discharged after an uneventful recovery.

**FINAL DIAGNOSIS**

The resected specimen was submitted for histopathological examination. Macroscopic findings revealed a relatively well-delineated greyish-white solid tumor measuring 1.7 cm × 1.4 cm × 1.1 cm obstructing the ampulla of Vater, with no macroscopically apparent infiltration of the pancreatic tissue (Figure 2A). On histology, the tumor was composed predominantly of papillary structures lined by pseudostratified mildly dysplastic epithelium (Figure 2B and C). Focal areas with high-grade dysplasia were also found (Figure 2D), representing less than 25% of the tumor. However, an invasive component was lacking. There was a sharp transition to poorly differentiated grade 3 NEC (Figure 3A), measuring 11 mm in the greatest diameter, with a mitotic count of more than 20 mitoses per 10 high power fields (Figure 3B). Immunohistochemical analysis of the neuroendocrine tumor revealed cells positive for synaptophysin, insulinoma-associated protein 1 (Figure 3C), diffusely positive for cytokeratin (CK) 7, focally positive for CK19, diffusely positive for thyroid transcription factor-1 (TTF1), and negative for chromogranin A, CK20, gastrin, insulin, somatostatin, and glucagon. The proliferative index (Ki-67) was 100% (Figure 3D). The papillary-tubular component lacked immunoreactivity for neuroendocrine markers, CK20, and TTF1, but was diffusely positive for CK7, CK19, and mucin 2. There was no lymphovascular or perineural invasion. Surgical margins were negative. No metastases to 25 examined lymph nodes were found. The histological features were consistent with a combined IAPN with high-grade dysplasia and poorly differentiated NEC.

**TREATMENT**

Pancreatectoduodenectomy (Whipple procedure) with lymphadenectomy was performed for tumor removal. Considering the final histopathologic diagnosis, close postoperative surveillance was advised at a multidisciplinary team meeting for neuroendocrine tumors.
OUTCOME AND FOLLOW-UP

The postoperative course was unremarkable and the patient was discharged from the hospital on postoperative day 6.

Further diagnostic work-up of the patient was performed with the aim of excluding the possibility of a metastatic NEC, especially in view of CK7 and TTF1 positivity. She therefore underwent an 18F-FDG PET/CT scan 1.5 mo after the surgery, which showed no metabolic activity in a previously described 4 mm peripheral lesion in the laterobasal segment of the left lower pulmonary lobe. Furthermore, no metabolically active lesions were found elsewhere in the body suggestive of distant NEC metastases.

Postoperatively, the patient attended regular follow-up visits and CT evaluation every 3 mo. Follow-up chest CT scans showed no evidence of disease spread to the lungs and no changes to a previously described pulmonary lesion. However, several small (the largest one measuring 15 mm) hypervascular lesions in the right liver lobe, suggestive of liver metastases, were observed on abdominal CT scan 9 mo after the surgery (Figure 4). Systemic therapy with cisplatin and etoposide was therefore initiated.
DISCUSSION

Simultaneous coexistence of two distinct tumors can result from either proliferation of a single precursor cell with divergent differentiation (composite tumors), or combined growth of two different neoplastic clones arising from distinct precursor cells (collision tumors)\cite{10}. Mixed neuroendocrine–non-neuroendocrine neoplasms (MiNENs) are a conceptual category of epithelial neoplasms in the gastro-entero-pancreatic tract displaying a coexistence of neuroendocrine and non-neuroendocrine components, each comprising at least 30% of the neoplasm\cite{2}. The term was introduced by La Rosa et al \cite{11} in 2016 to better address the morphological and biological heterogeneity of this group of neoplasms, as opposed to their previous classification under the category of mixed adenoneuroendocrine carcinomas\cite{2,11}. Despite a combination of adenocarcinoma and NEC being the most frequent, mixed digestive neoplasms encompass a heterogeneous spectrum of possible combinations between neuroendocrine neoplasms (typically poorly differentiated NEC) and other epithelial tumors of the tubular
digestive tract (adenoma, adenocarcinoma, and squamous cell carcinoma) and pancreas (ductal adenocarcinoma, acinar cell carcinoma, IPMN, and serous cystic neoplasm). Nevertheless, neoplasms in which the non-neuroendocrine component consists solely of a carcinoma precursor do not fit the definition of MiNENs according to the 2019 WHO classification[2]. Based on available molecular data, the two components of MiNENs exhibit common molecular alterations, indicating a monoclonal origin from a common pluripotent epithelial stem cell capable of bidirectional differentiation toward endocrine and exocrine phenotypes[10-12]. In contrast, collision tumors result from two distinct cell populations giving rise to two separate but adjacent components with no mixed or transitional area in between, exhibiting a completely different genetic landscape[10].

Whether the tumor described in our patient represents a true mixed neoplasm with both exocrine and endocrine differentiation, or whether it is a coincidental collision tumor seems unclear. In our case, NEC is associated with IAPN, which is a preinvasive neoplasm. Similarly, individual reports can be found in the literature concerning NEC associated with intracholecystic papillary-tubular neoplasm (ICPN) in the gallbladder[13-16] or IPMN in the pancreas[17-19]. However, the literature data regarding the histogenesis of such tumors is not clear. Alternatively to the concurrent existence of two distinct independent lesions, some authors suggest that the two components of the tumor potentially arise from either a common progenitor capable of differentiation in several directions or by transdifferentiation of one tumor cell to another[20,21]. Meguro et al[14] described a case of mixed adenoneuroendocrine carcinoma arising from ICPN associated with pancroaticobiliary malignancy. Based on the histopathologic appearance, they proposed a transdifferentiation from poorly differentiated adenocarcinoma to NEC as the most possible histogenesis of the tumor[14]. Furthermore, Sciara et al[15] performed immunohistochemical and molecular analysis of a gallbladder MiNEN composed of ICPN, adenocarcinoma, and NEC and revealed the same mutation profile, namely, TP53 mutation c.700T>C in all three components, supporting the hypothesis of their monoclonal origin. On the other hand, Stukavec et al[17] studied chromogranin A and CD57 as markers of neuroendocrine differentiation in pancreatic NEC combined with IPMN and, based on the pattern of immunoreactions, refuted the hypothesis that the two components share a common origin from one progenitor neoplastic cell. However, in most previously described cases of IPMN or ICPN presumably related with a neuroendocrine component, the papillary component showed variable areas of high-grade dysplasia together with invasive carcinoma[14,16,18,19]. In our case, a full differentiation spectrum is lacking since IAPN shows mainly low-grade dysplasia with only small foci of high-grade dysplastic changes, comprising less than 25% of the tumor and no invasive component. We could postulate that the IAPN component gave rise to invasive adenocarcinoma, which very early transdifferentiated to NEC, as has been shown in colorectal NEC with adjacent glandular adenoma or adenocarcinoma components. In these tumors, extensive molecular analysis has provided evidence that the two components share a common clonal origin and that their separation occurs early during malignant transformation, with subsequent independent mutational evolution[10,22]. Moreover, typical genetic founder mutations of the classical colorectal adenoma-carcinoma sequence found in colorectal NECs strongly suggest their evolution from colonic mucosa through a similar malignant transformation process, with additional subsequent transdifferentiation into a neuroendocrine cell phenotype[22]. Genetic data allowing definite conclusions regarding the molecular origin of ampullary NEC are non-existent. In our case, therefore, NEC arising from IAPN could be suggested but remains hypothetical, allowing a strong possibility that the two tumor components derived from two distinct pathologic events and their co-occurrence is only coincidental.

Due to the rarity of such tumors, their clinical and pathological behavior remains largely unknown, as do appropriate therapeutic measures. In the case of MiNENs, their outcome is highly dependent on the type of neuroendocrine and non-neuroendocrine components, giving rise to different prognostic categories according to the grade of malignancy of each component[11]. In the present case, whether it is a true mixed neoplasm or not, the tumor’s pure counterparts are associated with contrasting clinical outcomes. Non-invasive IAPNs show a favorable prognosis with 3- and 5-year survival of 100% after successful removal[1]. The prognosis of invasive IAPNs is still significantly better than that of conventional invasive carcinomas of the ampulla, although the difference in survival rate at 5 years did not reach statistical significance (3-year survival rate 69% vs 44%, P < 0.01 and 5-year survival rate 45% vs 28%, P = 0.06 for invasive IAPNs vs other invasive ampullary carcinomas, respectively) [1]. On the other hand, NECs are highly aggressive neoplasms, usually even more so than the common types of carcinoma arising at the same site[2]. Reported overall survival for patients with localized disease was 38 mo in a Surveillance, Epidemiology and End Results data analysis of 2546 patients with high-grade gastrointestinal NECs[23]. In comparison, the overall survival of 28.6 mo was reported for localized gastro--entero-pancreatic MiNENs in a large multi-center series[24]. Specific data on ampullary NEC or MiNEN survival are lacking, but their prognosis seems dismal. Vanoli et al[6] collected a retrospective series of 203 duodenal and ampullary neuroendocrine neoplasms treated surgically or endoscopically, among which 22 were ampullary NECs. Most NECs caused patient death in a median of 10 mo from diagnosis, with only one patient being alive without disease 42 mo after surgery[6]. Similarly, among 18 surgically treated ampullary neuroendocrine neoplasms reported by Milanetto et al[7], disease recurrence occurred in all four cases of NECs, with a median disease-free survival of 14 mo after R0 pancreateoduodenectomy. Despite systemic treatment of recurrence, all four patients eventually died due to NEC progression, after a median follow-up of 23 mo[7]. Given the shorter survival time and high
risk of recurrence after upfront surgery, the authors proposed alternative treatment approaches for ampullary NECs, provided that biopsy availability is ascertained before the final therapeutic decision [7]. Adjuvant chemotherapy after R0 resection seems to offer improved survival[25,26]; however, the clinical relevance of this finding cannot be determined solely on the basis of individual reported cases.

Since no guidelines or solid evidence exist to support the best way of adjuvant or other types of treatment, it seems reasonable to plan the treatment according to the standard of care for the most aggressive and/or predominant component of the tumor from the same site of origin, in our case ampullary NEC. Based on the European Neuroendocrine Tumor Society guidelines for gastro-entero-pancreatic NECs, surgical resection together with platinum-based postoperative chemotherapy is advised in the case of localized disease, although supported by low-level evidence[23,27]. After complete resection of localized NEC, follow-up visits with conventional imaging (CT or magnetic resonance imaging) should be scheduled every 3-6 mo during the first 2 to 3 years and then every 6-12 mo up to 5 years after surgery[27]. In the case of coexistence of two different tumors, clinical patterns might differ significantly[24]. We thus recommend that newly diagnosed cases are discussed at multidisciplinary team meetings to tailor postoperative treatment and follow-up appropriately. The present case showed significant mitotic activity and an elevated proliferation index, as confirmed by diffuse detection of Ki-67 in 100% of cells. However, no lymph node metastases were demonstrated in any of the 25 examined lymph nodes. The patient did not undergo adjuvant systemic treatment initially; however, she was kept under close surveillance. Systemic therapy with cisplatin and etoposide was initiated after liver metastases were discovered on follow-up CT 8 mo after the surgery.

CONCLUSION

We describe, to the best of our knowledge, the first case of IAPN associated with NEC. The pathogenesis of this rare entity is considerably unclear, with problems arising in differential diagnosis between mixed neuroendocrine–non-endocrine neoplasm or collision of two distinct tumors. Radical resection is the treatment of choice for resectable tumors, although the prognosis appears unpredictable. Further investigations including molecular analyses are required to advance the biological understanding of this rare disease and identify the appropriate treatment strategy.

FOOTNOTES

Author contributions: Zavrtanik H reviewed the literature and contributed to manuscript drafting; Luzar B performed the pathological analysis; Luzar B and Tomažič A critically revised the manuscript for important intellectual content; all authors read and approved the final version of the manuscript.

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Commentary on "Primary orbital monophasic synovial sarcoma with calcification: A case report"

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Abstract

The present letter to the editor is related to the study titled “Primary orbital monophasic synovial sarcoma with calcification: A case report”. Orbital synovial sarcoma is one of the rare intraorbital masses seen in adult and pediatric populations. Some case reports in the literature revealed that synovial sarcoma may contain calcifications. Therefore, it is important to make differential diagnosis among calcified orbital masses in childhood.

Key Words: Orbital tumor; Synovial sarcoma; Calcification; Children; Histopathology; Radiology

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Core Tip: This letter to editor serves to contribute additional information regarding differential diagnosis and immunohistochemical features to the article. We hope that by using radiographic and immunohistochemical features, we can assist in differentiating calcified orbital masses in the pediatric population.

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TO THE EDITOR

We read the article “Primary orbital monophasic synovial sarcoma with calcification: A case report”[1] with great interest and appreciated the authors for this comprehensive case report. We also thought that it might be favorable to contribute additional information about differential diagnosis and shortly immunohistochemical features to the discussion. For this purpose, we focused on the differentiation among the pediatric intraorbital calcific masses.

In the literature, intraocular[2] and extraocular[3-5] synovial sarcoma cases have been reported. Retinoblastoma is one of the most common intraocular tumors with calcification in children under 5 year old. The presence of calcification is an essential feature[6]. It is hypointense on T2 gravimetric imaging (WI), and slightly hyperintense on T1WI on magnetic resonance imaging (MRI) compared with the vitreous humor. Besides, heterogeneous enhancement can be seen on post-enhanced imaging. This case report reported intraocular synovial sarcoma in a 48-year-old female patient[2] and retinoblastoma was not included in the differential diagnosis due to the possible age factor.

Rhabdomyosarcoma is one of the relatively more common masses in children. On computed tomography (CT), it is usually seen as an extraconal irregular ovoid, well-circumscribed mass. If there is an adjacent bone destruction, concurrent calcification can be seen. As its size increases, it becomes more heterogeneous and its borders are unclear. The eyelid thickening is a typical finding even without an extension. On MRI, it is hypointense on T1WI and hyperintense on T2WI[7].

Synovial sarcomas should also be differentiated from metastases. The most common pediatric orbital metastases are neuroblastoma. The presence of a primary tumor in the retroperitoneum or posterior mediastinum would facilitate the diagnosis[7]. Hyperdense appearance of neuroblastoma metastases on CT series is also helpful in differential diagnosis[7]. Ewing sarcoma metastasis can also be considered in children. Immunohistochemical features are helpful in differentiating Ewing sarcoma from the synovial sarcoma. EMA and CK7 are helpful in diagnosing synovial sarcoma, while CD99/Fli-1 is helpful in Ewing’s sarcoma[8]. In addition, calcification can be seen as a result of dystrophic calcification in metastatic tumors, unlike the others[3].

Dermoid cyst is one of the most common orbital masses in children. Since it may contain calcification, it should be included in the differential diagnosis of synovial sarcoma. Bone changes may be the cause. The cystic component, fluid levels, and the presence of fat attenuation (associated with high T1 signal on MRI) are helpful in the differential diagnosis[7]. In addition, diffusion restriction on diffusion weight imaging, non-enhancement in post-contrast images, and smooth contours can aid in differential diagnosis[6].

Infantile hemangioma is the most common tumor in infancy and although calcification is rarely present, it should be considered in the differential diagnosis. It is usually located extraconally and makes some changes to adjacent bone like expanding or scalloping, but invasion occurs extremely rare. It is enhanced homogenously after contrast administration. On T1WI, the well-defined marginated mass is often isointense to hyperintense compared to muscle, and moderately hyperintense on T2WI with flow voids within the tumor. The presence of a flow void is an important feature to differentiate from the other masses[7].

Meningiomas account for 2% of primary orbital tumors and they are caused by the periosteum of the orbital wall. It may show coarse diffuse calcifications and sclerosis in the optic foramen that are helpful in the diagnosis. Although not specific, central radiolucent line may be seen[3,6].

Peripheral nerve sheath tumor (PNST) is one of the calcified intraorbital tumors. Histopathologically, it can express S100, EMA, CK7, CK19, TLE 1, and SOX10 as synovial sarcoma. On the other hand, while PNST expresses CD34, it is rarely seen in synovial sarcoma[3,9].

Finally, we could contribute to the current study about immunohistochemical features of synovial sarcomas. They nearly all express EMA (+) and cytokeratin (especially CK 7) (+), and 30% of them express focal S100 (+). CD99 (+) is also expressed in 60%-70%, and LTE1 (+) occurs in > 90%. In contrast, CD34 is rarely/seldom expressed. The current study presented that EMA, CK 7, and S-100 were negative and CD34 was positive in immunohistochemical study, unlike the previous studies[3,5,9].

FOOTNOTES

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