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Transmission of severe acute respiratory syndrome coronavirus 2 via fecal-oral: Current knowledge

Filipe Antônio França da Silva, Breno Bittencourt de Brito, Maria Luísa Cordeiro Santos, Hanna Santos Marques, Ronaldo Teixeira da Silva Júnior, Lorena Sousa de Carvalho, Samuel de Sousa Cruz, Gabriel Reis Rocha, Gabriel Lima Correa Santos, Kathlen Coutinho de Souza, Rebeca Gabrielle Almeida Maciel, Daiana Silva Lopes, Natália Oliveira e Silva, Márcio Vasconcelos Oliveira, Fabrício Freire de Melo

Abstract

The pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in more than 93 million cases and 2 million deaths in the world. SARS-CoV-2 respiratory tract infection and its main clinical manifestations such as cough and shortness of breath are well known to the scientific community. However, a growing number of studies have reported SARS-CoV-2-related gastrointestinal involvement based on clinical manifestations, such as diarrhea, nausea, vomiting, and abdominal pain as well as on the pathophysiological mechanisms associated with coronavirus disease 2019. Furthermore, current evidence suggests SARS-CoV-2 transmission via the fecal-oral route and aerosol dissemination. Moreover, studies have shown a high risk of contamination through hospital surfaces and personal fomites. Indeed, viable SARS-CoV-2 specimens can be obtained from aerosols, which raises the possibility of transmission through aerosolized viral particles from feces. Therefore, the infection by SARS-CoV-2 via fecal-oral route or aerosolized particles should be
conceptualization, methodology, formal analysis, investigation, and supervision.

Conflict-of-interest statement: There is no conflict of interest associated with any of the senior author or other coauthors contributed their efforts in this manuscript.

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In December 2019, cases of pneumonia of unknown etiology were reported in Wuhan, China. The disease would be later named corona virus disease 2019 (COVID-19), and researchers found that it is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[1]. According to the World Health Organization, from the beginning of the pandemic to the writing of this article, more than 93 million cases and 2 million deaths were reported globally[2]. The SARS-CoV-2 belongs to the β-genus of the Coronaviridae family. Its main target is the human respiratory system, and its transmission occurs mainly with personal contact through droplets originated from infected individuals. Droplet transmission involves exposure of an entry point such as mucosa or conjunctiva to potentially infectious particles[3,4]. This infection classically involves respiratory tract symptoms such as dry cough and shortness of breath as well as associated fever, myalgia, myalgia, and fatigue[5]. The patients can also present with gastrointestinal (GI) manifestations, including diarrhea, nausea, abdominal pain, and GI bleeding[6,7]. Interestingly, in January 2020, the first COVID-19 case in the Americas presented with diarrhea. Stools were collected from the patient, underwent analyses, and were later found to be positive for SARS-CoV-2 RNA through reverse transcriptase polymerase chain reaction (RT-PCR) test[8].

The angiotensin-converting enzyme type 2 (ACE2) receptor, which is expressed in alveolar[9], gastric, and rectal epithelial cells as well as in enterocytes from the small intestine[10,11], seems to play a crucial role in the infection pathogenesis[12,13]. Viral binding to ACE2 allows SARS-CoV-2 to enter host cells[14]. In addition, the viral presence in the feces of infected patients or asymptomatic people indicates a possible fecal-oral transmission route[11]. Studies have shown that the ACE2 receptor may contribute to this route, allowing the occurrence of GI infection. The colonization of the GIT via ACE2 may lead to viral spread through stools, which may or may not be preceded by the onset of diarrhea and occur before or after respiratory tract-related clinical manifestations[15,16]. RT-PCR tests of rectal and anal swabs collected from pediatric patients were positive within 10 d after hospital discharge following mild
COVID-19, even after patients turned asymptomatic and RT-PCR from nasopharyngeal samples were negative[17]. In asymptomatic adult patients, there was viral detection in the stools for up to 42 d as well, whereas nasopharyngeal samples were negative, showing a possible GI involvement regardless of the occurrence of respiratory complaints[18]. In this sense, it has to be emphasized the possible significant implications of this potential transmission route and the possibility of its use for early identification of the SARS-CoV-2 infection as well.

THEORY FOR PATHOPHYSIOLOGY OF GI TRACT INFECTION AND LIVER AND GI SYMPTOMS

Pathophysiology of GI tract infection
The way SARS-CoV-2 infects GI tract (GIT) remains unclear. Of note, there is an evident genetic similarity between this virus and the SARS-CoV (70%), which infects the human body by attaching to the ACE2. Therefore, researchers hypothesized that this receptor could also play a role in SARS-CoV-2 manifestations[19]. Indeed, ACE2 was subsequently identified as the operative receptor of SARS-CoV-2, and, since it is distributed throughout almost all organs, including the small intestine, colon, rectum, and liver epithelia, this receptor may explain the viral presence in the GIT[20,21]. Besides ACE2, serine protease TMPRSS2 seems to be important in the SARS-CoV-2 infection[22]. That enzyme activates the S protein, which facilitates the entry of the virus into cells through the action of its two subunits, S1 and S2. The S1 unit is responsible for binding cell receptors, whereas S2 promotes the fusion between viral and cell membranes[23]. Therefore, the virus depends on both ACE2 and TMPRSS2 to invade host cells[24], as illustrated in Figure 1.

The pathophysiology in humans is not yet fully understood. Because clinical studies in humans are scarce, many experimental studies have been performed with mice. A study showed that a decrease in the levels of tryptophan absorption might be associated with the pathophysiology of the intestinal infection by SARS-CoV-2 in a murine model. This phenomenon can be explained by the need for ACE2 activation for the absorption of the aforementioned amino acid and the competitive binding of the receptor by the SARS-CoV-2. The mice that underwent the infection had an imbalance in their intestinal microbiota and a higher susceptibility to develop colitis, a condition that has been reversed with the administration of glycine tryptophan dipeptide during the study[25].

Another phenomenon that may contribute to the worsening of COVID-19 is the “cytokine storm”, an exacerbated expression of pro-inflammatory cytokines. Studies have observed higher levels of cytokines including interleukin (IL)1β, IL1RA, IL2, IL6, IL7, IL8, IL9, IL12p70, IL15, IL17A, interferon γ, and tumor necrosis factor α in patients with severe COVID-19 than individuals who experienced a milder disease[6]. Ye et al [26] highlighted the gut-lung axis as a potential cause of the intestinal manifestations in COVID-19. The effector CD4+ T cells play a role in GI immunity and chronic enteritis, using the C-C chemokine receptor type 9 to enter the GIT environment. Since C-C chemokine receptor type 9+ CD4+ T cells are highly expressed in the lung during infections with viral pathogens, this may explain intestinal damage and the onset of symptoms such as diarrhea. Moreover, the aggressions against the GIT mucosa can lead to damage to the intestinal barrier, which predisposes to infections by other external pathogens and the onset of GI symptoms[27].

Complementarily, the liver is also affected by the SARS-CoV-2 infection. The ACE2 is expressed in biliary epithelial cells, allowing viral access to the hepatobiliary system [28]. The most common repercussions associated with this organ are increased levels of alanine aminotransferase, aspartate aminotransferase, and aggravation of preexisting liver damage[29]. The intense systemic inflammatory response that can occur in COVID-19 patients, as previously discussed in this topic, may contribute to those repercussions[30,31]. Another important factor is the potential hepatotoxicity caused by drugs used in COVID-19 treatment. Medications such as lopinavir and ritonavir are associated with hepatic dysfunction among inpatients with SARS-CoV-2 infection[32].

GI symptoms
A study analyzing 4243 patients from six countries observed the occurrence of GI symptoms such as loss of appetite, nausea/vomiting, diarrhea, and abdominal pain in 17.6% of the cases. The lack of appetite was the most common symptom (26.8%),
followed by diarrhea (12.5%), nausea/vomiting (10.2%), and abdominal pain (9.2%) [33]. In another analysis including 6686 patients, the prevalence of digestive symptoms was 15%, and nausea/vomiting, diarrhea and loss of appetite were the most common manifestations, with incidences of 6%, 9%, and 21%, respectively. Of note, the symptoms are similar among adults and children. Moreover, patients with GI symptoms had their COVID-19 diagnosis delayed as compared to individuals without GI manifestations[34]. Concerning early GI manifestations of COVID-19, Redd et al.[35] found that, among 318 patients, 61.8% reported at least one GI symptom at the time of hospital admission. Another study found that these manifestations were more common during hospitalization (49.5%) than at the moment of admission (11.6%)[36].

In a study performed with 1942 outpatients, 53.3% presented with at least one GI symptom, with loss of appetite affecting almost half of the patients (47%) and 24.2% of the individuals reporting diarrhea[37]. Pan et al.[38] examined 204 patients with COVID-19 admitted to three hospitals in Hubei, China and noticed that 103 had digestive symptoms such as loss of appetite (n = 81), diarrhea (n = 35), vomiting (n = 4), and abdominal pain (n = 2) (Table 1). The diarrhea was the only GI symptom that occurred as a mild-to-severe manifestation in some patients, and, as the patients’ condition worsened, the digestive symptoms tended to become more intense. Moreover, abdominal pain can be considered as an indicator of severity in patients with COVID-19, being it important for decision-making during clinical management. Kumar et al.[39] observed that patients experiencing severe disease have a 7-fold higher
chance to present with abdominal pain than non-serious cases.

In China, in an analysis with 651 patients, 74 had at least one digestive symptom, including nausea (n = 10), vomiting (n = 11), and diarrhea (n = 53). Only three cases had all the aforementioned digestive symptoms, and four individuals had both nausea and vomiting. Among patients with GI manifestations, the more frequent complication was liver damage, which was observed in 17.57% of the cases. Moreover, one person developed shock and five had severe acute respiratory syndrome [40]. Sulaiman et al [41] confirmed that GI manifestations are common among individuals infected with SARS-CoV-2, and that they are reported mainly as initial symptoms, preceding respiratory symptoms. This study estimates that about half of COVID-19 patients may have GI symptoms along with fever and/or respiratory symptoms.

Regarding hepatic damage, high levels of important markers were registered, such as elevated serum bilirubin in 9% of 1471 patients and prolonged prothrombin time in 7% of 750 cases [42]. Similarly, 243 out of 1450 patients had an abnormally high level of aspartate aminotransferase, and 197 out of 1347 individuals had a high level of alanine aminotransferase [43].

ANAL SWAB AND RNA DETECTION IN FECES

Since March 2020, the detection of SARS-CoV-2 in intestinal biopsies and stool samples has been reported in several studies [28]. Therefore, some authors have highlighted the possibility of fecal transmission of the virus [44].

Currently, there are studies that prove and validate the detection of SARS-CoV-2 RNA in stool samples [45]. In addition, anal swabs (AS) are used for the diagnosis and monitoring of COVID-19, especially to evaluate the possibility of hospital discharge of patients [46]. A timeline that compares the viral load detected in AS and throat smears (TS) during the stages of the disease found that, although TS samples detect viral load earlier, AS detects the virus for longer periods [47].

A Chinese study including 57 individuals has noticed the presence of SARS-CoV-2 viral RNA in extrapulmonary sites. They found that the RT-PCR detection of the viral RNA in stool samples or AS increased the likelihood of increased clinical severity [48]. A study from December 2020 indicates that the use of enteric samples may be effective for the monitoring of the natural course of COVID-19 [49]. The findings regarding the detection of viral RNA in stool are shown in Figure 2. It demonstrates an evolution regarding the development of a new tool for the management of COVID-19 patients [1, 8, 50-52].

The detection of viral RNA in feces has already been observed in individuals infected with another type of coronavirus, the Middle East respiratory syndrome coronavirus [53]. A study that included 3028 patients observed a positivity of 85.8% for SARS-CoV-2 in fecal nucleic acid tests with COVID-19 patients. It was also reported that 71.2% of the patients were still positive for fecal nucleic acid after samples from the respiratory tract became negative for the virus [54]. A study that included children with COVID-19 detected SARS-CoV-2 fecal RNA in more than 91% of the cases, with viral detection in feces for up to 70 d [55]. Data from studies evaluating the duration of positivity of stools for SARS-CoV-2 among infected individuals are shown in Table 2 [56-68]. These findings reinforce the hypothesis raised by several authors regarding possible transmission of SARS-CoV-2 via fecal-oral.

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<tr>
<td>Redd et al [35]</td>
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<tr>
<td>Lin et al [36]</td>
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<tr>
<td>Pan et al [38]</td>
</tr>
<tr>
<td>Jin et al [40]</td>
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<td>Sulaiman et al [41]</td>
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GI: Gastrointestinal; ND: Not described.
TRANSMISSION VIA FECAL-ORAL AND VIA AEROSOLS

Since the first detection of SARS-CoV-2-positive stool samples[6,16,48,66,68-72], the possibility of viral transmission through the fecal-oral route and fecal aerosols has been widely debated. Scientists have gathered their efforts in order to elucidate these issues and to determine the viability of viral particles found in air and stool samples.

**Fecal-oral transmission**

Studies have emphasized the risk of COVID-19 contamination from hospital surfaces and personal fomites. In an evaluation of contaminated surfaces in hospital rooms, researchers found that most samples that were found to be positive for SARS-CoV-2 RNA were from bathrooms[73]. This could indicate the possibility of fecal viral loads being more likely to remain on surfaces than viral particles released from other biological secretions, reinforcing the possibility of fecal-oral transmissions. Another paper found that five out of 27 toilet flushes tested were positive for viral RNA and all the five patients that used these bathrooms had GI symptoms[74]. This could indicate a relationship between enteric manifestations and viral shedding through feces, but further studies are needed on the topic.

Complementarily, cytopathic effects have been observed in Vero cells infected by SARS-CoV-2 isolated from feces of COVID-19 patients[75]. Moreover, the latter

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<th>Country</th>
<th>Age</th>
<th>RT-PCR</th>
<th>Stool</th>
<th>PSDI</th>
<th>Respiratory</th>
<th>PRDI</th>
<th>Relevance information</th>
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<td>1</td>
<td>Xie et al[56]</td>
<td>China</td>
<td>4-9 yr</td>
<td>AS-PS</td>
<td>4/4</td>
<td>8-33 d</td>
<td>11-21 d</td>
<td>One patient with positive stool RNA 54 d after hospital admission</td>
<td></td>
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<tr>
<td>2</td>
<td>Ge et al[57]</td>
<td>China</td>
<td>55 yr</td>
<td>FS-RS</td>
<td>1/1</td>
<td>18 d</td>
<td>7 d</td>
<td>Positive stool RNA 22 d after negative respiratory</td>
<td></td>
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<tr>
<td>3</td>
<td>Lo et al[58]</td>
<td>China</td>
<td>27-64 yr</td>
<td>FS-PS</td>
<td>10/10</td>
<td>5-19 d</td>
<td>9-24 d</td>
<td>Some patients had positive stool even with negative respiratory</td>
<td></td>
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<tr>
<td>4</td>
<td>Zhang et al [17]</td>
<td>China</td>
<td>6-9 yr</td>
<td>AS-PS</td>
<td>3/3</td>
<td>16-20 d</td>
<td>7-14 d</td>
<td>The anal swab was positive after 10 d of discharge</td>
<td></td>
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<tr>
<td>6</td>
<td>Wang et al[60]</td>
<td>China</td>
<td>35-56 yr</td>
<td>FS-PS</td>
<td>5/5</td>
<td>11-30 d</td>
<td>5-9 d</td>
<td>Even after a negative respiratory test, IgM was positive on 2 consecutive occasions</td>
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<td>Wang X et al[61]</td>
<td>China</td>
<td>24-42 yr</td>
<td>FS-PS</td>
<td>2/3</td>
<td>30-36 d</td>
<td>-</td>
<td>15-29 d</td>
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<td>8</td>
<td>Xing et al[62]</td>
<td>China</td>
<td>ND</td>
<td>FS-PS</td>
<td>3/3</td>
<td>8 d-4 wk</td>
<td>2 wk</td>
<td>Positive stool RNA 8-20 d after negative respiratory</td>
<td></td>
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<td>9</td>
<td>Chen et al[63]</td>
<td>China</td>
<td>42-62-yr</td>
<td>AS-FS</td>
<td>28/42</td>
<td>1-24 d</td>
<td>1-19 d</td>
<td>Eighteen patients remained positive for viral RNA in the feces after the pharyngeal swabs turned negative</td>
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<td>10</td>
<td>Wu et al[64]</td>
<td>China</td>
<td>ND</td>
<td>FS-PS</td>
<td>33/74</td>
<td>27, 9 d</td>
<td>16, 7 d</td>
<td>Fecal positive 47 d after the onset of the first symptoms</td>
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<tr>
<td>11</td>
<td>Li et al[65]</td>
<td>China</td>
<td>33-73 yr</td>
<td>FS-RS</td>
<td>5/13</td>
<td>Until 38 d</td>
<td>5-14 d</td>
<td>Positive stool RNA 14-15 d after negative respiratory</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Du et al[66]</td>
<td>China</td>
<td>9 mo-14 yr</td>
<td>FS-PS</td>
<td>7/10</td>
<td>Mean 34.43 d</td>
<td>Mean 9 d</td>
<td>Seven patients positive stool RNA 2 wk after discharge but negative respiratory and urine</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Xiao et al[67]</td>
<td>China</td>
<td>10 mo-78 yr</td>
<td>FS-PS</td>
<td>39/73</td>
<td>1-12 d</td>
<td>ND</td>
<td>ND</td>
<td>Seventeen patients positive stool RNA after negative respiratory</td>
</tr>
<tr>
<td>14</td>
<td>Xu et al[68]</td>
<td>China</td>
<td>2 mo-15 yr</td>
<td>AS-PS</td>
<td>8/10</td>
<td>1-27 d</td>
<td>1-21</td>
<td>Eight patients positive stool RNA after negative respiratory</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Fan et al[69]</td>
<td>China</td>
<td>3 mo</td>
<td>AS-PS</td>
<td>1/1</td>
<td>1-28 d</td>
<td>1-14</td>
<td>Positive stool RNA 14 d after negative respiratory</td>
<td></td>
</tr>
</tbody>
</table>

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; AS: Anal swabs; PS: Pharyngeal swabs; FS: Fecal sample; RS: Respiratory samples; PSDI: Positive stool duration interval; PRDI: Positive respiratory duration interval; ND: Not described; IgM: Immunoglobulin M.

**Table 2 Detection of severe acute respiratory syndrome by coronavirus 2 RNA in anal swabs or fecal sample**
analysis through electron microscopy found viral particles with similar morphology to the novel coronavirus in fecal samples\cite{75-77}. These studies were essential to elucidate if the positive results from RT-PCR tests in fecal samples were due to actual virions or only represent RNA from the inactivated virus.

**Transmission through fecal aerosols**

It is well established that SARS-CoV can be transmitted through fecal aerosols after the analysis of the Amoy Gardens incident in Hong Kong, in which multiple residents from an apartment complex were infected due to faulty pipelines that led to the spread of aerosols from the feces of infected patients\cite{78}. The question raised with the new pandemic is whether or not SARS-CoV-2 is also able to remain viable through the process of aerosolization and to be transmitted.

Some works showed the presence of SARS-CoV-2 in air samples taken from patient’s rooms\cite{74,79}. In two studies, researchers have observed cytopathic effects in Vero cells by viral particles collected in air samples. In one of these studies, the samples were observed through electron microscopy, which detected the presence of SARS-CoV-2 virions\cite{80}. In the other investigation, a full genome sequencing was obtained from purified material from air samples and the viral genome was the same as the genome obtained from the infected patient’s nasopharyngeal swab\cite{81}. This indicates that viable viral particles can be obtained from aerosols, and it raises the question of possible transmission from aerosolized virus shed through feces. Interestingly, in a study, researchers were not able to replicate viruses in Vero Cells from aerosol particles examined\cite{82}. However, as Pan et al\cite{83} have shown, the collection of viral particles using non-ideal air samplers could be the cause of viral inactivation of some specimens, which could impede the observation of cytopathic effects.

In two studies, researchers have tested the time of SARS-CoV-2 survival in aerosol suspensions. The first one found that the virus was able to survive for at least 3 h (the duration of the experiment)\cite{84}. The second one searched for viral RNA through RT-quantitative PCR and found traces of the virus up to 16 h after the aerosolization of the particles, which were later visualized through an electron microscope and presented a shape consistent with the SARS-CoV-2 at the 10th minute of the experiment\cite{85}. These studies show that SARS-CoV-2 is able to remain viable for long periods, and aerosols can be a dangerous form of infection.

Among studies evaluating the possibility of animal infection with virus from fecal samples, Jeong et al\cite{86} intranasally inoculated viral particles that were isolated from the stool of confirmed COVID-19 patients in ferrets. Some animals showed an increase
in viral load throughout the period of infection and tested positive for the virus a few days later. All ferrets had symptoms of the disease after inoculation. In another study, Lee et al.[87] used Syrian Golden Hamsters to inoculate intranasally and orally SARS-CoV-2 in variable doses. They found that hamsters that underwent intranasal inoculation developed more severe respiratory symptoms and similar GI inflammation to those that received the virus orally, but these results were not statistically significant ($P > 0.05$). Both groups tested positive for the virus in fecal samples and saliva[87]. This finding could indicate that in the case of fecal-oral transmission, COVID-19 manifestations could be less severe than through aerosols, but viral shedding from the infected patients would still be an important factor to consider.

Research has also shown that SARS-CoV-2 persistence time depends on multiple factors such as pH, temperature, and humidity, with the longest viability time at 4 °C temperature in a pH of 9[88]. Strategies with the use of this knowledge and standard disinfection procedures should be applied in order to reduce the risk of surface contamination, and special attention should be given to bathrooms in order to prevent transmission from their fomites. Ong et al.[89] found contamination in 87% of surfaces in a patient’s room before cleaning as opposed to no contamination in rooms of patients after the cleaning, showing the importance of precaution during the disinfecting process. In the case of the first SARS coronavirus from 2003, studies have reported that virus viability is highly affected by the pH of the patients’ feces[90]. Analysis should be conducted to evaluate if this applies to SARS-CoV-2 as well.

Overall, although not totally proven, the possibility of infection by SARS-CoV-2 through the fecal-oral route or aerosolized particles should be considered. In any case, proper cleaning processes and prophylactic measures should be performed in order to avoid contact with the virus through fomites or aerosols until the possibility of both types of transmission are properly elucidated.

**ENVIRONMENTAL FACTORS ASPECTS**

Studies that evidence the detection of SARS-CoV-2 in fecal samples raise attention to the risks of human exposure in the environment[91]. The indirect transmission through fomites has been already well documented, especially when individuals touch contaminated surfaces and then take the hands to the mouth, nose, or eyes without first cleaning them[92]. Besides, it is assumed that improper disposal of solid waste associated with viral stability on solid surfaces could lead to contamination of surface water from household or hospital waste[93]. Furthermore, a possible spread of the virus to drinking water sources is assumed when an infected person defecates in open environments. In addition, there is a possible risk of viral transmission in shared toilets[94]. Moreover, Li et al.[95] showed that the flow of water during flushing the toilet can spread viral particles through aerosols.

Although the transmission of SARS-CoV-2 by sewage aerosol is not yet confirmed[93], some studies (Table 3)[96-107] show the detection of SARS-CoV-2 RNA in wastewater. Arslan et al.[108] and Pandey et al.[93] highlight that this can be beneficial from a wastewater-based epidemiology perspective because the viral presence in wastewater can be an early warning as well as a monitoring and surveillance tool for COVID-19. However, they highlight the risk of recurrent outbreaks due to the continued presence of the virus in those media.

Recent surveys have shown that around 2.3 billion people do not have access to a basic sanitation service, and 844 million people do not have a drinking water service worldwide. Another study reports that developing countries have inefficient wastewater treatment[108]. In addition, Pandey et al.[93] emphasized the difficulty of inspection in the least developed countries owing to the absence of a proper sewage system. Besides, Arslan et al.[109] suggested that various societies do not have the basic conditions to inactivate the coronavirus from the water. Therefore, the treatment of water[93], the use of disinfection methods with high doses of disinfectant products[110], and public guidelines on hygienic measures[111] are convenient in that context.

**CONCLUSION**

The current knowledge about the dynamics of the infection in the GI tract strongly suggests a possible transmission through the fecal-oral route. In addition, the spread of infected aerosolized feces in hospital environments, bathrooms, and surfaces draws attention to this issue, which has not been considerably taken into account by health
Main findings

Six out of 12 samples tested positive. Two positive detections within a 6-d period from the same wastewater treatment plant on February. No SARS-CoV-2 RNA was detected; and (2) March: SARS-CoV-2 RNA detection increased concomitant with the increase in COVID-19 prevalence.

Increase in SARS-CoV-2 RNA samples was concomitant with the increase in the number of active COVID-19 patients in the city.

SARS-CoV-2 RNA was detected from all samples.

SARS-CoV-2 RNA was detected quantitatively from all samples.

SARS-CoV-2 RNA was detected in the three locations.

SARS-CoV-2 RNA was detected in septic tanks after disinfection with sodium hypochlorite.

Two out of 15 wastewater samples tested positive.

One of 5 secondary-treated wastewater samples tested positive.

Six out of 12 samples tested positive.

SARS-CoV-2 RNA was detected in 85% of untreated wastewater samples; SARS-CoV-2 RNA was not detected in wastewater treatment plants.

agencies in discussions on infection prevention. The contamination of water by SARS-CoV-2 in sewers, wastewater treatment plants, and rivers, possibly from fecal samples, evidences a major public health problem, especially in developing countries. However, further studies are needed in order to elucidate completely the SARS-CoV-2 transmission via the fecal-oral route.

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Transmission of SARS-CoV-2 via fecal-oral


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Nutrition, nutritional deficiencies, and schizophrenia: An association worthy of constant reassessment

Olakunle James Onaolapo, Adejoke Yetunde Onaolapo

Abstract

Schizophrenia is a mental health disorder that occurs worldwide, cutting across cultures, socioeconomic groups, and geographical barriers. Understanding the details of the neurochemical basis of schizophrenia, factors that contribute to it and possible measures for intervention are areas of ongoing research. However, what has become more evident is the fact that in targeting the neurochemical imbalances that may underlie schizophrenia, the type of response seen with currently available pharmacotherapeutic agents does not provide all the answers that are needed. Therefore, the possible contribution of non-pharmacological approaches to schizophrenia management is worthy of consideration. In recent times, research is beginning to show nutrition may play a possibly significant role in schizophrenia, affecting its development, progression and management; however, while attempts had been made to examine this possible relationship from different angles, articles addressing it from a holistic point of view are not common. In this review, we examine existing scientific literature dealing with the possible relationship between nutrition and schizophrenia, with a view to elucidating the impact of diet, nutritional deficiencies and excesses on the aetiology, progression, management and outcome of schizophrenia. Secondly, the effect of nutritional supplements in prevention, as sole therapy, or adjuncts in schizophrenia management are examined.

Key Words: Diet; Brain; Mental health; Nutritional psychiatry; Psychosis; Schizophrenia spectrum disorders

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INTRODUCTION

Globally, the societal and economic burden of mental health disorders have continued to increase, with available data currently showing an increasing prevalence of a number of these psychiatric disorders in high- and upper-middle income economies [1]. In 2016, mental health and addictive disorders were reported to have affected over 1 billion people worldwide, accounting for about 7% of the global burden of disease measured in disability adjusted life years and approximately 19% of years lived with disability [1]. However, there have been suggestions that these data (despite being high) are still grossly underestimated [2].

Schizophrenia (which is a component of the schizophrenia spectrum disorders) is a chronic, debilitating and complex mental health disorder characterised by impairments in cognition, mood, perception of reality and interpersonal relationships [3]. Worldwide, the case prevalence of schizophrenia has been reported to have risen from 13.1 million in the 1990s to about 20.9 million in 2016 [4]. Despite schizophrenia having a low prevalence (lifetime prevalence of about 1%), the burden of schizophrenia is mainly disability-related [4]. It is associated with significantly higher suicide rates, premature deaths and inability to sustain gainful employment [5-8]. The increasing burden of neuropsychiatric disorders (schizophrenia included) has been attributed partly to public health neglect (linked to stigmatisation) and the absence of effective and affordable treatment options [1]. Hence, in the last few decades, there has been a renewed drive to develop less toxic/more effective therapies and novel strategies for the management of schizophrenia and other mental health disorders.

Recently, there have been reports that nutrition, nutritional deficiencies and excesses are important determinants of mental health [9-12]. Over the years, nutritional interventions have been considered as possible preventive and therapeutic options first in high-prevalence mental health disorders like depression and anxiety and more recently in low prevalence disorders such as schizophrenia [10,13,14]. Nutritional interventions are also crucial to combatting the physical health inequalities and decrements in life-expectancy associated with the psychotic-spectrum [15]. Therefore, there is a growing body of knowledge examining the impact of nutrition, nutritional deficiencies/excesses and nutritional interventions on aetiology, progression and management of schizophrenia. In this article, we examine the existing scientific literature dealing with the possible relationship between nutrition and schizophrenia. Secondly, the effect of nutritional supplements in prevention, as sole therapy, or adjuncts in schizophrenia management are examined.

NUTRITION IN MENTAL HEALTH AND DISEASE

Mental health disorders have at present become a growing societal concern, with recent data continuing to show that the economic, social and health burden of psychiatric disorders (including depression, anxiety and schizophrenia) is rising globally [9,16,17]. However, in recent years, the inadequacy of conventional...
therapeutic options and the need for more effective preventive or therapeutic strategies are directing the focus of research towards examining the possible relationship between nutrition, brain function and the risk of mental health disorders [9,16].

The inkling or proof of the concept that nutrition is important in the maintenance of mental health arose from the descriptions of diseases such as pellagra, beriberi, scurvy and phenylketonuria (which are some of the earliest known human diseases with psychiatric presentations). The pathogenesis of these diseases was linked to nutritional deficiencies and was corrected by nutritional supplementation[15]. Since this period, studies have continued to demonstrate that deficiencies of a number of nutrients, including vitamins (B1, B6, B9, B12) could be linked to the development of psychiatric symptoms or increased risk of developing mental health disorders in adulthood[19-21].

In the last decade or more, the understanding of the crucial role played by environmental factors as determinants of psychiatric disorder risks has increased tremendously. Also, data demonstrating the impact of lifestyle modifications on several non-communicable diseases such as diabetes mellitus and cardiovascular disease are increasing advocacy that lifestyle modification could also be beneficial in addressing mental health disorders[22,23]. Although information is still evolving, the fact that several environmental factors are adaptable has led to suggestions that nutrition or nutritional supplementation could be beneficial in the maintenance of mental well-being or the management of mental health disorders[22].

Normal development of brain structure and function is dependent to a large extent on the availability of amino acids, lipids, minerals and vitamins, which are mainly sourced from dietary intake[17,24]. Hence, there have been suggestions that diet, being a modifiable determinant, can be targeted for the maintenance of mental health and possibly the management of neuropsychiatric disease[25].

The emerging, yet rapidly evolving field of nutritional psychiatry supports the clinical consideration of dietary modifications or the use of nutritional supplementation in the prevention and/or management of psychiatric disorders[26]. There have been reports demonstrating the relationship between the adoption of healthy dietary practices (diets rich in vegetables, whole grains, fruit, nuts, and fish) and the risk of developing mental health disorders like depression was inversely proportional [27-30]. While the possible mechanisms through which dietary strategies and/or interventions could be beneficial in mental health are still being studied, there have been reports suggesting dietary interventions or nutritional supplementation act by modulating biological pathways (oxidative stress, inflammation, neurogenesis, the gut–brain axis)[16]. There have also been reports suggesting that nutrition and dietary composition could directly impact determinants of mental health risk including the gut microbiome, endogenous hormones of the gastrointestinal tract, gut neurotransmitters and neuropeptides[17,31].

Pathophysiology of schizophrenia

Our understanding of the pathophysiology of schizophrenia had in times past been dependent on the concept that schizophrenia was for a large part a hyperdopaminergic state[32,33]. Proposed in the 1960s following the discovery of the antipsychotic benefits of chlorpromazine, the original dopamine hypothesis was a successful heuristic approach to understanding the symptomatology of schizophrenia and response to management[3,33]. The increasing individual and economic burden of schizophrenia has swayed research in the direction of searching for ways to understand better the aetiology of schizophrenia towards the discovery of more effective and efficient treatment and preventive options. Currently, schizophrenia is being described as a complex disorder whose pathophysiology has been attributed to the dysregulation of multiple pathways, including glutamatergic, dopaminergic and γ-aminobutyric acid-ergic neurotransmitter systems[34]. Deficits in acetylcholine muscarinic receptors have also been described. Other factors include inflammation, oxidative stress, autoimmunity and genetics[34].

The modified dopamine hypothesis has attributed the hyperdopaminergic state observed in most patients with schizophrenia to an increased presynaptic striatal dopaminergic activity, which is a final common pathway through which a number of the other factors (numerous genetic and/or environmental) can result in the development of schizophrenia[35,36]. The broadening of the dopamine hypothesis has allowed aetiological factors to be classified as either upstream or downstream[35]. While current treatment options are directed towards addressing the downstream factors responsible for neurotransmitter dysfunction. There have been suggestions that more effective treatments could be achieved if drugs and/or other interventions are
directed at manipulating the upstream factors[35].

**Diet and nutritional factors in schizophrenia pathogenesis**

Current evidence from studies on the impact of diet and dietary intake (Figure 1) in schizophrenia shows that compared to normal controls, persons with schizophrenia have poor dietary practices characterised by increased intake of sodium, cholesterol and higher saturated fats, with low fibre content[37-40]. Increased consumption of sugars and processed foods have also been reported[41-43]. These poor dietary choices have been suggested as possible causes of obesity, metabolic syndrome and high mortality figures, which have been associated with schizophrenia[14,43]. There have also been reports that diets low in omega-3 fatty acids or D-vitamins could also increase risk of developing psychosis[40,44]. The unhealthy dietary practices of persons with schizophrenia have been suggested to result from dysregulation of the reward circuitry, mediated by increased dopamine activity in the mesolimbic pathway and brain regions responsible for the control of cognition[45,46]. The development of obesity, eating disorders, food cravings and addictive behaviours observed in persons with schizophrenia have also been linked to this pathway[47-49].

There have been reports suggesting that the incidence of coeliac disease and non-coeliac gluten sensitivity is higher in patients with schizophrenia compared to the general population[50,51]. Coeliac disease is an autoimmune disorder characterised by inflammation-induced intestinal injury arising from the consumption of gluten-rich diet such as barley, wheat, rye and bulgur. A few studies have reported the triggering of psychotic symptoms by gluten in persons with gluten intolerance[52]. Food sensitivities that are characterised by the elevation of immunoglobulin G antibodies to wheat gliens and bovine milk caseins have also been observed in persons with schizophrenia[53].

Nutritional deficiencies that occur as a result of inadequate intake or the poor absorption of nutrients that are critical to the sustenance of human health have also been recognised as possible risk factors for the development of psychiatric disorders including schizophrenia[13]. Also, nutrition and nutritional composition of foods have also been implicated in mental health. Earlier reports had shown that increased intake of foods deficient in critical compounds such as essential fatty acids[54,55] or rich in substances that can elicit an autoimmune reaction such as gluten could be linked to the development of brain disease and more recently mental illness including schizophrenia[13,22,28,56].

Schizophrenia has also been associated with the development of nutritional deficiencies and metabolic disorders. The results of clinical studies and systematic reviews have demonstrated a higher incidence of metabolic syndrome in patients with schizophrenia compared to the general population; this has been attributed in part to poor eating habits and possibly side-effects of pharmacotherapy[57,58]. Results of biochemical tests had also reported high homocysteine levels as well as low levels of vitamins B9, B12, C and E in the blood of newly diagnosed patients and patients with long-term schizophrenia. Decreased brain levels of vitamin B12 have also been reported in schizophrenia[59]. Deficiencies in vitamin D have also been implicated in schizophrenia, and developmental deficiency of D3 has been associated with an increased risk of developing schizophrenia in adulthood[13,60,61]. There have also been suggestions that low maternal vitamin D levels do not constitute a continuous risk factor for the development of schizophrenia; however, below a critical threshold, it could be associated with an increased risk of developing schizophrenia[13,62]. Deficiencies or excesses of essential trace elements including calcium, zinc, selenium, copper and manganese have also been observed in persons with schizophrenia[63-66].

Further buttressing the importance of vitamins and minerals in schizophrenia are results of clinical studies that had also shown that supplementation with a number of these vitamins was associated with reduction in symptoms and the amelioration of neurological deficits associated with schizophrenia[13,55].

**Mechanisms through which nutrition and nutritional factors influence schizophrenia pathophysiology**

The mechanisms through which diet, nutrient and/or nutritional deficiencies cause schizophrenia or worsen its severity are still being studied. However, a number of modalities (Figure 2) have been suggested. These include factors like poor diet, poor dietary practices and/or nutritional deficiencies that have been linked with the development of hyperhomocysteinaemia, derangement of oxidant-antioxidant status, immune dysregulation and alterations in the levels of pro-inflammatory markers. The importance of oxidative stress and inflammation in schizophrenia had been described...
in the neuroprogressive hypothesis, which considered alterations in oxidative stress and immune-inflammatory markers as possible mechanisms in the pathophysiology of schizophrenia[67-69].

The gut microbiota, which plays a strategic role in food digestion, metabolism and storage of fats/absorption of monosaccharides, has also been reported to be influenced significantly by dietary choices. Several studies have reported that dietary composition and nutritional status are very important modifiable factors in maintaining gut microbiome composition and gut microbial diversity[31,70,71].

There is also growing interest in the relationship that exists between diet and the gut microbiota, and how this relationship impacts schizophrenia pathophysiology and management. However, it is worthy of note that while diet is an important factor determining the composition of the gut microbiota, other factors such as stress and sleep can also alter it. Also, interindividual and time-defined variations in their composition make it harder to define accurately gut microbiota dysbiosis. In recent times, there has been increasing evidence of the importance of the multidimensional relationship that exists between the gut microbiota and the brain, especially its ability to influence the brain through the utilisation of immunologic, endocrine and neurocrine signalling pathways[72]. Alterations in the composition of the gut microbiota and microbial metabolite have been reported to influence the integrity of the gut and bodily immune responses. Gut dysbiosis has been reported in persons with schizophrenia, with reports that increase in the *Succinivibrio* and *Corynebacterium*...
bacterial genera exacerbated schizophrenia symptom severity[73]. Gut dysbiosis also increases susceptibility to infections and inflammation[74]. However, direct proof that diet-induced change in gut microbiota may be a direct cause of schizophrenia symptoms is harder to obtain. Also, dietary manipulations have not been shown to be consistently successful in alleviating schizophrenia symptoms. So far, the link between diet and schizophrenia has been suggested to involve the induction of neuroinflammation and modulation of the gut microbiota; these in turn have been associated with worsening symptoms of schizophrenia in some cases.

Gut-dwelling microbes such as bacteria have the potential to alter neurotransmitter equilibrium through production and/or consumption of a wide range of mammalian neurotransmitters such as dopamine, noradrenaline, serotonin, or γ-amino butyric acid; a number of which are closely-linked to the pathogenesis of schizophrenia[75]. Already, evidence from animal studies (and even some human studies) suggest that gut bacteria can be used to manipulate neurotransmitter equilibrium to impact host physiology and that microbiota-based interventions can alter neurotransmitter levels[76]. However, how this knowledge can be used to develop a robust preventive and curative strategy for schizophrenia is still a challenge.

Studies have reported that diets that are low in anti-inflammatory or rich in pro-inflammatory factors (omega-6 fatty acids are pro-inflammatory in contrast to omega-3 fatty acids that are anti-inflammatory) activate or worsen neuroinflammation, and if left uncontrolled, can induce pathologic changes of schizophrenia and exacerbate schizophrenia symptom severity[77,78]. Exposure to diets rich in gluten has been associated with an increase in the expression of human leukocyte antigen markers, which increase cells susceptible to attacks by T-cells, allowing the release of pro-inflammatory cytokines. Also, there have been reports suggesting that a number of other immune pathways such as the complement protein (C1q) are activated in persons with schizophrenia[86].

A number of the B vitamins, including B2, B6, B9 and B12, are the sources of coenzymes and cofactors needed in one carbon metabolism[79]. One-carbon metabolism is crucial to cell proliferation and survival; therefore, deficiencies in these B vitamins (particularly B9 and B12) have been associated with severe alterations in normal cell biology. There is alteration of S-adenosyl methionine production, impairment of nucleotide synthesis, reduction in cell proliferation and a global hypomethylation of deoxyribonucleic acid[80]. More recently, alterations in one-carbon metabolism resulting in elevation in the level of homocysteine have been considered an independent risk factor for schizophrenia[79]. Homocysteine is a non-protein neurotoxic amino acid that can alter brain structure and function, especially during early phases of brain development[79-81]. The interaction of homocysteine with glutamatergic transmission has also been suggested as one of the possible links between homocysteinaemia and schizophrenia[82]. There have also been suggestions that the activity of homocysteine on other neuromodulators such dopamine, serotonin and acetylcholine could be linked to the development of schizophrenia[82-84].

Deficiencies or low levels of antioxidant vitamins such as C, E and beta carotene have been reported to cause oxidative stress[85]. There is overwhelming evidence demonstrating the crucial role played by oxidative stress in the pathophysiology of schizophrenia[86,87]. Higher lipid peroxidation levels, alterations in plasma and brain levels of antioxidants and/or antioxidant enzyme activity have also been observed in persons with schizophrenia[87-90]. Oxidative stress has also been described as a possible link between vitamins deficiencies and schizophrenia[86]. Studies have also shown that antioxidant vitamins such as C and E offer protection against cellular damage due to either inflammation or highly reactive oxygen-species[85].

**NUTRITION IN SCHIZOPHRENIA THERAPY**

In the last few decades, the crucial role played by nutrition in the maintenance of mental health has continued to be emphasised. The dynamic relationship between adequate intake of dietary nutrients and optimal mental health has also been reported[91,92]. The need to use nutritional interventions to achieve general health and well-being was the beginning of orthomolecular medicine. Orthomolecular medicine is defined as the restoration and maintenance of health through the administration of adequate amounts of substances normally occurring in the body. It allows the use of endogenous and natural compounds as either supplement in conditions of nutritional deficiencies or in the provision of additional requirements in conditions of increased demand[93]. Although, in the past, it had been regarded as a non-scientific approach
to healing, the availability of increasing scientific evidence supporting its benefits in aging-related disease[94] and, more recently, in the management of a number of neuropsychiatric disorders (including depression and schizophrenia) is redefining its importance in clinical medicine[94,95].

Evolving knowledge regarding the impact of derangements in one-carbon metabolism, oxidative stress, autoimmunity, inflammation and the gut microbiome on the neuropathophysiology of schizophrenia[56,96,97] is leading scientists to suggest potential mechanisms that allow for the use of diet, nutrition and nutritional supplements as sole or adjunctive therapies in the management of psychiatric disorders such as schizophrenia[36].

**Dietary intervention as a therapeutic target in schizophrenia**

In the last half century, modifying dietary behaviours for the prevention and management of chronic disease has been a crucial area of research[98-102]. There is now overwhelming evidence that modifying important dietary habits, and dietary composition such as the consumption of vegetables/fruits, and increasing intake of fibre, polyunsaturated fats, and omega-3 fatty acid (in contrast to omega-6) have significant and sustained general health benefits[103,104].

More recently, the benefits of dietary choices and nutritional factors in sustaining mental health[105,106] especially in preventing the development of medical and metabolic complications are generally being recognised in psychiatry. Also, the use of dietary interventions particularly in the management of schizophrenia is slowly evolving. Gradually, emphasis is being placed on the need to include dietary interventions as sole (in the case of psychosis due to nutritional deficiencies) or adjunctive therapies in the management of positive and/or negative symptoms in schizophrenia[92,107].

Healthy diets such as the Dietary Approaches to Stop Hypertension (DASH) and the Mediterranean diet are lifestyle changes or dietary modifications have been shown to be beneficial in the prevention, risk factor reduction and management of chronic diseases. Several studies have demonstrated that strict adherence to these dietary choices have rewarding effects on diabetes, cardiovascular diseases, obstructive sleep apnoea, chronic kidney disease, arthritis, cancer and metabolic diseases[104,108-110]; with significant impact on reducing total mortality[104,111].

The Mediterranean diet, which reflects the eating habits of the Mediterranean or Middle East countries, is based on the consumption of fresh vegetables, cereals, olive oil and plants; with low consumption of meat[104]. While the DASH diet, which was designed by National Institute of Health funded researchers in the 1990s to aid in the prevention and treatment of high blood pressure, was also shown to be effective in lowering blood cholesterol levels. It is a diet rich in vegetables, fruits, low-fat dairy products, whole grains, nuts, grains, fish, meat and poultry[110]. Dietary interventions have proven to be successful in reducing the risk factors for a number of chronic diseases including diabetes mellitus, cardiovascular disease, stroke, metabolic syndrome and in some mental health disorders including depression and anxiety[112].

The benefits of good nutrition in schizophrenia have been self-reported[113] and while the details of its benefits are still being studied scientifically, proponents of these alternative treatment approach have suggested that the beneficial effects of good nutrition and or dietary interventions could be multipronged. Good nutrition and healthy diets can impact schizophrenia symptom severity, duration of episodes, and the incidence of negative symptoms[113]. Also, there have been reports that persons with schizophrenia are more likely to have co-morbid health problems, including obesity, chronic inflammation, metabolic syndrome, autoimmune disease and cardiovascular disease[40,113], all of which when they occur in the general population benefit from nutritional intervention. This has led to suggestions that these nutritional interventions could help in reducing schizophrenia mortality, especially when it is a sequela of these co-morbid conditions[114,115]. In a few instances, there have also been suggestions that dietary interventions could be beneficial in schizophrenia, especially if there is a causal relationship between diet and schizophrenia[114].

The earliest instances of dietary intervention in schizophrenia were from suggestions that gluten-free diets could be successful in mitigating schizophrenia or mitigating against its severity[116,117]. However, while a few studies (Table 1) have demonstrated the ability of diet free of gluten to improve functioning in schizophrenia or decrease symptoms severity[118-121], there have also been several studies that have reported no effect[122,123].

In a double-blind gluten-free vs gluten-rich diet study, Vlissides et al[120] reported significant improvement in symptoms measured on a psychosis in-patient’s profile. Jackson et al[124] tested the feasibility and efficacy of administering gluten-free diet in
DASH: Dietary approaches to stop hypertension; PUFA: Polyunsaturated fatty acid.

2 patients with schizophrenia who were either positive for anti-tissue transglutaminase/anti-endomysial antibodies (coeliac disease) or antibodies to gliadin (indicative of gluten sensitivity). They reported that gluten-free diet was well-tolerated in patients with schizophrenia, resulting in no adverse effects; also, in both patients (irrespective of the antibodies), improvements in schizophrenia symptoms and extrapyramidal side-effects were observed[124]. Porkins et al[122] and Storms et al[123] in separate studies that compared the effects of a gluten-free diet or added gluten in patients with schizophrenia reported no significant effect of gluten-free diet on tests and rating scales. However, in those who received gluten–rich diet, a significant improvement was observed in tension-anxiety and anger-hostility[123]. The potential adverse effect of gluten-free diet has also been reported. De Palma et al[125] reported that the administration of gluten-free diet to persons who do not have coeliac disease or non-coeliac gluten sensitivity was associated with alteration of the gut microbial flora and an increase in host immune activation.

Ketogenic diets are high in fat but low in carbohydrate and have been shown to be successful in weight loss and/or control, reduction of cardiovascular risks and the management of diabetes mellitus[126,127]. While it has also been shown to be beneficial in the management of Alzheimer’s disease and seizure disorders[126,129], there is however a dearth of scientific information on its benefits in schizophrenia. Kraft and Westman[130] published a case report that demonstrated the complete amelioration of schizophrenia symptoms in a 70-year-old Caucasian woman with long-standing schizophrenia following the commencement of a ketogenic diet.

Currently available literature points to the fact that the beneficial effects of a gluten-free diet is limited to a small subset of persons with schizophrenia (those with coeliac...
disease or non-coeliac gluten sensitivity). So, there have been suggestions that alternative dietary modifications such as diets high in fibre, the DASH diet or Mediterranean diet, which are associated with minimal side-effects, could become beneficial as adjunctive therapies in improving immune, metabolic and cardiovascular events linked to the premature mortality observed in schizophrenia. Soric et al.[131] conducted a 3-mo randomised controlled study to examine the benefits of the DASH diet in reducing metabolic syndrome parameters in hospitalised schizophrenic patients and observed no significant difference in the prevalence of metabolic syndrome between the intervention group and control after 3 mo of dietary intervention[131]. However, the result of another interventional study carried out in a sample of young persons with first episode schizophrenia showed reduced sodium load and caloric intake compared to baseline[14]. The Mediterranean diet has also been suggested to be beneficial in schizophrenia, largely due to its ability to reduce pro-inflammatory markers, cardiovascular disease risk and immune markers; while improving the ratio of omega-3 to omega-6 fatty acids[131-133].

Overall, while there have been several suggestions of the possible benefits of dietary modifications and interventions in the management of schizophrenia, the dearth of scientific information in this regard limits its use.

**Nutritional supplements as therapeutic targets or adjuncts in schizophrenia**

There is a great deal of interest directed towards the use of nutritional supplements such as vitamins and trace elements either as therapeutic targets or adjuncts in the management of schizophrenia (Table 1). While this is an evolving area of medicine, evidence of the strong correlation amongst nutritional deficiencies, mineral excess/deficiencies and the awareness of the impact of oxidative stress, neuroinflammation and immune mediated responses in the pathophysiology of schizophrenia are increasing research into the benefits of nutritional interventions and nutritional supplements in schizophrenia management. Also, more recently, there is increasing consideration of diet and nutrition as important modifiable factors in mental health disorders; with a growing body of evidence showing that nutritional supplementation with vitamins, essential fatty acids, minerals and trace elements not only provide additional physiological benefits but could also act as adjuncts to pharmacologic therapy[16,25].

The earliest suggestions that vitamins could provide therapeutic benefits in schizophrenia possibly arose from reports that associated schizophrenia with vitamin deficiencies[85]. These benefits have been attributed to their ability to act by using mechanisms that are separate from those employed by the current pharmacologic agents. The result of clinical studies had reported that supplementation with folic acid, pyridoxine and vitamins B12 and C were beneficial in ameliorating schizophrenia symptoms when used alone or as adjuncts with conventional therapy[85]. Also, the results of preclinical[69,92,134,135] and clinical studies[95,136-138] have continued to provide evidence in support of the beneficial effects of other nutritional supplements in schizophrenia; although there have also been a few dissenting reports. Gama et al. [134] reported that the administration of omega-3 fatty acid polyunsaturated fatty acid (PUFA) supplements to adolescent rats was protective against the development of behavioural changes in a ketamine model of schizophrenia, features that are synonymous to positive, negative and cognitive symptoms of schizophrenia[134]. In another study, Zügno et al.[139] observed that pre-treatment of adolescent rats with omega-3 fatty acid was also protective against decreased inhibition of the startle reflex, lipid peroxidation and decreased antioxidant status in different brain regions (prefrontal cortex, hippocampus, striatum). In humans, Amminger et al.[95] examined the ability of omega-3 fatty acid supplementation to protect against the development of first-episode psychosis in adolescents and young adults (13 to 25 years of age) with subthreshold psychosis. They observed that in the group administered omega-3 PUFA, there was a decrease in the rate of transition to full-threshold psychosis and a decrease in the positive and negative symptoms, compared to those administered placebo[95]. There have also been consistent reports of positive effects of omega-3 fatty acids supplementation in schizophrenia[140,141]. Chen et al.[140] following a metaanalysis of randomised, double-blind, placebo-controlled clinical trials reported that while omega-3 fatty acid PUFA supplementation was effective in reducing clinical symptoms in persons with prodrome and/or first episode schizophrenia, mixed results were observed in persons with chronic schizophrenia[140]; suggesting that it may not be consistently beneficial in this subset. While examining the effect of omega-3 fatty acids on the development of hostility and psychopathology amongst hospitalised persons with acute violent schizophrenia, Qiao et al.[141] observed no significant effect of the adjunctive use of omega-3 fatty acids supplementation on symptoms,
when compared to conventional therapy alone. Similarly, improvements in symptoms had been reported for eicosapentaenoic acid supplementation in persons with early schizophrenia[136,142], while there have also been reports of no benefits of eicosapentaenoic acid in persons with chronic forms of schizophrenia[143,144].

A number of other preclinical studies had also examined the effects of other dietary supplements such as zinc or melatonin as therapeutic targets and/or adjuncts in mouse models of schizophrenia[29,92,107]. Onaolapo et al[107] reported that zinc administered (either alone or with standard antipsychotics) was associated with a reversal of ketamine-induced alteration in open-field behaviours, working memory, social interaction, antioxidant status and lipid peroxidation. Onaolapo et al[92] also examined the ability of dietary zinc supplementation to mitigate the development of ketamine-induced schizophrenia-like behaviours in prepubertal and aged mice. Results showed age-related decrease in ketamine-induced alterations in behaviours (open field memory and anxiety) acetylcholinesterase activity and oxidative stress parameters[92]. Dietary supplementation with melatonin has also been shown to reverse schizophrenia-like symptoms in mice, with benefits comparable to standard medications[29].

The benefits of dietary supplements in mitigating the pro-oxidant and other drug-related side-effects of antipsychotics like haloperidol have also been reported in mice [135] and in humans[145]. Sivrioglu et al[145] examined the effects of combining antioxidant supplements (omega-3 fatty acid, vitamins E and C) in schizophrenia patients with ongoing haloperidol therapy over a 4 mo period. Results showed an improvement in clinical symptoms and a decrease in the severity of side-effects induced by haloperidol[145]. Dietary supplementation with zinc had also been shown to reverse haloperidol-induced changes in open field behaviour and spatial working memory, while potentiating haloperidol induced anxiolysis; suggesting that co-administration of haloperidol with zinc can reduce some side-effects that are known to be associated with haloperidol therapy[135].

As research continues to reveal the relationships that link nutrition to the expression of symptoms, and the progression of schizophrenia, it is becoming apparent that the roles of nutrition might emerge to be larger than previously-thought. The pro- or anti-inflammatory effects of some food components are already known. However, while the impact of gut bacteria on neurotransmitter levels is now being understood; the indirect route from consumed food to possible changes in neurotransmitter balance appears more difficult to navigate.

CONCLUSION

Overall, despite our current knowledge of the possible links between nutrition and schizophrenia, and some tentative pathways for this relationship, the larger challenge remains how to get to the point where precision dietary manipulation becomes a widely-accepted approach to schizophrenia prevention and a day-to-day management strategy.

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Grounded theory qualitative approach from Foucault's ethical perspective: Deconstruction of patient self-determination in the clinical setting

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Abstract

This paper aims to explain the construction of the autonomous subject from Foucault's ethical perspective for the qualitative analysis of interprofessional relationships, patient-professional relationships, and moral ethics critique. Foucault tried to break loose from the self, which is merely the result of a biopolitical subjectivation and constituted an interpersonal level. From this, different elements involved in the decision-making capacity of patients in a clinical setting were analysed. Firstly, the context in which decision-making occurs has been explained, distinguishing between traditional practices involved in self-care and the more modern conceptions that make certain possible transformations. Secondly, an attempt is made to explain the formation of the medicalisation of society using the transformations of what Foucault called "techniques of the self". Finally, the ethical framework for a subject's "self-creation", insisting more on the exercises of self-subjectivation, reinforcing the ethics of the self by itself, the "care of the self", has been explained. The role of the patient is understood as an autonomous subject to the extent that the clinical institution and the professionals involved comprehend how the patient’s autonomy in the clinical environment is constituted. All these elements could generate grounded theory on the qualitative methodology of this phenomenon. The current ethical model based on universal principles is not useful to provide a capacity for patients decision-making, relegating to the background their opinions and beliefs. Consequently, a new ethical perspective emerges that aims to return the patient to the fundamental axis of attention.

Key Words: Decision making; Personal autonomy; Foucault; Principle-based Ethics; Bioethics, Qualitative methodology, Grounded theory

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Core Tip: The current model of decision-making for patients in the clinical setting has major limitations. A new perspective using the concepts of Foucault’s ethics from grounded theory allows to analyse the phenomenon and propose changes. From a critique of principlist ethics, this study attempts to configure elements of analysis to build a new theory on how professionals should act to achieve real self-determination of patients in decision-making.

INTRODUCTION

Perspectives of self-determination vs optional autonomy of the patient

Although numerous studies have evaluated decision-making in clinical practice, they focus on decision-making in a shared way, and the short-term results[1] focused on the cognitive or affective effects of the patients but not accepting ethical arguments or rational evidence[1,2]. This suggests the necessity to consider long-term consequences, including interventions, patients, teams, organisations, and health systems[2].

Most of the investigations are directed towards the interaction of professionals with patients, often without considering factors at the level of interpersonal relationships or the health system model[3-5]. This illustrates a very reductionist perspective on the decision-making capacity of patients. Some authors[6] indicated the necessity for a deeper approach from new perspectives that raise key points, such as evaluating the quality of a decision-making process addressing the ambivalence that emerges when these perspectives are recognised.

The duality between the so-called mandatory autonomy that defends self-determination vs the optional autonomy, which is more established in our health model, is in constant discussion due to the results or consequences that each of these generates in decision-making[7,8]. In terms of cognitive-affective results, psychological clarity or recognition of the emotional work inherent in choosing between several alternatives has not yet been resolved[9]. Even in recent decades, various tools or methods of communication from professionals to patients and families have been designed to ensure the latter's autonomy[10]. The Mayo Clinic conducted few studies with observational measures and informed consent through conversational interaction strategies between professionals and patients[11].

Even a systematic review by Michalsen et al[12] highlights that decision-making models in settings such as the intensive care unit (ICU) should be based on exploring interprofessional relationships to favour inter- and intra-team communication, the central axis of Foucault’s analysis and power relations.

All these attempts standardise the quality of health decisions. Still, they have not allowed progress in the real self-determination of patients beyond the ability to choose according to professional preferences[13]. Even then, it should be mentioned that there are more than 100 clinical trials evaluating decision-making aids that seem to increase satisfaction[14]. As the most significant barriers, apart from lack of time and resources, professionals’ attitudes are considered the key factor[15,16].

Elwyn et al[6] and Carman et al[17] concluded that much is known about shared decision-making between professionals and patients. Still, there is very little approach from a patient’s self-determination perspective in ethical deliberation. From this premise, the need for self-determination of patients is addressed, undoubtedly taking into account all the questions that arise in its real implementation in the practice of decision-making in the clinical field.

Lindberg et al[18] considered that the first factor of analysis arises when self-determination is offered to the patient. The professionals consider the patient sufficiently prepared to decide or a circumstance that they believe the patient should decide. This temporary aspect is considered an annulment in the patient’s ability to make decisions as a professional’s choice.
The problem is that until timing becomes an option from the moment a professional concludes that a patient will have to make decisions, this capacity is completely nullified[19]. They can be minor routine problems or much more relevant.

Self-determination has been conceptualised but little investigated, affected by traditional paternalism[18] as indicated among other reasons along with legitimisation of limiting freedom through the defense of prospective self-determination by considering the professional where the patient, in the future, might prefer another decision, is contradictory, even if it is good for the patient. Our responsibility to respect others must be durable in time to achieve real self-determination and not in a portion of time[20-22], as defended by Foucault’s proposal of the subjective construction.

QUALITATIVE APPROACH TO FOUCAULDIAN ETHICS

In a hospital, it is necessary to check the connection between the patient’s autonomy and exercise power in daily practices to understand and articulate Foucauldian ethics. For this reason, the mechanisms and procedures in the exercise of normalisation strategies, homogenisation, impositions, restraints, oppressions and knowledge that determine the patient’s autonomy capacity in making decisions must be analysed.

The perspective of the Foucauldian ethics analyses the autonomy based on the codes that currently configure the behaviours allowed or forbidden instead of personal choice that opens a new possibility of understanding ethics. This analysis allows establishing a new way of understanding the subject as being autonomous. Constructing a new way of understanding ethics is important in clinical settings as it provides fundamental competencies in patients’ decision-making and breaks the current limitations.

A significant number of studies have reported the patient’s autonomous decision-making, although they have dealt from different angles and ethical approaches. Health care professionals consider it a significant aspect of practice, and debate on this aspect is ongoing among the experts[22-28].

Some authors share that the patient’s decision-making is halfway at the crossroads between two ethical positions: Paternalism and informed choice[23-25]. In the paternalistic models, the health care professionals decide on behalf of the patient based on the best discourse they do for them, which could mean a breach of respect for the patient’s autonomy. Whereas in the informed consent-based models, the health care professionals provide the patients with information and then make their own decisions. This position raises several ethical dilemmas: on one side, when the patients want to receive the complete information about their health problem before granting any consent; on the other side, the role of the patients family in the decision-making process[8,9,27].

According to some studies[28], a culture of domination prevails among the North American and European professionals in the clinical setting, trying to generate a type of patients that follow the medical paradigm. Some investigations[29-32] raise different cultural conceptions on the patient’s informed consent and the family’s part in decision-making.

Several authors classify differences in the patient’s decision-making into restrictive or open conceptions. Both conceptions have been related to the ethical positions indicated above. The restrictive conception responds to a paternalistic attitude and the open conception with the patient’s informed choice[23,33,34], allowing us to examine the tensions between both.

Regarding the more restrictive conception[23], authors indicated the following: (1) Patients had got their preferences for their medical care, and obtaining those preferences and taking decisions are the responsibility of the health care professionals; (2) Professionals respect the patients informed autonomy of making the best decision to meet the best possible clinical results; and (3) Patients and professionals can, and sometimes must, discuss the preferences. However, the process must conclude with a choice based on scientific evidence and the professional’s expertise, taking into account the patients preferences.

Joseph-Williams et al[35], Epstein and Peters[36], Nelson et al[37], as well as Sevdalis and Harvey[38] claim that professionals might misunderstand this proposal. They use their privileged situation to build up the patients preferences based on domination and their own preferences without establishing an equal relationship with them[39]. This could decide the type of relationship between the professionals and patients for autonomous decision-making.
Carrying on with the restrictive perspective, health care professionals do not consider that all patients’ preferences have the same value or should be taken into account when making decisions, placing some needs ahead of others[40]. Walker[40], and Cribb and Entwistle[23] consider this a drawback for the professionals when promoting a person’s autonomy. In addition, in an evidence-based model, the health care professionals seek a consensus among the preferences of patients, making a choice based on their values; but intend to emphasise the predictable clinical results to make a decision.

In a clinical setting, the ideas of the professionals working with the patients are crucial in any decision-making process. The restrictive perspective of this process stands for the option of negotiating with the patients in some cases, but not always [23]. Authors suggest that professionals and patients should only discuss the health care options together if the patients want to decide based on the effects of different options, according to scientific evidence and their preferences. The option of deciding together always depends on ensuring that their best or most beneficial option is chosen[41]. Wirtz et al[42] argue that the patients would only share their preferences based on the expert knowledge of the professionals, who normally discuss the appropriate options according to the scientific evidence.

Many authors consider this restrictive perspective an excessively simplistic approach[23-25,41] despite being the most established clinical practice.

The open guidance on the patients’ decision-making, although on a theoretical level, is the most widespread one, showing certain limitations regarding operability on a practical level[23,43]. The starting point is the perception that the relationships between professionals and patients are different from other kinds of social relations. Emanuel and Emanuel[44] already suggested that relationships between professionals and patients are normally fixed and marked by the role of each professional in the health care team. Professionals follow technical aspects or protocols for the action, combining with the limited knowledge of the patients for their care. Therefore, in the decision-making process, it is essential to consider the inter-professional relationships and roles of professionals to understand the relationships between them.

The open perspective considers that it is possible to use the expertise of professionals to help patients reflect and adapt their preferences as a part of their autonomous decision-making while avoiding standardised, and institutionalised rules [23]. These authors pointed out the need to analyse the power structures in the relationship between professionals and patients and how they impact the vulnerability of the autonomy of patients.

In decision-making both the restrictive and the open perspective confront; the ethical commitment between a paternalistic or an open approach basically depends on the individual skills of health care professionals. Identifying these relationships will contribute to avoiding the excessive and dominant use of power. In addition, creating a suitable environment allows the development and practice of the qualities of professionals and the capabilities of patients[13].

Several studies illustrate that the autonomy and self-determination of patients are rarely prioritised by professionals, who even reject those patients and demand more information as well as power for decision making. The professionals prefer clinical aspects rather than the autonomy of patients[26,29,45]. Hence, fixed and confined health care is established, which is completely institutionalised, leading to the behaviour of the patients[46-50].

Based on the criticism of the current ethical model in the clinical setting from the perspective of Foucault, this study aims to analyse the autonomy of patients in decision making and the influencing factors (Figure 1).

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**DESTRUCTION OF PRINCIPISM ETHICS AND SOCIETY’S MEDICALISATION**

From Foucault's point of view, society's medicalisation is structured like a real technology of the social body, thus playing a decisive part in the biopolitical production of society. The population is a theoretical problem but a technical dilemma that demands procedures of intervention and modification[51].

This incursion of power in life is what Foucault called “biopower”[52]. This is understood as a societal control mechanism for people’s lives[53] and refers to the exercise of power at economic, historical and social levels and consigns biological life as a political event. In a clinical setting, this biopower is expressed as a set of techniques and strategies expressed in statistics related to health, development and
Figure 1 Foucault’s ethical perspective: Deconstruction of patient self-determination in the clinical setting.

According to Dzurec\cite{54}, a connection between medicine and family reorganises family life in three dimensions: (1) The family is transformed into a privileged biopolitical system, a perfect tool in health administration, where the construction of social dwelling as a health space is encouraged. In the age of biopolitics, the family works as the preservation, control, and life production mechanism; (2) Hygiene acquires a connotation of a public issue, associated with epidemics, morbidity, average life span and mortality. The implementation of a community health system consolidating the state of collective hygiene is fundamental; and (3) Authors instructed an administrative physician is acting as the original nucleus of social economy and sociology and establishing the organisation of a political-medical area of influence on the population with prescriptions focused on diseases and behaviour. These aspects explain the social medicalisation and creation of a medical-administrative system, promoting social control.

A therapeutic framework with a new design of the hospital environment comes into existence. It consists of creating an individualised space around every patient, which is adjustable following the disease development and concentrates absolute power within the clinical organisation in the hands of physicians. Also, generating a permanent record of all the events is critical for producing specific knowledge\cite{53}. Thus, modern medicine is a social medicine configured as the technology of a social body.

Foucault\cite{55} describes three models developed in different European countries: The medicine of the State, urban medicine, and the labour force medicine. The medicine of the state is an exhaustive observation of morbidity, the normalisation of medical practice and knowledge, and the creation of an administration to control clinicians and medical bureaucrats. The medicine of the labour force is the transformation of the population into a more appropriate and long-lasting labour force and an innocuous political force indicating no threat to the bourgeoisie. To refine the quarantine scheme, the urban developed the concept of environment and health\cite{55}.

According to Foucault\cite{55}, these models caused four modifications in society’s medicalisation. Firstly, the State has to ensure people’s health in the interest of preserving their physical strength, labour force, and production capacity, turning the rights of humans to maintain their bodies in good health due to State’s action. Secondly, the preponderance of the hygiene concept considering the relationship between the individual and the State. Thirdly, the expenses assigned to health care, the cost of labour interruption, and the calculation of the risks affecting the individual’s physical well-being determine a new level of concerns in the field of macro-economy. Lastly, health becomes a focus of political struggles and debates.

All these aspects demonstrate the extent of the medical paradigm in contemporary culture due to the incorporation of medicine in the biopolitical mechanism. According to Foucault\cite{56}, body care, physical health, and the concern about illnesses prove to be especially decisive in such a regime.

Medicine has acquired an authoritarian power with normalising functions, which widely exceeds diseases and the demand of patients\cite{56}. Physicians and their knowledge are the key parameters for the invention of a normalised society. Thus medicine is no longer a mere instrument of the economic system; it has entered and
turned into one of its components. Hence its appreciation changes and health becomes a consumer item. Health has entered the trading game with laboratories, pharmaceutical companies, physicians, clinics and insurance companies as production agents and real patients and potential ones are its consumers. Physicians become the core agents of medicalisation, the simple distributors of drugs in a market of suffering and promised health.

The medicalisation of today’s society is independent of medicine, medical officials and health institutions since their logics run all over society as a commodity. Biopolitics has used medical discourses and technologies, family intervention, hospital structures and consumption systems to conquer new forms of political appropriation of life[57].

This control of society through the medicalisation of life has also influenced the applicability of bioethics in the health field. Bioethics has become a mere logical instrument for applying a series of universal principles based on efficiency, consistency and application criteria[58]. Many authors refer to this conception as principalism[59-63].

Some authors have defined this principlism as legitimising a biomedical discourse or an “oppressive status quo” of principles[49]. McGrath[64] has indicated that the currently advocated bioethical model uses principles that create an illusion about the autonomous decision-making capacity of patients. Principles give sense to the meanings and values of a health care institution which defines, describes and limits what can or cannot be done. In other words, these principles provide the descriptions, rules, permissions and prohibitions of social and individual actions[17,46].

From the Foucauldian ethics, the main criticism towards principlism is based on the idea that the resolution of ethical conflicts is referred to professional experts in this area, without considering the patient’s opinion, autonomy, and capacity for decision-making. This is the reason that critical ethics suggests a bioethical reflection based on the power and its effects on neutralised discourses superseded by the experts in ethics [65].

This gives room to an ethical trend that advocates that, without an analysis of power and its complexities, bioethics cannot consistently examine the social, political and even economic aspects of ethical conflicts[58].

Thus the concept of power develops in the discourse of ethical-critical reasoning, which moves away from the idea of valuing principles above the context and routes towards a discursive understanding of autonomy. It deals with examining how personal choice is the reality built by several health organisations. Critical ethics suggests that the substantial rationalism of principlism must be challenged by the contextualisation process of the bioethical problems from the power and the discourse [64].

Therefore ethics should depart from the point that there is no clear and distinctive idea expressed by the structuring of principles[64,66]. The ethical response does not consist of applying certain principles in difficult situations but rather interprets service provision where ethics expresses the organisation discourses.

For this reason, it is important to introduce the Foucault’s concept about biopolitics and its implication on ethics. Biopolitics arises from the analysis as a principle and a method of rationalising the exercise of government and breaks the “reason of state”. The rationalisation of governmental practice implies paying attention to control, regulation, supervision, order and administration[67].

Ethical practice is intended to offer alternative actions and respect for individual subjectivity. This gives rise to a concept of Foucauldian ethics based on the individual’s subjectivity.

In a clinical environment, Foucault’s ethics is understandable as the dimension of the relationship between the real behaviours and the codes or systems of prohibitions, prescriptions and assessment. These determine representing a person as a moral individual who sets the forms or modes of subjectivation[68].

In the first of these forms of subjectivation, the philosopher describes the response to the technologies, where caring tries to eliminate what we depend on and re-position us in the world as causes and effects.

The second form of subjectivation is the codes. Foucault defines these forms as historical structures representing the individual as the subjects of their actions and not mere agents. At this point, a serious question arises about the requirement of universality in the historical construction of ethics. Its ethical concept, not organised as an authoritarian, unified moral, equally imposed on everybody, gains strength. Foucault suggests non-universalising, non-normalising ethics without a disciplinary structure and not based on scientific knowledge.
In the final form of subjectivation, Foucault considered defining the culture of the self, the social practices as practices of the self[69]. Foucault talks about the independence or relative autonomy of the relationship with oneself regarding the codes. He considers that the individual materialises and establishes a moral individual, a struggle for freedom and a victory to obtain the command[70].

This command overflows through many different doctrines, adopts the form of an attitude that permeates the ways of life and articulates in a set of procedures and exercises which can be mediated and taught, representing a practice which develops even interpersonal and institutional forms and giving a place to the production of knowledge[71].

According to Foucault, medical care takes intense attention to the body, especially when both kinds of diseases, those of the soul and body, can communicate mutually. This transference represents a point of the individual’s fundamental weakness[69].

Thus, it is necessary to find the existing connection between the patient’s autonomy and the professional’s exercise of power by analysing the relationship between them and their backgrounds. Therefore an analysis of the discourses and the power relations are embedded in the daily practice of the health professionals in their relationship with the patient, the family, and the health care system of the health care professionals allows articulating Foucauldian ethics.

Departing from considering power as a strategy exerted and present in all social practices, although sometimes easily recognisable, it is not always clearly visible in a clinical setting because of its subtle exertion through persuasion and manipulation. Power is expressed in strategies of normalisation, homogenisation, impositions, subjections, oppressions, times, spaces and the knowledge which operate in professional relations and the background of the professional practice.

In decision-making, this analysis can identify the legitimacy of certain ways of the action of nurses and behave before the patient’s autonomy. It is important to make visible what discourses dominate the professional practice and identify the transforming or emerging discourses that seek to open up alternatives of significance, understanding and action to the naturalised discursive practices in the profession and the current health system, as new Foucauldian ethics.

Foucault[67] presents the importance of power relations in the knowledge generated from different disciplines. Each discipline builds unequal positions for exerting power by placing some in a more privileged position than others.

In the epistemological ladder of professional knowledge as a minor science, nursing is considered, which has led to marginality and a maternal stereotype of the nurse in the dominant or major science of medicine[72]. These aspects determine that the physicians are related to their hegemony in the health field. By referring to the nurse, the role that she acquires in the physician’s context is dominated.

This analysis shows different kinds of power strategies, from the more emotional or therapeutic ones to self-management or the more self-applied or subjectivised ones.

The perspective of the Foucauldian ethics allows an analysis of the professional relationships based on the codes that determine what behaviours are permitted or forbidden in the professional practice, in a person, neither tough nor standardised choice, which makes understanding ethics. This means analysing those elements which cause nurses to move away from understanding the value of a set of principles above the context and moving towards a discursive comprehension of the autonomy of patients[64].

GROUNDED THEORY FROM FOUCALDIAN ETHICS AND AUTONOMY IN THE PATIENT’S DECISION-MAKING IN A CLINICAL SETTING

The French philosopher not considered the subject as a fundamental point if the result of a subjectivation process involves a set of particular practices and techniques. Foucault tried to break loose from the “self”, which is merely the result of a biopolitical subjectivation and constituted an interpersonal level, an “ethic of the self” as a point of resistance to disciplinary power. So, subjects come to recognise themselves as subjects of knowledge, of power relations and ethical relationships to the self[73].

Podsakoff and Schriesheim[74] associated this power directly due to an interpersonal relationship where the influenced subject is recognised as a referent that influences and seeks closeness with him/her. Laswell and Kaplan[75] directly relate power to participate in decisions, where the adoption of decisions constitutes this interpersonal process, and therefore, power represents an interpersonal relationship. Hence it will be a critical element in the analysis of the ability to patient’s decision
Foucault holds that the idea of constituting ethics of the self-conceived is an art of resistance to biopolitical normalisation. Thus philosophy as part of the self becomes a key element in the struggle that involves the resistance to normalisation and forcing the individual back to himself/herself and tying him/her own identity in a constraining way.[76,77]

The philosopher points out that ethics focuses on the following propositions: the core of philosophy is ethics; freedom is the foundation of ethics; ethics revolves around the subjectivation techniques or the care of oneself. So ethics as the care of oneself can be created about one's own existence; makes a person stronger for political resistance; involves the willingness to care for other human beings.

For Foucault, the ethics of subjectivation arises from the ethical substance, the subjection modes, the forms of development, and the moral subject's teleology; and all these are explained in greater depth.

Foucault talks about the substance of ethics as the subject’s proper transformation from his/her historical and social context.[78] Ethics substance forms part of the individual who must establish themselves as the main subject of their moral behaviour, which makes up their feelings and different ways of working of the moral subject. Therefore, it is proposed to consider the patient’s beliefs, values, and preferences to construct a free subject in the decision-making process to apply the ethical substance.

The subject modes define the subject’s relations with rules and how the subject recognises those rules as obligations within a particular social and cultural context. These modes are the norms and codes established in the health institutions that set the pace of the decision-making process. Thus, the patient’s relationship with the rules established in the clinical setting is configured through the subject modes. The determination of what the patient can and can not do and what decisions correspond to their care with the permission of the professionals and the institution are important.

Foucault calls forms of elaboration or ethical work. As individuals in a society, we are determined by social, political and cultural norms and, therefore, as institutional norms configure patients. These norms, obligations and codes determine the transformation of the patient into a moral subject, responsible for his/her own behavior as he/she is allowed to be in one way or another. From this, the relationship between the subjects transforms into a moral individual with his/her own behaviour.

This ethical work arises from learning the pre-established social rules, the control those rules have on the subject's behaviour and the subject's own struggle against those rules when his/her wishes and health are at stake. Thus the role played by the individual as an autonomous and free subject is understood -teleology of the moral subject.

Foucault refers to the moral subject's teleology as the final result of the established social rules and standards that produce a specific mode of being. However, he does not consider that this result involves strict obedience to the set rules, but establishing a relationship with oneself leads to a new behaviour.[79]

In addition, Foucault introduces the technologies of the self as a basic and central element of ethical development. He suggests how people in every society use techniques which allow the individuals to perform a certain number of operations on their own bodies, souls, thoughts and behaviours by their own means. The subjects do independently, change themselves, and reach a certain level of perfection, happiness, purity, and supernatural power.

The self’s technologies determine how people's actions and behaviour concerning the rules, regulations, and codes imposed on them will finally be. Then the subjects distinguish between the codes, determining what actions are allowed or prohibited and the codes, which determine the positive or negative values of different possible behaviour.[80] This distinction configures the kind of relationship one should have with oneself, which determines how it is supposed that the individual establishes himself/herself as a moral individual of his/her own actions[67,71].

This relationship with oneself introduces four major aspects: (1) What part of myself or my behaviour concerns moral behaviour, which in our society configures the main command of morality, the feelings; (2) The way how people are invited or encouraged to accept their moral obligations; (3) The self’s auto-determination refers to what measures help us transform ourselves into ethical subjects. This means the ethical substance which moderates our actions and deciphers what are; and (4) What kind of being do pursue when subjects act morally, called “telos” and related to the effective behaviour of people with the existing moral codes on the one hand, and the relation of oneself with these four aspects on the other side[80].
Foucault refers to these positional changes as the techniques of the self, which the patients set in motion once hospitalised, ensuring their integrity and autonomy in making decisions about their own body and behavior[81]. The self’s technologies determine how patients’ acts and behaviour will ultimately be about the rules, norms, or codes imposed on them[80]. This behaviour will be free and autonomous, as far as the subject can understand how he/she is supposed to establish themselves as a moral individual of their own actions -technologies of the self.

Thus it is not enough to say that the subject establishes himself/herself in a symbolic system. The subject does not establish themselves in symbols but in real, historically analysable practices[80].

Finally, two concepts should be mentioned to analyse the Foucauldian ethics from the care of the self: the culture of the self and the culture of freedom.

The care of the self is a permanent, life-long practice that tends to ensure the continuous exertion of freedom[82]. It is about freeing ourselves from the set rules - subjection mode- to access our own behaviour or subjectivation technique. This means the proper care of oneself and the proper way of life.

Distinguishing between traditional practices involves self-care and the more modern conceptions that make certain possible transformations. From this construction of the subject, the different elements involved in the decision-making capacity of patients in a clinical setting are analysed. Firstly, the context in which decision-making takes place is explained. Secondly, an attempt has been made to explain how the medicalisation of society has been produced through transformations of being, using the “techniques of the self” as referred by Foucault. Finally, the ethical framework for a subject’s “self-creation” is explained, which insists more on the exercises of self-subjection, reinforcing the ethics of the self by itself, the “care of the self”.

All this configures the culture of the self or how we get rid of the established rules to access our own behaviour or subjectivation. This means our own way of life, its own subjectivation technique, and no prescription[83,84].

The institution determines the manners of subjection to which the patient is submitted to construct the self. It could be indicated that the patients find themselves immersed in the complex machinery of the clinical environment. The obligations imposed by the institution become a way of subjection for the full autonomy pursuit of patients. In their political discourse, the professionals and clinical institutions advocate the idea of patient-centred care quality. When analysing the quid of the institution, it is discovered that professionals do not get a message of quality objectives but, on the contrary, focused on optimising financial resources.

The initial message becomes an element of fictitious political marketing and generates a health organisation that commercialises health, a direct consequence of the effect of biopolitics on health. This situation makes the nurse feeling disappointed, unmotivated, frustrated and lacking future projection, even resigned to believe that there is no way to change it. All the above conveys that the management bodies are unmotivated, frustrated and lacking future projection, even resigned to believe that there is no way to change it. All the above conveys that the management bodies are considered distant without any practical utility[85].

The institution’s exercise of power generates a more subtle process called colonisation or instrumentalisation of the health system, as proposed by some authors [22,86]. This process is nothing more than the normalisation of clinical practice using standards and protocols, collateral generating internal relations between professionals, which are very rigid and based on the hierarchy of professional categories.

These two elements, normalisation and institutional market ethics, help generate the concept of a dominated patient in a health organisation, subject to the rules, schedules, available resources, and, therefore, keep to patients, without any possible decisions. At this level, the patient’s autonomous capacity is completely invalidated.

In light of the patient’s domination, several challenges for health institutions arise, which open up space where the participation of patients in decision-making can be real. Gilbert[87], Osborne[88] and Beresford[89] advocate for reducing bureaucratic complexity reconsidering the objectives of the health system focused on the patient instead of the market values and opting out of consumerism as the economic value of care. This perspective would respond to the use of technologies that allow reconstruction of the patient’s autonomy, as it is presently understood, to give way to self-determination. Thus the Foucauldian ethical study becomes important when constituting the patient as an ethical individual in his/her relation with the institution to set his/her behaviour or, as the telos of the relationship referred by the French philosopher[55].

The inter-professional relationship is another key factor that defines the patient’s participation and power rates as the subject. According to several professional stereotypes, the healthcare team is configured to focus on physical and clinical
complications. Medical criteria dominate the practice of other professionals, where the physician orders and the nurse executes. In other words, the physician exerts an absolute power, and the nurse is a subtle and often a silenced power.

This interaction between power and scientific knowledge relegates decision-making to the patient, as far as the professionals leave him/her, and ineffective communication flows between professionals or even their interpersonal relationships come into play. The nurse’s discourse slightly criticises that these interprofessional relations may influence the care provided to the patient but fail to recognise that these relations may limit the patient’s decision-making capacity.

It could be that the improvement in communication between professionals, training for communication abilities and the reorganisation of professional skills challenge the enhancement of inter-professional relations and teamwork[26]. These challenges and examining the dynamic relationship between scientific knowledge and power[90] produce resistance to reverse the limitations in the patient’s autonomy[91,92].

According to Foucault[56], the science or scientific truth model determines the construction of one discipline dominating the other, as in medical science and nursing. This truth establishes the norms a patient could submit to when visiting the hospital and accepting the game’s rules.

Thus professionals and institutions provide the truth to the patient’s normality, establishing a manner of subjectivation in the clinical setting. This approach to the productive dynamics of power helps to make visible the mechanisms and strategies of knowledge performed by the professionals as a set of forces that passes the patients, producing and using them. This explains why the power exerted by the professionals over the patient through persuasion, confidence, and paternalism results in patients as products and prescribes certain models of speech, behaviour, and organisation of care without considering the patient’s criteria[93].

On the relationship between nurse and patient, several opportunities of technologies of the self are outlined to enhance the latter’s capacity to make decisions. However, few asymmetrical power relations appear, where the nurse creates one space of participation or another, depending on their attitudes and the one perceived from the patient. Participation is understood not as a real power of decision but as a limited degree for the patient to decide about some aspects of patient care. Even if the nurse prefers a patient who goes with the flow, is compliant and cooperating with the prescribed care, this strategy shows the greatest benefit for the patients. They will be informed and active in their care, maintaining a good relationship with the nurse.

The nurse recognises the ongoing socio-cultural shift as to the kind of patient who attends the health system. Nurses think that patients need to be better informed, and if patients are not, they ask for it and claim higher levels of participation and power of decision[94].

These transformations meet Foucault’s premise that where there is power, there is resistance. Thus the power of the professionals and the institutions finding their limit in the patient’s resistance and care of the self. In this way, professionals and institutions design a profile of struggle, incorporating tactics of this power as a base to justify certain behaviour of the nurse, such as persuasion and coercion, when faced with the patient’s rejection and refusal of the proposed care.

The danger of any relationship of power is the possibility that it solidifies in a kind of domination[77]. In this case, the real task of the nurse is to constantly defend and reaffirm the transformations in the patient’s power of decision to maintain the patient’s autonomy; therefore, the need for ethics conceived as the care of freedom arises[57].

The Foucauldian ethics suggests a resistance to the relationship framework between knowledge, power and subjectivity, currently imposed in the clinical setting. It could be accepted that the patients can exercise power over them, of the construction and the creation of their care. Then the care of the self as a practice between the professionals and the patients appears to avoid the shift in domination[95].

To articulate the proposal of Foucauldian ethics with the results obtained from an earlier study[94], with the assistance from professionals, the patients need to detach from the imposed constraints to gain the freedom of decision on their care.

From this perspective of ethics as freedom and culture of the self, it is key to consider patients’ feelings, beliefs, and values before making any decision about their care. This ethical work emanates from pre-established norms of the control of rules about the behaviour and struggles of the patients against these rules when their health is at risk.

Care of the self would materialise through breaking with established norms and exercising the patient’s freedom. That is, a capacity to make real decisions about the patient’s care, where the professionals are simply guides. A professional allows the
patients to make their own decisions based on their beliefs and values among the different possibilities.

For example, in a situation where the patients must choose between performing a surgical intervention or not, the professionals must provide the alternatives, explaining the risks and benefits and finally respecting the patient's choice, even if it is not the best for the professionals or the most beneficial. Therefore, the patients must make their criterion prevail as an inherent right and resist the persuasions of the professionals.

Although defended by principalist ethics in its principle of autonomy, this proposal is confined to a series of limitations such as life-threatening risks, risks to public health, and mental incapacity. In addition, the influence of the principle of beneficence prevents the professionals from considering that decisions that are not the most beneficial are based on the rejected clinical criteria. The patients are not persuaded to choose them.

If applied, in this case, principlist ethics, the decision before a conflict of opinions between the patients and the professionals, would value the risks and benefits for the patients. Although it would take into account the opinions and values, professionals would take a back seat, and in the final decision, the clinical criterion would prevail.

From this, the patients establish a new behaviour, which frees them from the strict compliance of the game rules in a clinical setting, not to work against them, but to adapt them to the decisions regarding their health.

It could be that the forms of constraints established in the clinical setting cannot be eradicated. Still, the patient’s exercise of autonomy must emerge from the strategies and a shift in certain forms of institutional domination. Likewise, institutions should avoid the solidification of dominating power, configuring the patient as a passive care objective. It cannot be expected that each patient, from his/her own ethics, assumes a common, universal and strict criterion, as the institutions pretend. Breaking with this homogenising dynamics of the clinical practice and universalised ethics will encourage the patient’s autonomy in decision-making.

The originated debate on freedom and domination methods requires a practical consideration of care of the self and, therefore, a culture of the self. The current method of ethical decisions based on the universalising desire of utopia should be substituted by altering the limits imposed on the patients and enhancing the possibility of freedom.

Ultimately, the opportunities unfolding in the patient’s autonomous decision-making, according to the perspective of the Foucauldian ethics, are based on recognising the patient’s personal decision by the clinical institutions and professionals. For this purpose, universalising, normalising, and per se legal moderation styles should be opted out with a disciplinarian structure and scientific knowledge. As long as professionals do not break free from the obsession with exerting power within their inter-professional and patient relations, they will still be entangled in the knowledge-power complexes that generate the control of people as bodies or as the population with no personal identity[70].

A patient’s independence or autonomy about professionals and the institutions will constitute a free moral subject and a victory over the dominating rules[95]. The patients exercise autonomy in a real clinical context, which participates as before and decides on all the received care[78].

CONCLUSION

It has been shown that the main subjection modes in patient’s autonomy in a clinical setting are the standards of the health institution, the exercise of a hegemonic power in the relationships between professionals and the asymmetry in the relationship of professionals with the patients.

In addition, the current ethical model based on universal principles is not being useful to provide a capacity for patient decision-making, relegating to the background their opinions and beliefs.

Consequently, a new ethical perspective emerges that aims to return the patient to the fundamental axis of attention. It proposes to break with the discourse of patient-centred care or patient that participates in the decisions so that it is a subject that decides what should be done and how to do it with the help of the institution and the professionals. An institution that belongs to the user and professionals who work for a patient.
Therefore, this change will not be possible without the professionals committing themselves to help strategies or technologies to allow the patient to resist and modify the current regulations and impositions. It will not be possible without the professionals contributing to the patients building a culture of the self in the health institution.

These key concepts of the Foucauldian ethics of power, technologies of the self and care of the self allow developing a grounded theory on qualitative methodology to analyse patient self-determination in the clinical setting.

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Diabetes mellitus and COVID-19: Understanding the association in light of current evidence

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections have posed a problematic healthcare situation worldwide since December 2019. Diabetes mellitus is associated with an increased risk and severity of coronavirus disease 2019 (COVID-19). While interacting with various other risk factors, high blood sugar was found to reduce immunity and increase the replication of SARS-CoV-2. Oxidative stress and the release of pro-inflammatory cytokines are greater in diabetic individuals than in healthy people, worsening the outcome of SARS-CoV-2 infection in diabetics. Increased expression of furin and angiotensin converting enzyme 2 (ACE-2) receptor in the hyperglycemic environment may promote the entry of SARS-CoV-2 in the host cell. COVID-19 infection primarily modulates immune and inflammatory responses, and may cause a cytokine storm, resulting in possible lethal outcomes in diabetics. An experimental report suggests that ACE expressed in the pancreas and the SARS-CoV-2 virus invariably destroy β-cells which contain ACE-2 receptors and results in acute diabetes. Moreover, COVID-19 also causes hyperglycemia in an individual with diabetes which may be related to insulin resistance and destruction of β-cells during SARS-CoV-2 infection. Early observations also suggest a correlation between oral hypoglycemic agents and the risk of COVID-19. This review focused on the possible cause and mechanism involved in SARS-CoV-2 infection in diabetics and the role of antidiabetic drugs in COVID-19.

Key Words: Diabetes mellitus; SARS-CoV-2; COVID-19; Angiotensin converting enzyme 2; Antidiabetic drug; Cytokine storm
INTRODUCTION

Coronaviruses (CoVs) (family: Coronaviridae, order: Nidovirales) are recognized as a large family of single-stranded RNA viruses responsible for mild to severe respiratory infections. The presence of distinct spikes with rounded tips on the surface of the virus provides the appearance of having crowns; hence the virus named coronavirus (in Latin 'corona' means crown)[1-3]. The first case of coronavirus was reported in 1960 as a cold[4]. CoVs belong to four genera, namely α-CoV, β-CoV, γ-CoV and δ-CoV. Mammals can be infected by α-CoV, β-CoV and δ-CoV, while γ-CoV and δ-CoV can infect avian species. In the 21st century, before coronavirus disease 2019 (COVID-19), two CoVs of the genera β-CoV, namely severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), emerged as significant public health concerns[1,2]. In 2002, SARS-CoV was first found in China, and in 2012 the first case of MERS-CoV was reported in Jordan[3]. In December 2019, COVID-19 was first reported in Wuhan, China and soon emerged as the most dangerous infectious disease of the century. Angiotensin-converting enzyme 2 (ACE-2) is considered the dominant host receptor of COVID-19 expressed in different organs in humans, and COVID-19 uses the ACE-2 receptor to enter host cells [4,5]. A total of 110749023 confirmed cases, including 2455131 deaths due to COVID-19, have been reported globally as of 21st February 2021 [as per WHO Coronavirus Disease (COVID-19) Dashboard, https://covid19.who.int/].

Diabetes mellitus (DM) is characterized by a spectrum of metabolic disorders and has become one of the most significant global public health concerns in the 21st century. The prevalence of DM is increasing rapidly worldwide among all groups of people without any barrier and is also responsible for the burden on socio-economic development[6,7]. The International Diabetes Federation (IDF), in its report (IDF Diabetes Atlas 2019), estimated that 463 million people (20-79 years age group) live with DM globally, with a projected increase to 700 million by 2045. The IDF Diabetes Atlas also predicted that almost half of these people (232 million) were unaware of their diabetic condition, and approximately 374 million adults are at risk of developing type 2 DM[8]. DM is considered one of the top 10 causes of death, and in 2019, the IDF predicted 4.2 million deaths due to DM globally[7,8]. People with DM are at increased risk (2-3-fold) of all-cause mortality. DM is responsible for various complications and the link between increased risk of infections and DM is well established. People with DM have a high risk of various infections[7,9].

The overall burden of DM and its complications is increasing significantly, and COVID-19 poses a problematic situation for those with DM.

RESPIRATORY COMPLICATIONS OF DM

Diabetic patients are susceptible to a sequence of acute or chronic complications such as microvascular and macrovascular complications, infection and are at risk of
premature death[9]. Defective pulmonary function is well documented in diabetic patients. A decrease in lung function and forced vital capacity, obstruction of the peripheral airway, and decreased capacity for carbon monoxide (CO) pulmonary diffusion have been observed in diabetic patients. In diabetic individuals, sympathetic and parasympathetic neuropathy is responsible for a series of pulmonary function deficits[10]. Pulmonary autonomic neuropathy is responsible for reducing mucociliary clearance and thus enhancing the risk of lung infections. Defective muscle metabolism and neuropathy of the phrenic nerve decrease respiratory muscle strength in diabetic individuals. It is well established that hyperresponsiveness increases through the Rho-associated protein kinase (Rock) pathway in diabetics[10]. Hyperglycemia is also responsible for oxidative stress by enhancing the generation of reactive oxygen species (ROS), reactive nitrogen species and advanced glycation end products (AGEs)[9]. Increased blood glucose level has been found to promote lung fibrosis, chronic inflammation, and inflammatory cytokine release. Higher glucose concentrations promote susceptibility to pulmonary infections[10]. Alterations in the levels of inflammatory cytokines have been reported in diabetics. Glycation was found to decrease class I major histocompatibility complex (MHC) expression on the surface of myeloid cells responsible for impaired cell immunity in diabetic patients[11]. Impaired neutrophil and macrophage function including chemotaxis, adherence, free radical induced destruction of microorganisms, phagocytosis, and respiratory burst have been well established in diabetics[10,11]. In DM, a decreased complement system C4 and humoral immunity linked with a reduced number and response of T cells enhances susceptibility to infection. Increased blood sugar and insulin resistance in type 2 diabetic patients weaken collective surfactant D-associated host defenses of the lung. In diabetic individuals, loose junctions between epithelial cells in the airway enhance the transepithelial glucose gradient and an upsurge in the concentration of glucose in airway surface liquid, reducing the defense mechanism in the airway against infection[10]. Immunoglobulin glycation usually occurs in diabetic patients in proportion with the upsurge in hemoglobin (Hb)A1c, which may damage the antibody biological activity[11]. The risk of lung infection due to different microorganisms such as Streptococcus pneumonia, Staphylococcus aureus, Klebsiella pneumonia, Pseudomonas aeruginosa, influenza virus, fungus, i.e., Mucorales and Aspergillus species is increased in diabetic people, and such infections may increase morbidity and mortality in diabetics[10-12].

PREVALENCE OF SARS-COV-2 INFECTION IN DIABETICS

Singh et al[13] reviewed various research papers (13 articles from China, two from Italy and two from the United States) to understand the risk of COVID-19 in diabetics. Evolving data showed that DM was associated with 5.3%-58.0% of patients with COVID-19. The papers also showed that COVID-19 patients with DM were more frequently associated with severe or critical disease conditions varying from 14% to 32% in areas[13]. In the study by Abdi et al[14] who reviewed 18 papers, it was concluded that the cumulative prevalence of DM in COVID-19 individuals was 14.5%. They also reported that those with DM were more prone to developing severe COVID-19 and increased mortality[14]. Increased blood glucose level is considered an independent factor that can increase the severity of COVID-19 and mortality[15]. Faghir-Gangi et al[16], in their report, concluded that the pooled prevalence of DM in individuals with COVID-19 was 14%, based on the analysis of 23 articles. Another research group analyzed various studies up to April 2020 and reported 451.9 cases of DM/1000 patients with MERS-CoV, 90.38 cases/1000 patients with SARS-CoV-1, and 100.42 cases/1000 patients with SARS-CoV-2. The mortality rate was found to be 10%, 6% and 36% for SARS-CoV-2, SARS-CoV-1, and MERS-CoV, respectively. Research also pointed towards fewer studies on determining the exact situation concerning SARS-CoV-2 and DM[17]. Kumar et al[18] analyzed 33 articles and concluded that DM in individuals with COVID-19 was associated with a two-fold increase in mortality and severity of SARS-CoV-2 compared to non-diabetic people. A meta-analysis reported that the pooled prevalence of obesity and diabetes in SARS-CoV-2 infected patients was 29% and 22%, respectively. The study also indicated that the severity of COVID-19 in diabetic patients was greater and may require hospitalization compared to non-diabetic people[19]. Shang et al[20] analyzed 76 studies involving 31,067 COVID-19 patients and concluded that diabetics with COVID-19 had a more severe infection (21.4% vs 10.6%) and higher case-mortality rates (28.5% vs 13.3%) as compared to non-diabetics. COVID-19 patients with DM had a considerably higher risk of severe infection and mortality[20]. Chen et al[21] analyzed the impact of
COVID-19 on blood glucose. They found that severe COVID-19 infection was linked with higher blood sugar, and the level of HbA1c was slightly higher in individuals with severe COVID-19 than in patients with mild COVID-19. Another meta-analysis of 65 observational studies that included 15794 participants found that the overall prevalence of diabetes was 12%, and in the case of severe COVID-19, the prevalence of DM was 18%[22]. Mantovani et al[23] also reported a similar phenomenon after analyzing 83 papers that included 78,874 hospitalized COVID-19 patients and summarized that the pooled prevalence of DM was 14.34%. They also reported that the prevalence of DM in COVID-19 patients was higher in non-Asian vs Asian countries and in the older age group (> 60 years). Preexisting DM showed an approximately 2-fold higher risk of having severe/critical COVID-19 illness and an approximately 3-fold enhanced risk of in-hospital mortality[23]. Current evidence indicates that people with DM are more prone to COVID-19 infection, and the risk of severity in diabetics is greater than that in non-diabetics.

**LINK BETWEEN DM AND COVID-19**

The spread and severity of SARS-CoV-2 infection among individuals can be linked to health status and exposure. Several reasons for this have been highlighted by researchers around the world and may be responsible for the extent and severity of COVID-19 during the last year. It is well established that the extent and severity of COVID-19 is linked to diabetic status. DM is considered one of the worse risk factors for COVID-19 and COVID-19 was found to increase the risk of mortality in diabetics. Some of the possible mechanisms explaining this situation are discussed here. Figure 1 summarizes the possible associations between DM and COVID-19.

**Altered glucose metabolism**

Elevated glucose level in diabetic patients is considered an independent risk factor in the early effect of COVID-19[24]. Elevated glucose level associated with severe pancreatic problems can lead to worsening of the pancreatic condition. It was reported by different investigators that there was a substantial difference between infection caused by SARS-CoV-2 in diabetic and non-diabetic individuals. A recent analysis showed that diabetic patients had a higher risk of 79% compared to non-diabetics[25, 26]. In addition, fluctuations in biochemical parameters (i.e., alanine aminotransferase; alkaline phosphatase (ALP); blood urea nitrogen (BUN); C-reactive protein (CRP); lactate dehydrogenase (LDH); D-dimer) were also reported in a diabetic patient and were considered important factors associated with the high level of blood glucose in diabetic patients[27]. Poor glycemic control in diabetic patients enhances the risk of COVID-19 and death. Another study concluded that HbA1c (> 86 mmol/mol) may be considered a mortality factor in diabetic patients (type 1 DM and type 2 DM) with COVID-19[28-30]. A retrospective study also mentioned that due to hyperglycemic conditions, the mortality rate was high, and it was found to be 41.7%. Poor glycemic control or hyperglycemia increased the rate of death of hospitalized COVID-19 patients[31]. Diabetic ketoacidosis or hyperglycemia has such an impact that it can quickly cause the death of patients with severe COVID-19. When patients stop taking glucose-lowering agents, there is a strong chance of SARS-CoV-2 binding to the ACE-2 receptors and spreading throughout different organs, effecting β-cell function and survival directly and causing deterioration of the metabolic syndrome[31,32].

It was found that increased blood glucose directly enhanced replication of SARS-CoV-2, and glycolysis sustains replication of SARS-CoV-2 through the generation of ROS in mitochondria and hypoxia-inducible factor 1α activation[7]. Natural killer (NK) cell activity was found to be reduced in those with impaired glucose tolerance, and DM might be one reason that makes diabetic people more susceptible to COVID-19[7].

**Altered immune response**

DM is responsible for the slow destruction of the immune response within the patient’s physiological system. DM-induced imbalance of the immune response can enhance the chance of dysregulation of immune modulators. Immunological dysregulation in diabetic patients is also considered a risk factor for SARS-CoV-2 infection and is also responsible for disease severity[7,33]. The diabetic condition causes a decrease in CD3+ T cell count, which may alter adaptive immunity and chronic inflammation. Low levels of lymphocyte and T-lymphocyte subtypes, including CD3, CD4, and CD8, were found in diabetics compared with non-diabetics. Thus, high blood sugar may affect lymphocytes and subset numbers in COVID-19[34]. Antigen presentation and
immunity against different pathogens, including CoV via the production of interferon gamma (IFN-γ), is controlled by CD4+ T helper (Th1) cells. SARS-CoV-2 was found to destroy circulating immune cells and enhance apoptosis of CD3, CD4, and CD8 T-cells, which is responsible for lymphocytopenia[35]. DM reduces neutrophil phagocytosis, chemotaxis and intracellular destruction of microbes. Deficiencies in adaptive immunity categorized as an initial delay of Th1 cell-mediated immunity activation and a delayed hyperinflammatory response are frequently witnessed in people with DM[35]. Individuals with DM also have altered primary immune cell function. In addition, reduced activity of NK cells, alteration in the activity and number of neutrophils and macrophages, and abnormal differentiation of T-cells have been reported in diabetic patients[36].

Cytokine storm
The expression of ACE-2 is observed in different locations such as the upper respiratory tract and lungs (type I and II alveolar epithelial cells), pancreas, heart, endothelium, renal tubular and intestinal epithelium. A conformational change in S-glycoprotein on the surface of SARS-CoV-2 occurs due to its binding with ACE-2. This process triggers proteolytic digestion by proteases (TMPRSS2 and furin) of the host cell and ultimately causes virion internalization. The entry of SARS-CoV-2 induces an inflammatory reaction with T helper cells and interferon γ produced. This process results in the generation of other inflammatory cells and causes the 'cytokine storm' [13]. It was reported that COVID-19 patients admitted to the ICU had increased plasma levels of interleukin (IL)-2, IL-6, IL-7, IL-10, granulocyte colony stimulating factor (GCSF), interferon gamma-induced protein 10 (IP-10), monocyte chemoattractant protein 1 (MCP-1), macrophage inflammatory protein-1A (MIP-1A), and tumor necrosis factor-α (TNF-α), indicating the cytokine storm and disease severity. The substantial rise in the level of IL-6 may be linked to mortality due to hyperinflammation in COVID-19 patients. Individuals with COVID-19 and hyperglycemia have increased cytokine release and immune responses[37,38]. Thus, SARS-CoV-2 infection is responsible for a rise in the levels of IL-1β, IL-4, and IL-10, IFN-γ, IP-10, and MCP-1 [38]. It was shown that people with DM have an impaired adaptive immune response. Due to the deficiency of an immunostimulant, DM causes an increased pro-inflammatory cytokine response indicated by the enhanced release of IL-1, IL-6, IL-8 and TNF-α. An increased basal level of cytokine might also be attributed to AGEs. Diabetic individuals have a constant low-grade inflammation facilitating the occurrence of a cytokine storm, which in turn is directly related to the severity of COVID-19 pneumonia and to subsequent death[38].
Expression of ACE, protease and other specific proteins

In DM, enhanced ACE-2, furin, and IL-6 expression and reduced T-cell function are linked to the risk and severity of SARS-CoV-2 infection. If the expression of ACE-2 increases in pulmonary cells, heart muscle, kidney, and pancreas, it increases the binding of SARS-CoV-2. In an experimental diabetic animal model, enhanced expression of ACE-2 in those tissues was recorded[13,39]. It was also reported that insulin may downregulate ACE-2 expression, while other hypoglycemic drugs such as glucagon-like peptide-1 (GLP-1) agonists and pioglitazone, may enhance ACE-2 expression. The binding of SARS-CoV-2 to ACE-2 can damage islets resulting in acute diabetes[39].

The relationship between ACE-2 receptors and diabetes is contentious. Through the envelope spike glycoprotein (S-protein), SARS-CoV-2 enters the host cell via ACE-2, and tissue expressing ACE-2 becomes the prime target and the lung is the worst affected organ[40]. ACE-2 has been reported to be expressed in the pancreas, especially in β-cells that produce insulin and overexpression of ACE-2 prevents β-cell dysfunction. Deletion of ACE-2 promotes oxidative stress in mice, followed by renin-angiotensin system (RAS) dysfunction and decreased glucose tolerance and insulin expression[41]. Specific tropism of SARS-CoV-2 occurs on the ACE-2 receptor in COVID-19, the expression of ACE-2 increases with an increase in pro-inflammatory cytokines TNFα, IL-1β, and IFN-γ at the initial stage of infection in patients without a previous clinical history of DM[42]. On entering the host cells, SARS-CoV-2 invariably destroys β-cells that contain the ACE-2 receptors, which may be the reason behind new-onset diabetes in individuals without preexisting diabetes[43]. Although new-onset diabetes in COVID-19 patients does not persist, these patients should be monitored for a longer time to assess hyperglycemia, which was observed three years after SARS infection due to transient damaged β-cells. The SARS virus also shares the same receptor in humans as SARS-CoV-2 virus, i.e., ACE-2, and binding to this receptor is reported to damage pancreatic islets and results in acute diabetes as ACE-2 expression is found in the pancreas[44]. Destruction of ACE-2 also occurs in the lung when infected by SARS-CoV-2. Although SARS-CoV-2 enters the cell via ACE-2, type II alveolar cells that express ACE-2 are predominantly destroyed following entry of the virus. ACE-2 in the lungs is expressed on the airway epithelium apical surface, where type II alveolar cells are responsible for lung surfactant that protects the lung[45]. It was also reported that SARS-CoV-2 has an approximately 4-fold greater affinity for ACE-2 compared to SAR-CoV-1[46]. It can be seen from the above findings that the presence of ACE-2 is essential for proper functioning of the body, and is essential due to its homeostatic role in the RAAS mechanism as well as in organs such as the kidneys, pancreas, and lungs. Nevertheless, to contain SARS-CoV-2 infection, inhibition of ACE-2 is vital. However, inhibition may impair various physiological mechanisms in the body.

Balance in the RAS system maintained by an ACE-1 and ACE-2 collaboration is important for local vasoconstrictor/proliferative (ACE-1/Ang-II/AT1-axis) and vasodilator/antiproliferative (ACE-2/Ang1-7/MA). Enhanced imbalance of ACE-1/ACE-2 may trigger RAS-driven injury that results in hyper-inflammation. Therefore, gene polymorphisms in ACE-1 and ACE-2 may alter their expression level that can cause enhanced capillary permeability, fibrosis, and apoptosis in lung cells, quickening lung damage and pulmonary shut-down triggered/worsened in COVID-19[46,47].

Furin, a type-1 membrane-bound protease, is involved in the cleavage of cell surface proteins that consequently release the spike fusion peptide; thus, the virus enters the cell through an endosomal pathway. Therefore, an increased level of furin increases the capability of the virus to enter the host cell. Diabetes linked with an increased level of furin might facilitate replication of the virus[13,35,39].

Successive cleavage of viral S-protein via transmembrane serine protease 2 (TMPRSS2) and furin can initiate viral entry to release viral genome into host cell ACE-2. A disintegrin and metalloproteinase 17 (ADAM17) and TMPRSS2/furin is located in the diabetic pancreatic β-cell membrane. A rise in glycosylated ACE-2, ADAM17 and TMPRSS2 expression in pancreatic islets and glycated SARS-CoV-2 S-protein in an individual with DM were observed. Thus, it is predicted that increased TMPRSS2 expression is linked to entry of the virus in humans[39,48]. The role of interferon-induced transmembrane proteins and ADAM17 was also investigated, and a possible association of their expression with SARS-CoV-2 infection and severity was suggested[39,48].

Vitamin D deficiency

It has been established that vitamin D works against viral disease and plays a crucial
role in protecting organs from damage. In diabetics, there is a high chance of reduced vitamin D level. Vitamin D deficiency may enhance the risk of COVID-19. The severity of COVID-19 arises due to damage in different organs by SARS-CoV-2. In contrast, a high level of vitamin D has a preventive effect on viral infection in diabetics[49].

Comorbidity and multi-morbidity in diabetic patients
DM is responsible for various complications such as hypertension, hyperlipidemia, obesity, cardiovascular diseases etc. Diabetic patients with comorbidities are very prone to COVID-19. The severity and mortality of COVID-19 is very high in diabetic patients with comorbidities[28]. Earlier studies revealed that diabetic patients with COVID-19 are at high risk for cardiovascular diseases (20.9%), hypertension (56.9%), and cerebrovascular diseases (7.8%) compared to non-diabetics. Long-term diabetics are at risk of various other comorbidities such as nervous system diseases, chronic kidney diseases, and recent studies have indicated that SARS-CoV-2 damages the kidney via the ACE-2 pathways[50,51]. It was found that SARS-CoV-2 can cause damage to β-cells directly, and insulin resistance accompanied by hypokalemia, cytokine and fetuin-A levels can also deteriorate in diabetic patients with COVID-19. Cardiovascular disease, collective comorbidity towards endocrine disease comprising DM, is a noteworthy contributor to COVID-19 morbidity[51-53].

ANTIDIABETIC MEDICATION AND COVID-19
DM is one of the most common comorbidities in COVID-19. Clinical management and treatment of DM in patients with COVID-19 or in diabetic patients who are more susceptible to SARS-CoV-2 infection is complex as the selection of antidiabetic medication in such cases is important in light of current evidence. Some of the antidiabetic drugs that enhance the expression of ACE-2 act as a double-edged sword. When prescribing antidiabetic drugs to diabetic patients with COVID-19 or to patients with new-onset diabetes, one should be very careful as most of these drugs increase the level of ACE-2 in various organs, including the lungs and pancreas, which may further enhance the infection. Patients infected with SARS-CoV-2 may develop acute lung injury (ALI) in the severe stage leading to acute respiratory distress syndrome (ARDS)[54,55].

Metformin is reported to increase the expression of ACE-2[56] as well as play an important role in the microvascular repair mechanism through AMP-activated protein kinase (AMPK) activation during ALI[57]. A recent retrospective study reported that metformin, a safe and inexpensive drug, decreased mortality in type-2 diabetic patients, mainly women, admitted to hospital with COVID-19. Apart from reducing pro-inflammatory cytokines such as TNFu and IL-6, increasing anti-inflammatory cytokine IL-10, stabilizing mast cells, and improving endothelial function, modulation of ACE-2 was found to be a major mechanism of metformin in reducing the severity of SARS-CoV-2 infection[58]. However, metformin discontinuation has been advised in the event of COVID-19 in diabetic patients as it is reported to cause lactic acidosis[59]. SARS-CoV-2 infection activates the NLRP3 inflammasome, leading to the production of a number of pro-inflammatory cytokines such as IL-1β, IL-6, and TNFα[60]. Glyburide, a sulfonylurea, is reported to inhibit the activation of NLRP3 inflammation by blocking the ATP-sensitive K+ channels (KATP)[61]. However, it is suggested that sulfonylureas such as glipizide, glibenclamide, tolbutamide, gliclazide, chlorpropamide, etc., should be stopped during COVID-19 infection to prevent hypoglycemia[59]. Diabetic patients and patients with hypertension are treated with ACE inhibitors, and angiotensin II type I receptor blockers (ARBs), which increase the expression of ACE-2[62] and are similar to the thiazolidinedione class of drugs. TNFα converting enzyme (TACE) cleaves ACE-2 into the soluble form sACE2, which circulates in the blood and is present in the extracellular spaces. As SARS-CoV-2 enters the cell via ACE-2, drug-induced modulation or increased expression of ACE-2 may allow entry of the virus, increase the viral load in diabetics and may lead to fatal consequences, which has been a concern among scientists. The formation of sACE2 may decrease the viral load in the body as it binds to SARS-CoV-2 but blocks its association with the host cell[63], thereby neutralizing it. ACE inhibitors, ARBs, and GLP-1 agonists are hypothesized to increase the level of sACE2 in the extracellular tissues, and may project sACE2 as a decoy receptor to neutralize the virus[64].

As reports of drugs augmenting the expression of ACE-2 in COVID-19 have received a mixed response around the globe, physicians have attempted to identify safer alternatives for diabetic patients with COVID-19. Of all the mentioned drugs,
insulin has been reported as a safer alternative in critically ill or new-onset diabetic patients suffering from COVID-19 as it is reported to decrease the level of disintegrin, pro-inflammatory cytokines, and metalloprotease (ADAM-17), thereby inhibiting the cytokine storm[15]. However, the administration of insulin also has certain disadvantages. Patients need to undergo continuous glucose monitoring to avoid hypoglycemia, and this may pose a possible health risk for the healthcare provider as this practice may increase exposure to COVID-19 patients. However, self-monitoring of glucose by patients or infusion using an insulin pump may be performed[65]. ACE-2 is thought to be the main SARS-CoV-2 receptor for entry into host cells; however, it was later found that the MERS-CoV receptor dipeptidyl peptidase-4 (DPP4) is also a potential target receptor for the spike receptor-binding domain of SARS-CoV-2, and this discovery paves the way for various therapeutic manipulations[54]. Interestingly, the DPP4 class of drugs viz., linagliptin, sitagliptin, saxagliptin, vildagliptin, and alogliptin are potent hypoglycemic drugs and are reportedly used specifically in obese diabetics and patients with improper renal function for a longer duration[66,67]. In certain African people, polymorphism of the DPP4 protein was related to a reduced incidence of MERS-CoV infection, which further suggests that DPP4 plays a protective role during MERS-type infection. However, it was found in an in-vitro setup that vildagliptin, sitagliptin, or saxagliptin were ineffective in blocking entry of coronavirus into host cells[15]. In a recently reported study of 1531 patients with COVID-19, it was observed that DPP4-inhibitors produced neither harmful nor beneficial effects and did not support the discontinuation of this class of drugs[68]. Thus, it is premature to predict the effect of DPP4-inhibitors in COVID-19 patients with DM as most of the published reports were carried out using a small set of patients showing only clinical outcomes; however, molecular aspects should also be verified. Recently, human recombinant soluble ACE-2 (hrsACE2) has been proved to be a new and promising therapy for diabetic patients with severe COVID-19. When hrsACE2 (0.4 mg/kg) was administered for seven days to a 45-year-old woman with non-pharmacologically controlled type-2 diabetes, she recovered gradually without showing any adverse effects, which demonstrated the beneficial effects of hrsACE2 which neutralized the SARS-CoV-2 viral load and protected organs expressing ACE-2 receptors[69].

Pioglitazone, another antidiabetic drug, may upregulate ACE-2 expression and might be linked theoretically with possible augmented susceptibility to SARS-CoV-2 infection. Pioglitazone was found to exhibit anti-inflammatory and antifibrotic effects, and reduced the release of different pro-inflammatory cytokines in monocytes and macrophages. Thus, some researchers suggested that the drug could be continued in diabetic individuals with moderate COVID-19 as it may be helpful in preventing the cytokine storm[70,71]. The use of SGLT2 inhibitors in diabetic patients with COVID-19 was not beyond criticism as they were found to enhance the expression of ACE-2 in the kidney. A study also recommended avoiding SGLT2 inhibitors in such cases as they enhanced the risk of dehydration and euglycemic diabetic ketoacidosis. Although, an SGLT2 inhibitor, i.e., dapagliflozin, was found to reduce lactic acidosis during hypoxia and reverse acid-base balance inside the cells, preclinical studies indicated that SGLT2 inhibitors could be helpful in averting the cytokine storm[70,71]. Insulin is preferred in diabetic patients with serious COVID-19. Insulin was found to exhibit an important role in the anti-inflammatory effect and decrease inflammatory markers in critically ill patients[70].

From the above-mentioned reports, it was observed that most antidiabetic drugs play a contentious role in diabetic patients with COVID-19 (Figure 2). Therefore, recommending an appropriate drug is not feasible. An in-depth retrospective study is warranted to determine the exact efficacy of these drugs against SARS-CoV-2 infection in diabetic patients.

**CONCLUSION**

COVID-19 is superimposing on the diabetes epidemic. Individuals with diabetes are more prone to SARS-CoV-2 infection, and severity of the disease is on the rise. Pathogenic links between DM and COVID-19 include altered glucose homeostasis, increased release of cytokinin that leads to the cytokine storm and enhanced oxidative stress. Alteration of the immune system, increased expression of ACE-2, and other enzymes such as furin are also crucial in diabetics, enhancing the risk of infection. Preexisting pathological pathways in hyperglycemic individuals elevate the risk of infectivity and are accountable for increased tissue injury and mortality. Antidiabetic drug-induced expression of ACE-2 may enhance the rate of viral entry. However,
many of these drugs can also exert beneficial effects. Therefore, caution is necessary when prescribing such drugs. However, the exact underlying mechanism for the differential effect in individuals with and without diabetes requires further study.

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Case Control Study

Pregnancy complications effect on the nickel content in maternal blood, placenta blood and umbilical cord blood during pregnancy

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Author contributions: Ding AL analyzed the data and wrote the manuscript; Ding AL, Hu H and Dong XD designed the research study; Ding AL, Hu H and Xu FP performed the research; Ding AL, Hu H, Xu FP, Liu LY and Peng J collected the samples; Dong XD contributed project support and technical guidance; All authors have read and approve the final manuscript.

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Institutional review board statement: This study was approved by the Medical Ethics Committee of the First People’s Hospital of Yunnan Province (approval number: KHLL-KY030).

Abstract

BACKGROUND
Nickel (Ni) may accumulate in the human body and has biological toxicity and carcinogenicity. Ni has an extensive impact on the health of pregnant women and fetuses during gestation.

AIM
To evaluate Ni exposure in pregnant women in Kunming, Yunnan Province, China; to describe the distribution of Ni in the maternal-fetal system and placental barrier function; and to investigate the effect of Ni exposure on fetal health in mothers with pregnancy complications.

METHODS
Seventy-two pregnant women were selected using a case-control design. The women were divided into two groups: The control group (no disease; n = 29) and the disease group [gestational diabetes (GDM), hypertensive disorder complicating pregnancy (HDCP), or both; n = 43]. The pregnant women in the disease group were further divided as follows: 14 cases with GDM (GDM group), 13 cases with HDCP (HDCP group) and 16 cases with both GDM and HDCP (disease combination group). Basic information on the pregnant women was collected by questionnaire survey. Maternal blood, placenta blood and cord blood were collected immediately after delivery. The Ni content in paired samples was determined using inductively coupled plasma mass spectrometry.
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INTRODUCTION

Gestational diabetes mellitus (GDM) and hypertensive disorder complicating pregnancy (HDCP) are common pregnancy complications. In recent years, the incidence of GDM and HDCP has been increasing[1]. GDM manifests mainly as hyperglycemia caused by impaired glucose tolerance during pregnancy[2]. It is associated with adverse pregnancy outcomes such as macrosomia, shoulder dystocia and neonatal hypoglycemia[3]. HDCP is the main factor associated with maternal morbidity and mortality in the perinatal period[4]. It may cause fetal intrauterine dysplasia and cardiovascular disease in adulthood[5]. In addition to the traditional pathogenic factors, new types of environmental exposure have attracted more and more attention.

With the continuous development of emerging technologies, nickel (Ni)-containing products are widely used in production and in life[6]. The presence of Ni is widespread in the environment. People are generally exposed to Ni through the air, their diet, consumer goods and other channels[7]. Ni may accumulate in the human body and has biological toxicity and carcinogenicity[8]. Ni has a more extensive impact on the health of pregnant women and fetuses during gestation. Studies have shown that there is a correlation between Ni exposure during pregnancy and the risk of pregnancy complications (such as GDM)[9]. Long-term exposure to Ni may lead to premature delivery and have certain effects on the respiratory and cardiovascular systems[10,11]. Maternal environmental exposure during pregnancy and lactation is a direct source of heavy metals in the fetus, and it has been proven that Ni transfers to the fetus through the placenta[12]. The embryotoxicity of Ni not only manifests as direct embryo damage to the placenta, but there are also cytotoxic effects[13]. Animal experiments have shown that exposure to Ni during pregnancy can lead to low birth weight, premature delivery and have certain effects on the respiratory and cardiovascular systems[14].

In this study, the distribution of nickel (Ni) in the maternal-fetal system and placental barrier function was described, and the effect of Ni exposure on fetal health in mothers with pregnancy complications was investigated. The results suggest that in the maternal-fetal system of women with pregnancy complications, the barrier effect of the placenta against Ni is weakened, thus affecting healthy growth of the fetus in the uterus. This study indicates that more attention should be focused on reducing Ni environmental exposure during pregnancy and improving the quality of the living environment in order to ensure normal development of the fetus.

RESULTS

Compared to the control group, age was higher and body mass index was greater in pregnant women in the disease groups (28.14 ± 2.54 vs 28.42 ± 13.89, P < 0.05; 25.90 ± 3.86 vs 31.49 ± 5.30, P < 0.05). The birth weights of newborns in the HDCP group and the control group were significantly different (2.52 ± 0.74 vs 3.18 ± 0.41, P < 0.05). The content of Ni in umbilical cord blood in the entire disease group was higher than that in the control group (0.10 ± 0.16 vs 0.05 ± 0.07, P < 0.05).

CONCLUSION

In the maternal-fetal system of women with pregnancy complications, the barrier effect of the placenta against Ni is weakened, thus affecting healthy growth of the fetus in the uterus.

Key Words: Heavy metal; Nickel; Gestational diabetes mellitus; Hypertensive disorder complicating pregnancy; Placental barrier; Newborn

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Core Tip: In this study, the distribution of nickel (Ni) in the maternal-fetal system and placental barrier function was described, and the effect of Ni exposure on fetal health in mothers with pregnancy complications was investigated. The results suggest that in the maternal-fetal system of women with pregnancy complications, the barrier effect of the placenta against Ni is weakened, thus affecting healthy growth of the fetus in the uterus. This study indicated that more attention should be focused on reducing Ni environmental exposure during pregnancy and improving the quality of the living environment in order to ensure normal development of the fetus.
weight or deformity in offspring[12]. The literature also suggests that the placenta can act as a barrier to heavy metals in the maternal-fetal system, which is defined by the ratio of maternal blood to umbilical blood.

However, there are few reports on the relationship between GDM and HDCP, Ni exposure, and the placental barrier. Therefore, the question arises as to whether in the presence of gestational complications (GDM and HDCP) more Ni will pass through the placenta and enter the fetus, thereby impacting fetal health? We will attempt to answer this question in this study.

MATERIALS AND METHODS

Screening of research subjects

A case-control design was adopted in this study; the 72 selected subjects were pregnant women who gave birth in the Obstetrics Department of The First People's Hospital of Yunnan Province between January 2019 and December 2019. The basic characteristics of the pregnant women and information regarding their newborns were obtained from hospital records and a questionnaire, which included pregnancy history, working environment, living environment, family history, maternal disease, etc. Women who had lived in the study area for a short period of time, had smoking or drinking habits, or had a history of occupational exposure to heavy metals were excluded. According to the diagnostic criteria of GDM and HDCP[1] and the health status, the pregnant women were divided into the control group (n = 29) and the disease group (n = 43). The control group included healthy women who delivered at term without pregnancy complications. The pregnant women in the disease group were further divided into the following groups: 14 cases of GDM (GDM group), 13 cases of HDCP (HDCP group) and 16 cases of both GDM and HDCP (disease combination group). This study was reviewed and approved by the Ethics Committee of Yunnan First People's Hospital, and the pregnant women provided written informed consent.

Sample processing and methods

After delivery, 10 mL of maternal blood, 10 mL of umbilical cord blood and 10-20 g of placental tissue were immediately collected and stored in an ultra-low temperature refrigerator at -80 °C. The samples were thawed before analysis, and 0.5 g of whole blood, 3 mL HNO$_3$ and 1 mL H$_2$O$_2$ or 1 g of placental tissue, 5 mL HNO$_3$ and 2 mL H$_2$O$_2$ were mixed, and the samples were digested in a microwave digestion tube at low pressure for 30 min. After digestion and cooling, the solution was diluted with 1% HNO$_3$ to 25 mL. The Ni content in samples was measured using an inductively coupled plasma mass spectrometer, and the standard curve was calibrated and verified by a multivariate standard solution. Each batch of 10 samples contained nine sample (blood/placenta) solutions and one blank solution.

Statistical analysis

IBM SPSS (Windows 17.0 version; IBM Corp., Chicago, IL, United States) was used to analyze the detection data, and the mean value, skewness and standard deviation were used to describe the distribution of Ni in the maternal-fetal system. An independent sample $t$ test was used to evaluate maternal and neonatal information and whether there were significant correlations between the content of Ni in samples and fetal birth weight and body length. $P < 0.05$ and $P < 0.001$ were considered statistically significant.

RESULTS

Basic characteristics of the mothers and newborns

A total of 72 pregnant women participated in this study; all were over 18 years of age (range: 21–44 years). The average age of pregnant women was 28 years in the control group, 30 years in the GDM group, 31 years in the HDCP group and 33 years in the disease combination group. The average body mass index (BMI) was 25.8 (kg/m$^2$) in the control group, 28 (kg/m$^2$) in the GDM group, 27.6 (kg/m$^2$) in the HDCP group and 29.7 (kg/m$^2$) in the disease combination group. All 72 pregnant women were compared to the control group, and the age and BMI of pregnant women in the HDCP group and in the disease combination group were significantly higher ($P < 0.05$), while
only BMI was significantly higher in the GDM group. In addition, the Apgar score of newborns in the three disease groups (GDM only, HDCP only, and the combination group) was significantly lower at 1 min and 5 min than that in newborns in the control group ($P < 0.05$). Figure 1A shows neonatal birth weight and birth body length in the control group and the disease groups. The dotted lines and shading represent neonatal birth weights and length within the normal range and the standard values (2.5–4.0 kg and 50 cm). Neonatal birth weight and birth body lengths were generally within the normal range, and these parameters in the disease group were 37% greater than the normal range. Compared with the control group, birth weight and body length in the GDM group and disease combination group were not significantly different ($P > 0.05$), but these parameters were significantly reduced in the HDCP group ($P < 0.05$, Figure 1b).

**Distribution of nickel in the maternal-fetal system**

Ni was detected in all paired samples in the control group and disease group (Figure 2A). Compared with the content of Ni in maternal blood, the content of Ni in umbilical cord blood in the control group was significantly reduced, whereas the content of Ni in umbilical cord blood in the GDM group and HDCP group was significantly enhanced ($P < 0.05$, Figure 2B). The content of Ni in maternal blood and umbilical cord blood was not significantly different in the disease combination group (Figure 2B). In addition, compared with the content of Ni in umbilical cord blood in the control group, the content of Ni in umbilical cord blood in the GDM group and HDCP group was significantly increased ($P < 0.05$, Figure 2B); and the content of Ni in umbilical cord blood was not significantly different between the control group and the disease combination group (Figure 2B).

**Effect of the placental barrier against nickel**

The placenta can act as a barrier to heavy metals in the maternal-fetal system. A higher ratio of heavy metals in maternal blood to heavy metals in umbilical blood greater than 1 indicates better placental barrier function[14]. In this study, we found that the proportion of women with a ratio greater than 1 was 85% in the control group, 60.47% in the entire disease group, 71.43% in the GDM group, 50.00% in the HDCP group, and 60.00% in the disease combination group. The effect of the placental barrier against Ni was weakened in the disease groups.

**DISCUSSION**

Weight management during pregnancy is an important part of pregnancy health care, and it has attracted the attention of researchers for many years. The high risk factors for gestational diseases mainly include individual factors, genetic factors and environmental factors[15]. Studies have shown that BMI during pregnancy is related to HDCP, GDM and pregnancy outcomes[16-18]. The BMI of pregnant women with HDCP is positively correlated with blood pressure[19]. Pregnant women with HDCP may present with fluid retention, which makes them heavier than healthy pregnant women[20]. The results of this study are consistent with current reports in the literature, in that they show that there is an interaction between the basic characteristics of pregnant women and pregnancy complications. However, specific metabolic mechanisms require further study. It has been long established that attention must be paid to maternal health and physical condition during pregnancy in order to improve the health of the mother and the infant.

The birth weight of the newborn is an important index in judging whether the fetus has grown normally in the uterus[21]. The health status of pregnant women is one of the factors affecting the birth weight of the newborn. Studies on HDCP have shown that the pathological mechanism involved in abnormal fetal intrauterine growth is complex and mainly attributed to placental vascular dysfunction as a result of reduced placental blood flow[22]. Fetal intrauterine growth depends on the effective transportation of nutrients by the placenta[23,24]. A decrease in placental blood flow leads to chronic fetal hypoxia and nutritional deficiency, resulting in intrauterine growth restriction (IUGR), premature delivery and even the possibility of death[4]. We found that there were significant differences between the HDCP group and the control group in terms of birth weight, length and Apgar score, which was consistent with the results reported in the literature. However, we assessed a limited number of indicators and samples; thus, we could not directly determine which factors (environmental exposure, individual differences, genetic factors) influenced fetal growth status in the
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Figure 1 Distribution of birth weight and birth length. A: Distribution of birth weight and birth length in control group and disease group; B: Birth weight and birth length were shown as mean ± SD. *P < 0.05. Control group: Healthy women who delivered at term without pregnancy complications; Combined disease group: The group with gestational diabetes (GDM) and hypertensive disorder complicating pregnancy (HDCP).

This study shows that pregnant women in Kunming, Yunnan Province experience exposure to environmental Ni. The detection of Ni in cord blood showed that Ni can be transferred to the fetus through the placental barrier. The placenta plays an important role as a barrier between maternal environmental exposure and transfer to the fetus, which influences their development[25]. By detecting Ni content in maternal blood, placenta blood and cord blood in the control group and disease group, we found that the placental barrier in the control group had a certain protective role, but the detection of Ni in cord blood in the control group showed that some Ni could still pass through the placenta and transfer to the fetus via the umbilical cord. Although the placenta has a high affinity for Ni, which prevents its transfer, the placental barrier does not protect the fetus from Ni[26].

The experimental data showed that the content of Ni in placenta blood and cord blood of pregnant women with gestational diseases (GDM group, HDCP group, disease combination group) was higher than that in the control group. Pregnant women with pregnancy complications may accumulate more Ni in the placenta through environmental exposure. Nickel has embryotoxicity and can induce lipid peroxidation in the placenta. This metabolic change can lead to a decrease in placental vitality and potential embryotoxicity. This affects embryo development[27], resulting in fetal IUGR. The transport of Ni in the placenta will change the morphology and permeability characteristics of the placenta during the development phase[28], resulting in weakening of the placental barrier function against Ni. As the intermediate medium for Ni transfer from mother to fetus, the placenta allows more Ni to enter the fetal side through the placenta. Although it has been reported that Ni can pass through the placenta[14], little is known about the toxic metabolic mechanism of Ni in the placenta.

The placenta is an important selective barrier to toxic substances during pregnancy[29]. However, some heavy metals (such as Ni) can interfere with the placental transport system and then cross the placenta[30,31]. Although the environmental
exposure level is far lower than the international standard\cite{29,32,33}, because the fetal physiological and biochemical levels are different to those of adults, the fetus is highly sensitive to harmful substances, even trace exposure levels\cite{34}. From our data analysis, we established that in pregnant women with pregnancy complications related to environmental exposure, the Ni placental barrier function showed different degrees of damage. Nickel placental barrier function varied from strong to weak in the following order: Control group, GDM group, disease combination group and the HDCP group. The placental barrier function against Ni in the control group was significantly better than that in all disease groups. The placental barrier function against Ni in the maternal-fetal system of the GDM group, HDCP group, and disease combination group was damaged to varying degrees, and it did not play a good role as a placental barrier. However, studies are needed to establish the mechanism by which Ni is transported and metabolized between the mother, placenta and fetus, to determine the toxic metabolic mechanism of Ni in the maternal-fetal system and to determine how prenatal exposure to Ni affects fetal growth \textit{in utero}. These studies should involve more paired samples and more detailed follow-up of the health status of newborns, as well as the use of advanced molecular biology methods to conduct in-depth studies on the samples.

The first advantage of this study is that the included population was in the third trimester, which can be used to evaluate exposure to Ni during pregnancy. The second advantage is the complete detection of Ni content in paired samples of maternal blood, placenta and cord blood, which can describe the dynamic changes in Ni in the maternal-fetal system. The third advantage of this study is the assessment of the placental distribution of Ni in the control, GDM and HDCP groups, and to compare the placental distribution of Ni in the maternal-fetal system in both healthy women

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{Distribution of nickel content in maternal-fetal system. A: Nickel (Ni) content in maternal blood, placenta blood and cord blood in control group and disease group; B: The Ni content in maternal-fetal system is shown as mean ± SD. *$P < 0.05$ vs Ni content in umbilical cord blood in control group; **$P < 0.05$ vs Ni content in maternal blood in same group. Control group: Healthy women who delivered at term without pregnancy complications; Combined disease group: the group with gestational diabetes (GDM) and hypertensive disorder complicating pregnancy (HDCP).}
\end{figure}
and those with gestational diseases (GDM and HDCP) in the general population. The diagnosis of gestational diseases was based on the standard hospital formal diagnosis, and other interference factors (such as the age of pregnant women 20-45-years-old and a non-occupationally exposed population) were strictly controlled. It also provides important clinical value for disease prevention in the future.

This study also has some limitations. Firstly, the sample size was small. Secondly, the research involved a case-control design, and the findings were not confirmed in an animal model and at the cell level. Thirdly, this study only screened the pregnant women living in the study area for a long time, and did not investigate and classify their diet and living habits, and did not take into account the potential influencing factors and the detection of Ni in other stages of pregnancy. In addition, this study was conducted in a provincial hospital. Although there were differences in some of the aspects studied, it does not represent the whole Kunming population. Therefore, we plan to increase the sample size and expand the scope of the study population in a follow-up study, with multi-dimensional assessment and analysis of the distribution and transfer characteristics of Ni in the maternal-fetal system in healthy women and in those with gestational diseases in the general population, as well as the toxicity of Ni.

**CONCLUSION**

This study has both advantages and disadvantages. It was found that pregnant women in Kunming, Yunnan Province experienced environmental exposure to Ni, which can be transferred to the fetus through the placental barrier. In the maternal-fetal system of women with pregnancy complications, the barrier effect of the placenta against Ni is weakened, thus affecting healthy growth of the fetus in the uterus. This study indicated that more attention should be focused on reducing Ni environmental exposure during pregnancy and improving the quality of the living environment in order to ensure normal development of the fetus.

**ARTICLE HIGHLIGHTS**

**Research background**
Gestational diabetes mellitus and gestational hypertension disease are common pregnancy complications. In addition to the traditional pathogenic factors, new types of environmental exposure have attracted more and more attention. With the continuous development of emerging technologies, nickel (Ni)-containing products are widely used in production and in life. Ni may accumulate in the human body and has biological toxicity and carcinogenicity. Ni has a more extensive impact on the health of pregnant women and fetuses during gestation.

**Research motivation**
This study has important reference significance for reducing Ni exposure during pregnancy, improving the quality of the living environment and ensuring the normal development of the fetus.

**Research objectives**
This study aimed to evaluate Ni exposure in pregnant women in Kunming, Yunnan Province, China.

**Research methods**
Basic information on the 72 pregnant women was collected by questionnaire survey. Maternal blood, placenta blood and cord blood were collected immediately after delivery. The Ni content in paired samples was determined using inductively coupled plasma mass spectrometry.

**Research results**
It was found that pregnant women in Kunming, Yunnan Province experienced environmental exposure to Ni, which can be transferred to the fetus through the placental barrier.
Research conclusions
In the maternal-fetal system of women with pregnancy complications, the barrier effect of the placenta against Ni is weakened, thus affecting healthy growth of the fetus in the uterus.

Research perspectives
Further research into the mechanisms, from the perspective of advanced molecular biology, will reveal the key role of nickel in gestational disease, placental barrier and birth outcome.

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Ding AL et al. Pregnancy complications effect on the nickel content


Retrospective Study

Clinical observation of Kuntai capsule combined with Fenmotong in treatment of decline of ovarian reserve function

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Author contributions: Lin XM designed the experiment; Chen M drafted the work, Chen HF, Wang QL and Ye XM collected the data; Lin XM analysed and interpreted data; Chen M wrote the article. Lin XM and Chen M contributed equally.

Institutional review board statement: This manuscript was approved by the Medical Ethics Committee of Zhanjiang Central Hospital.

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

Conflict-of-interest statement: The authors declared that there is no conflict of interest between them.

Data sharing statement: No additional data are available.

Open-Access: This article is an open-access article that was

Abstract

BACKGROUND
Decreased ovarian reserve function is an ovarian hypofunction disease that occurs in women before 40 years of age, leading to a decline in fertility and perimenopausal symptoms, such as irregular menstruation, amenorrhea, infertility, decreased libido, and autonomic nervous dysfunction. Fenmotong (FMT) is a compound mixture of estradiol tablets and estradiol didroxyprogesterone tablets, which can improve ovarian reserve function by supplementation of exogenous estrogen. However, this treatment has also been shown to cause breast pain, gastrointestinal discomfort, irregular vaginal bleeding, and changes in sexual desire. In severe cases, FMT can promote the development of breast cancer, endometrial cancer, and venous embolic disease.

AIM
To observe the effects of Kuntai capsules and FMT on endocrine indexes and uterine artery blood circulation in patients with decreased ovarian reserve function.

METHODS
Patients (130) with decreased ovarian reserve function, who were treated in our hospital from May 2018 to May 2020, were divided into two groups: The FMT group, in which patients were treated with FMT, and the observation group, in which patients were treated with Kuntai capsules. Chinese medicine symptoms scores, uterine artery blood flow parameters, ovarian ultrasound test indexes, pictorial blood loss assessment chart (PBAC) scores, and hormone levels were recorded, and total effective rates were calculated for both groups.

RESULTS
The total effective rate in the observation group was higher than that in the FMT group (P < 0.05). After treatment, primary symptoms, including low menstrual
volume, delayed menstruation, red color and thick consistency of menses, di-
ziness, palpitation, weakness at the waist and knee, insomnia and excessive
dreaming, irritability, and dryness and astringency of the pudendal canal in the
observation group decreased, and scores for primary and secondary symptoms in
the observation group were significantly lower than those in the FMT group \( (P < 0.05) \). The systolic peak flow rate (PSV), end-diastolic flow rate (EDV), ovarian
diameter, sinus follicle count, and resistance index (RI) of the uterine arteries in
the observation group and FMT group increased after treatment. Notably, the
PSV, EDV, ovarian diameter, and antral follicle count in the observation group
were higher than those in the FMT group, whereas the RI in the observation
group was lower than that in the FMT group \( (P < 0.05) \). The PBAC scores in the
observation and FMT groups increased after treatment, with that in the ob-
servation group becoming significantly higher than that in the FMT group \( (P < 0.05) \).
After treatment, estradiol (E2) and anti-Mullerian hormone (AMH) levels
increased, whereas follicle-stimulating hormone (FSH) levels decreased in the
observation group and FMT group; E2 and AMH levels became significantly
higher and FSH levels became significantly lower in the observation group than in
the FMT group \( (P < 0.05) \).

CONCLUSION

Compared with FMT, Kuntai capsules promoted uterine artery blood circulation,
improved menstruation, relieved symptoms, regulated endocrine function, and
improved curative effects.

Key Words: Kuntai capsule; Fenmatong; Ovarian reserve function decline; Endocrine
index; Blood circulation

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INTRODUCTION

According to the theory of traditional Chinese medicine (TCM), decreased ovary
reserve function belongs to the categories of “blood exhaustion”, “early break of
menopause,” and “syndrome before and after menopause”. The kidneys dominate
reproduction, kidney qi filling and kidney essence deficiency lead to Tiangui failure,
and blood stasis blocks collaterals. The syndrome of deficiency and excess is caused by
a lack of liver qi. The principle of treatment is to nourish the liver and kidney, calm the
mind, and eliminate stress. Kuntai capsules are a commonly used proprietary Chinese
medicine in the clinical treatment of menopause and postmenopausal syndromes
\[1-3\]. Although this treatment has been shown to alleviate symptoms\[4\], few studies have
evaluated the mechanisms of action of this treatment\[5-10\].

In this study, we evaluated the effects of Kuntai capsules compared with FMT on endocrine
indexes and uterine artery blood circulation in patients with decreased ovary reserve function.
MATERIALS AND METHODS

General information
In total, 130 patients with decreased ovarian reserve function treated in our hospital from May 2018 to May 2020 (28–40 years old; mean ± standard deviation: 33.88 ± 4.18 years) were divided into two groups according to the treatment plan after admission. There were no significant differences in general demographic characteristics between the two groups (P > 0.05; Table 1).

Diagnostic criteria
Decreased ovarian reserve function was defined according to the criteria defined by the Chinese Obstetrics and Gynecology committee[11-15], as follows: Less than 40 years of age; follicle-stimulating hormone (FSH) levels 15–25 IU and basic luteinizing hormone FSH greater than or equal to 2–3.6; menstruation disorders and rare menstruation occurring for more than 4 mo; and ultrasound showing fewer than five follicles in the ovary.

Syndrome differentiation for TCM was consistent with the standard of yin deficiency of the liver and kidney in the Diagnostic Efficacy Standard of TCM Diseases; the primary symptoms were reduced menstruation, delayed menstruation or amenorrhea, and discharge of a thick red substance, whereas secondary symptoms were dizziness and palpitations, sore waist and knees, insomnia and excessive dreaming, dryness of the vulva, irritability, and weak pulse.

Inclusion and exclusion criteria
The inclusion criteria were as follows: Diagnosed with decreased ovarian reserve function according to the above-listed criteria; TCM syndrome differentiation of liver and kidney yin deficiency syndrome; age greater than or equal to 18 years old and less than or equal to 40 years old; not taking other drugs; and complete clinical data available.

The exclusion criteria were as follows: History of endocrine drug use within the 3 mo prior to enrollment in the study; presence of pelvic infection, uterine fibroids, endometrial lesions, or other gynecological diseases; history of hyperandrogenemia, hyperthyroidism, hypothyroidism, or other endocrine diseases; presence of important organ diseases or hematopoietic, respiratory, and immune system diseases; and allergies to the study medications or components.

Methods
Patients in the FMT group were treated with a compound mixture of estradiol tablets and estradiol didroxyprogesterone tablets (trade name: Fenmatong; Dutch Abbott BiologicalsB.V.; 2/10 mg; registration number H20150345), oral white tablets (containing estradiol 1 mg) once per day for 14 d before the menstrual cycle, and gray tablets (containing estradiol 1 or 10 mg) once a day during the last 14 d of the menstrual cycle; the course of treatment was 28 d, and three consecutive courses of treatment were administered. Patients in the observation group were treated with Kuntai capsules (Guiyang Xintian Pharmaceutical Co., Ltd.; 0.5 g; Chinese medicine no. Z20000083) at a dose of four tablets per treatment, three times per day; the course of treatment was 28 days, and three consecutive courses of treatment were administered.

Detection method
Uterine artery blood flow parameters, including the systolic peak flow rate (PSV), end-diastolic flow rate (EDV), resistance index (RI), ovarian diameter, and antral follicle count were measured by ultrasound before and after three courses of treatment. The patients were instructed to avoid urination until collection, and the above indexes were evaluated in urine samples using a Philips IE33 color Doppler ultrasound with a probe frequency of 3.5 MHz.

The levels of serum sex hormone estradiol (E2), anti-Mullerian hormone (AMH), and FSH were detected via radioimmunoassay before treatment and on days 2–3 of the menstrual cycle. In the morning, 3 mL venous blood was collected from patients after fasting overnight and centrifuged at 3000 rpm for 10 min. The above indexes were detected using Roche E601 chemiluminescence immunoassays and a kit from Nanjing Jiancheng Bioengineering Institute.
Table 1 Comparison of two groups of general data (n = 65)

<table>
<thead>
<tr>
<th>Group</th>
<th>Age</th>
<th>Course of disease</th>
<th>Number of pregnancies</th>
<th>Pregnancy times (times)</th>
<th>BMI (kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fenmatong group</td>
<td>34.02 ± 3.89</td>
<td>3.45 ± 0.61</td>
<td>2.05 ± 0.36</td>
<td>1.32 ± 0.28</td>
<td>23.17 ± 1.24</td>
</tr>
<tr>
<td>Observation group</td>
<td>33.74 ± 4.29</td>
<td>3.38 ± 0.57</td>
<td>1.98 ± 0.45</td>
<td>1.37 ± 0.26</td>
<td>23.06 ± 1.48</td>
</tr>
<tr>
<td>t</td>
<td>0.390</td>
<td>0.676</td>
<td>0.979</td>
<td>1.055</td>
<td>0.459</td>
</tr>
<tr>
<td>P value</td>
<td>0.697</td>
<td>0.500</td>
<td>0.329</td>
<td>0.293</td>
<td>0.647</td>
</tr>
</tbody>
</table>

BMI: Body mass index.

Analysis of curative effects

After the treatment course, the treatments were assessed as being highly effective, wherein symptoms such as menstrual disorder, rare menstruation, vaginal dryness, and decreased libido disappeared, E2 Levels returned to normal, and FSH levels decreased by at least 50%; effective, wherein the above symptoms improved, E2 Levels improved but did not reach normal, and FSH levels decreased by 20% to 50%; or ineffective, wherein the above criteria were not met.

Scoring standard

TCM symptom scores were evaluated before treatment and 4 wk after treatment based on the Therapeutic Effect Criteria for Disease and Syndrome Diagnosis of TCM, including primary and secondary symptoms. The severity of symptoms was classified as none, mild, moderate, or severe, with scores of 0 to 6 for primary symptoms and 0 to 3 for secondary symptoms.

Pictorial blood loss assessment chart (PBAC) scores for menstrual bleeding were evaluated before treatment and 4 wk after treatment, according to the common score of blood staining degree and lost blood clotting for a single sanitary napkin. The blood staining degree was calculated as follows: 1, blood staining area less than or equal to 1/3; 5, blood staining area between 1/3 and 3/5; and 20, blood staining of the entire sanitary napkin. Lost blood clot:

Statistical methods

The data were processed using SPSS19.0, and quantitative indexes were described as means and standard deviations. Student’s t-tests and $\chi^2$ tests were used to compare quantitative data.

RESULTS

Comparison of curative effects between the two groups

In the observation group, highly effective treatment was observed for 47 cases (72.31%), whereas effective treatment was observed for 14 cases (21.54%). The total effective rate was 93.85%, which was higher than that in the FMT group (32 cases of highly effective treatment, 21 cases of effective treatment; total effective rate of 81.54%); this difference was statistically significant ($P < 0.05$; Table 2).

Comparison of TCM symptom scores between the two groups

Before treatment, TCM syndrome scores did not differ significantly between the observation group and FMT group ($P > 0.05$). After treatment, scores for primary symptoms, such as low menstrual flow, delayed menstruation, thick red discharge, dizziness, heart palpitations, weakness of the waist and knees, insomnia, excessive dreaming, and irritability, and scores for secondary symptoms, such as genital dryness, were significantly lower in the observation group than in the FMT group ($P < 0.05$; Table 3).

Comparison of uterine artery blood flow parameters and ovarian ultrasound detection indicators in the two groups

Before treatment, there were no significant differences in uterine artery blood flow parameters and ovarian ultrasound detection indexes between the observation and FMT groups ($P > 0.05$). After treatment, the PSV and EDV of the uterine artery
increased in the observation group, whereas the ovarian diameter and antral follicle count increased and the RI decreased in the FMT group. Additionally, in the observation group, the PSV (38.96 ± 3.11 cm/s), EDV (15.89 ± 1.57 cm/s), ovarian diameter (2.64 ± 0.14 cm), and antral follicle count (4.91 ± 0.43) were higher, whereas the RI (0.73 ± 0.10) was lower than those in the FMT group (P < 0.05; Table 4).

Comparison of PBAC scores between the two groups
The PBAC scores increased in both groups after treatment, and the PBAC score in the observation group was higher than that in the FMT group (P < 0.05; Table 5).

Comparison of hormone levels between the two groups
After treatment, E2 and AMH levels increased, whereas FSH levels decreased in both groups. In the observation group, E2 (57.96 ± 5.17 pg/mL) and AMH (0.29 ± 0.09 ng/mL) levels were higher than those in the FMT group, whereas FSH levels (10.14 ± 1.57 IU/L) were lower than those in the FMT group (P < 0.05). Additionally, the total effective rate in the observation group was higher than that in the FMT group (P < 0.05; Tables 6 and 7).

Safety analysis
None of the 130 patients had adverse reactions, such as abnormal echocardiograms, abnormal liver and kidney functions, or allergic reactions.

DISCUSSION
The mechanism of decline in ovarian reserve function is complex and related to heredity, immunity, environment, diet, psychological factors, repeated abortion,
Table 4 Comparison of uterine artery blood flow parameters between the two groups (n = 65, mean ± SD)

<table>
<thead>
<tr>
<th>Group</th>
<th>PSV (cm/s) Before treatment</th>
<th>PSV (cm/s) After treatment</th>
<th>EDV (cm/s) Before treatment</th>
<th>EDV (cm/s) After treatment</th>
<th>RI Before treatment</th>
<th>RI After treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fenmatong group</td>
<td>30.85 ± 3.14</td>
<td>35.42 ± 3.36</td>
<td>5.24 ± 1.14</td>
<td>12.19 ± 1.45</td>
<td>0.87 ± 0.10</td>
<td>0.81 ± 0.08</td>
</tr>
<tr>
<td>Observation group</td>
<td>30.41 ± 3.52</td>
<td>38.96 ± 3.11</td>
<td>5.30 ± 1.07</td>
<td>15.89 ± 1.57</td>
<td>0.86 ± 0.13</td>
<td>0.73 ± 0.10</td>
</tr>
<tr>
<td><em>t</em></td>
<td>0.752</td>
<td>6.234</td>
<td>0.589</td>
<td>13.958</td>
<td>0.492</td>
<td>5.036</td>
</tr>
<tr>
<td><em>P</em> value</td>
<td>0.453</td>
<td>0.000</td>
<td>0.758</td>
<td>0.000</td>
<td>0.624</td>
<td>0.000</td>
</tr>
</tbody>
</table>

PSV: Systolic peak flow rate; EDV: End-diastolic flow rate.

Table 5 Comparison of ultrasonic detection indexes of ovaries between the two groups (n = 65, mean ± SD)

<table>
<thead>
<tr>
<th>Group</th>
<th>Ovarian diameter(cm) Before treatment</th>
<th>Ovarian diameter(cm) After treatment</th>
<th>Antral follicle count Before treatment</th>
<th>Antral follicle count After treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fenmatong group</td>
<td>2.56 ± 0.12</td>
<td>2.60 ± 0.10</td>
<td>3.08 ± 0.57</td>
<td>4.64 ± 0.51</td>
</tr>
<tr>
<td>Observation group</td>
<td>2.57 ± 0.13</td>
<td>2.64 ± 0.14</td>
<td>3.12 ± 0.53</td>
<td>4.91 ± 0.43</td>
</tr>
<tr>
<td><em>t</em></td>
<td>0.456</td>
<td>1.874</td>
<td>0.414</td>
<td>3.263</td>
</tr>
<tr>
<td><em>P</em> value</td>
<td>0.649</td>
<td>0.063</td>
<td>0.679</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Table 6 Comparison of pictorial blood loss assessment chart scores between the two groups (n = 65, mean ± SD)

<table>
<thead>
<tr>
<th>Group</th>
<th>PBAC score Before treatment</th>
<th>PBAC score After treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fenmatong group</td>
<td>18.14 ± 2.98</td>
<td>21.74 ± 3.06</td>
</tr>
<tr>
<td>Observation group</td>
<td>17.95 ± 3.15</td>
<td>23.45 ± 2.77</td>
</tr>
<tr>
<td><em>t</em></td>
<td>0.353</td>
<td>3.340</td>
</tr>
<tr>
<td><em>P</em> value</td>
<td>0.724</td>
<td>0.001</td>
</tr>
</tbody>
</table>

PBAC: Pictorial blood loss assessment chart.

Table 7 Comparison of hormone levels between the two groups (n = 65)

<table>
<thead>
<tr>
<th>Group</th>
<th>FSH (IU/L) Before treatment</th>
<th>FSH (IU/L) After treatment</th>
<th>E2 (pg/mL) Before treatment</th>
<th>E2 (pg/mL) After treatment</th>
<th>AMH (ng/mL) Before treatment</th>
<th>AMH (ng/mL) After treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fenmatong group</td>
<td>18.21 ± 2.44</td>
<td>13.76 ± 2.06</td>
<td>25.38 ± 3.24</td>
<td>44.23 ± 4.05</td>
<td>0.22 ± 0.05</td>
<td>0.26 ± 0.07</td>
</tr>
<tr>
<td>Observation group</td>
<td>18.14 ± 2.26</td>
<td>10.14 ± 1.57</td>
<td>24.89 ± 4.77</td>
<td>57.96 ± 5.17</td>
<td>0.21 ± 0.08</td>
<td>0.29 ± 0.09</td>
</tr>
<tr>
<td><em>t</em></td>
<td>0.170</td>
<td>11.330</td>
<td>0.685</td>
<td>16.855</td>
<td>0.855</td>
<td>2.121</td>
</tr>
<tr>
<td><em>P</em> value</td>
<td>0.866</td>
<td>0.000</td>
<td>0.495</td>
<td>0.000</td>
<td>0.394</td>
<td>0.036</td>
</tr>
</tbody>
</table>

FSH: Follicle-stimulating hormone; E2: Estradiol; AMH: Anti-Mullerian hormone.

improper contraceptive methods, and chronic ovarian diseases, among other factors [16-18]. The incidence of decline in ovarian reserve function caused by increases in life and work pressures placed on modern women is increasing every year, with a tendency to occur at younger ages. Abrahami et al.[19] believe that unexplained infertility in young women may be a risk signal for decreased ovarian reserve function and can be used as a quantitative rather than qualitative risk factor[19]. In a cohort study, Yücel et al.[20] found that the decline in ovarian reserve function may be an
undiagnosed cause of unexplained infertility. In Western medicine, estrogen and progesterone replacement therapy is the first-line treatment for ovarian function decline, and FMT is a representative drug used for such treatment. Supplementation with exogenous estrogen and progesterone can inhibit the release of FSH and restore follicular development and ovulation through a negative feedback mechanism. The Leangkoonsathian et al.[21] study suggested that estrogen and progesterone supplementation could improve the sleep quality of postmenopausal women.

In this study, we found that treatment with Kuntai capsules combined with FMT was associated with improved menstruation, reduced menstruation, delayed menstruation, thick red discharge, dizziness and palpitations, sore waist and knees, insomnia and excessive dreaming, irritability, pudendal dryness, and other symptoms. The mechanisms may be related to the effects of FMT on regulating the hypothalamus-pituitary-ovary axis through negative feedback by supplementation with estrogen and progesterone to promote follicular development and ovulation[21]. Water extracts of cooked *Rehmannia glutinosa* in Kuntai capsules can regulate the response of the human body to gonadotropin and modulate endometrial receptivity. Moreover, donkey-hide gelatin can promote the function of the hematopoietic system, regulate calcium balance, improve autonomic nervous function, and alleviate symptoms of the perimenopausal period. Berberine in *Coptis chinensis* and baicalin in *Scutellaria baicalensis* Georgii not only have antipathogenic effects but also have anti-inflammatory, antipyretic, sedative, and hypnotic effects. β-Sitosterol contained in *Radix Paeoniae Alba* has pharmacological effects, such as hypolipidemic, anti-inflammatory, and antitumor effects. *Poria cocos* can increase the level of sex hormone secretion and protect the secretory function of the ovary.

The decrease in blood supply to the uterus and ovary is an important cause of decreased ovarian reserve function. Some researchers studied the effects of ovarian blood supply on ovarian function in healthy hybrid adult female dogs. Ligation of ovarian vessels caused a continuous decrease in 17β-estradiol and progesterone in experimental animals as well as follicular necrosis and fibrosis of ovarian tissue. These findings suggest that ligation of ovarian vessels should be used as an alternative to ovariectomy. In the current study, we found that Kuntai capsules combined with FMT promoted uterine artery blood circulation, improved ovarian blood supply, prevented ovarian atrophy, and facilitated follicle formation, as demonstrated by detection of uterine artery PSV and EDV, RI, ovarian diameter, and antral follicle counts before and after treatment. This is because TCMs in Kuntai capsules that promote blood circulation and tonify blood, such as *Rehmannia glutinosa* and Ejiao, can dilate the uterine artery, reduce vascular resistance, increase local blood perfusion, and reduce ischemic injury to the uterus and ovary, which is beneficial to the recovery of ovarian function.

E2 is produced by granulosa cells of growing follicles and is a common index used to monitor follicular growth and ovarian reserve function. AMH is a glycoprotein secreted by primary follicles, preantral follicles, and antral follicular granulosa cells that can inhibit the activation of primordial follicles and slow the rate of ovarian reserve depletion. Because early follicular secretion of AMH is not regulated by FSH and the level of AMH is relatively stable throughout the menstrual cycle, AMH is used as a relatively objective index for evaluation of ovarian function. FSH is a sex hormone secreted by the pituitary under stimulation of hypothalamic gonadotropin-releasing hormone, which is regulated by negative feedback of E2 and inhibit B. Increases FSH levels can lead to early collection of follicles and shortening of the menstrual cycle. In this study, we found that Kuntai capsules combined with FMT regulated endocrine function in the treatment of decreased ovarian reserve function, as demonstrated by detection of the above hormone indexes. These findings provided important insights into the mechanisms through which Kuntai capsules and FMT improved ovarian reserve function.

**CONCLUSION**

In this study, we found that Kuntai capsules combined with FMT for the treatment of decreased ovarian reserve function promoted uterine artery blood circulation, improved menstruation, alleviated symptoms, regulated endocrine function, and improved curative effects. However, we only included patients with decreased ovarian reserve function, and not all patients had fertility problems. Therefore, we did not observe pregnancy and delivery rates for the patients after treatment. Therefore, in future clinical studies, patients with fertility problems can be screened to further explore whether Kuntai capsules combined with FMT could increase fertility rates in
the treatment of ovarian reserve function decline.

**ARTICLE HIGHLIGHTS**

**Research background**
Decreased ovarian reserve function, also known as premature ovarian failure, is characterized by a decrease in the level of estrogen in the body, resulting in a series of low-estrogen symptoms that adversely affect the physical and mental health of patients.

**Research motivation**
From the direction of traditional Chinese medicine (TCM) to find ways to treat the decline of ovarian reserve.

**Research objectives**
This study aimed to observe the clinical manifestations of Kuntai capsule combined with Femmotong in treating decline of ovarian reserve function.

**Research methods**
Patients (130) with decreased ovarian reserve function, were divided into two groups: The FMT group, and the observation group, in which patients were treated with Kuntai capsules. The clinical indexes including TCM symptom score and uterine artery blood flow parameters were recorded, and the total effective rate of the two groups was counted.

**Research results**
The total effective rate in the observation group was higher than that in the FMT group (\(P < 0.05\)). Secondary symptoms decreased in both groups, and the scores of primary and secondary symptoms in the observation group were lower than those in the femoston group (\(P < 0.05\)). The observation group was more conducive to promoting uterine artery blood circulation, improving ovarian blood supply, preventing ovarian atrophy, and facilitating follicular formation.

**Research conclusions**
Effect of Kuntai capsule combined with femoston on ovarian reserve function decline is better than that of femoston alone.

**Research perspectives**
Therefore, we did not observe pregnancy and delivery rates for the patients after treatment. Therefore, in future clinical studies, patients with fertility problems can be screened to further explore whether Kuntai capsules combined with FMT could increase fertility rates in the treatment of ovarian reserve function decline.

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1941 [PMID: 32489080 DOI: 10.19540/j.cnki.cjcmmm.20191127.502]


Retrospective Study

Short-term effect and long-term prognosis of neuroendoscopic minimally invasive surgery for hypertensive intracerebral hemorrhage

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Institutional review board statement: This study was approved by the Harrison International Peace Hospital Ethics Committee.

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

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Data sharing statement: No additional data are available.

Open-Access: This article is an

Abstract

BACKGROUND
Hypertensive intracerebral hemorrhage is a common critical disease of the nervous system, comprising one fifth of all acute cerebrovascular diseases and has a high disability and mortality rate. It severely affects the patients’ quality of life.

AIM
To analyze the short-term effect and long-term prognosis of neuroendoscopic minimally invasive surgery for hypertensive intracerebral hemorrhage.

METHODS
From March 2018 to May 2020, 118 patients with hypertensive intracerebral hemorrhage were enrolled in our study and divided into a control group and observation group according to the surgical plan. The control group used a hard-channel minimally invasive puncture and drainage procedure. The observation group underwent minimally invasive neuroendoscopic surgery. The changes in the levels of serum P substances (SP), inflammatory factors [tumor necrosis factor-α, interleukin-6 (IL-6), IL-10], and the National Hospital Stroke Scale (NIHSS) and Barthel index scores were recorded. Surgery related indicators and prognosis were compared between the two groups.

RESULTS
The operation time (105.26 ± 28.35) of the observation group was min longer than that of the control group, and the volume of intraoperative bleeding was 45.36 ± 10.17 mL more than that of the control group. The hematoma clearance rates were 88.58% ± 4.69% and 94.47% ± 4.02% higher than those of the control group at 48 h
INTRODUCTION

Hypertensive intracerebral hemorrhage is a common clinical critical illness of the nervous system, accounting for one-fifth of all acute cerebrovascular diseases with a high incidence of disability and mortality[1]. Various factors cause the blood vessels in the brain to rupture into the brain parenchyma. Nearly a quarter of patients die within one day of illness due to the disease. The mortality rate in one month is greater than 50%[2] having a serious impact on the quality of life of patients. Some Chinese scholars report that the incidence of hypertensive cerebral hemorrhage is 50-80 people per 100000, with the highest rate of death and disability among various types of strokes. Presently, operative treatment is a significant therapy for hypertensive intracerebral hemorrhage[3]. Operative treatment aims at clearing the intracranial hematoma and relieving intracranial pressure effectively, thus reducing secondary brain injury. Currently, hard-channel minimally invasive puncture drainage and neuroendoscopic minimally invasive surgery are the common methods[4]. Both these methods have advantages, such as minimal invasion, quick recovery, excellent prognosis, etc. However, there are no reports comparing these two methods in clinical practice[5]. Therefore, the objective of this study was to compare the effects of hard-channel minimally invasive puncture drainage and neuroendoscopic minimally invasive surgery on hypertensive intracerebral hemorrhage.

MATERIALS AND METHODS

General information

We enrolled 118 patients with hypertensive intracerebral hemorrhage in our hospital...
from March 2018 to May 2020; they were divided into two groups on the basis of operation strategy. The control group underwent hard-channel minimally invasive puncture drainage and the observation group underwent neuroendoscopic minimally invasive surgery. Each group had 59 cases. The inclusion criteria were as follows: (1) Conforming to the standard of “all kinds of cerebrovascular disease diagnosis”, and diagnosed as supratentorial hematoma on head computed tomography (CT); (2) Age ≥ 18 years, and ≤ 75 years; (3) Was the first episode and a score of Glasgow Coma Scale ≥ 6; (4) Traditional craniotomy was intolerable; (5) Admission time < 24 h; and (6) Clinical information was integrated. The exclusion criteria were as follows: (1) Patient with herniation of the brain; (2) Volumes of hemorrhage < 20 mL or > 70 mL; (3) Hemorrhage from ruptured intracranial aneurysm or cerebrovascular malformation; (4) Combined with principal organs diseases of the heart, liver and kidney; (5) Patients with disordered coagulation mechanism; and (6) Used antibiotics, glucocorticoid and immunosuppressant treatment for a long time.

Methods
In the control group, we carried out hard-channel minimally invasive puncture drainage, conducted CT positioning after moderate local anesthesia to confirm the depth of hematoma and angle of puncture, usually selecting the maximum level center of hematoma as the target of puncture, and avoiding blood vessels and important functional areas. The incision was made on the patient’s scalp; the dura was pierced with a puncture needle and the F12 silicone ventricular drainage tube was inserted in the hematoma center, and connected to an extracorporeal drainage tube with a general suction volume of 20%-30%. Additionally, 50000 U of urokinase was injected into the hematoma cavity every day after completion, closed the tube, and opened the drainage two hours later for 3-7 d until 80%-90% of the hematoma was removed, drew out the tube.

In the observation group, we performed neuroendoscopic minimally invasive surgery by making a 3-4 cm cut where the maximum level of hematoma volume was present after moderate local anesthesia drilled within the skull plate, 1-1.5 cm closest to the hematoma center, separated the local brain tissue with bipolar electrocoagulation after incising the dura, punctured using a trocar along the direction of CT-identified the hematoma and applied the tube and suction equipment to clean the hematoma with monitor guidance, used bipolar electrocoagulation for hemostasis at the bleeding source, reserved ectocoelic drainage tube of hematoma, utilized gelatin sponge to fill the drill, and sewed up the incisions after removing the trocar.

Indicators of observation and methods of detection
Cytokine levels; National Hospital Stroke Scale (NIHSS) score; variation of Barthel index between the two groups before and after surgery; indices, such as operation time, bleeding volume, and hematoma clearance rate; and rate of complication and prognosis within 6 mo after surgery of the two groups were compared. The NIHSS score has a total score of 42 ranging from 0 to 42; a score < 7 is classified as mild neurological impairment; a score of 7–15 signifies moderate defect; a score > 15 is classified as severe defect. The Barthel index has a total score of 100. The score is directly proportional to independence and inversely proportional to dependence. Prognosis within 6 mo was assessed by the Glasgow Coma Scale (GCS score), with class I being death, class II being vegetative state, class III and IV being severe and mild disability respectively, and class V being good recovery. Class IV-V have a good prognosis.

Statistical analysis
Data was analyzed using SPSS19.0. (IBM SPSS Statistics for Windows, version 19, IBM Corp., Armonk, NY, United States). Description of measuring index with mean ± SD, application of t test, count data with χ² test, there was Statistical significance was set at P < 0.05.

RESULTS

Comparison of general information between two groups
There was no significant difference in the between-group comparison of general information of sex, age, hemorrhage location, etc. between two groups (P > 0.05) (Table 1).
Table 1 Comparison of general information between two groups

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Male/female</th>
<th>Age (yr)</th>
<th>Hypertension duration (yr)</th>
<th>Volume of hematoma (mL)</th>
<th>GCS score (point)</th>
<th>Hemorrhage location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>59</td>
<td>33/26</td>
<td>57.63 ± 9.32</td>
<td>11.25 ± 2.05</td>
<td>51.85 ± 12.69</td>
<td>9.12 ± 2.32</td>
<td>43 (72.88)</td>
</tr>
<tr>
<td>Observation group</td>
<td>59</td>
<td>35/24</td>
<td>56.86 ± 11.04</td>
<td>11.31 ± 1.97</td>
<td>52.14 ± 12.17</td>
<td>9.05 ± 2.41</td>
<td>41 (69.49)</td>
</tr>
<tr>
<td>χ²/t</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>0.709</td>
<td></td>
<td>0.409</td>
<td>0.162</td>
<td>0.127</td>
<td>0.161</td>
<td>0.167</td>
</tr>
</tbody>
</table>

Comparison of surgical related indicators between two groups

The observation group had a longer operation time of 105.26 ± 28.35 min than the control group, and a higher volume of intraoperative hemorrhage of 45.36 ± 10.17 mL than the control group. Hematoma clearance rates of the observation group at 48 h and 72 h postoperatively were 88.58% ± 4.69% and 94.47% ± 4.02% respectively, and higher than those of the control group (P < 0.05) (Table 2).

Comparison of cytokine level, NIHSS score and Barthel index score between the two groups

On postoperative day 14, serum P substances (SP) level increased in the two groups, whereas tumor necrosis factor-α (TNF-α), interleukin (IL)-6, IL-10 Levels decreased compared to their preoperative values. The above-mentioned cytokines in the observation group were higher than in the control group (P < 0.05). Similarly, on postoperative day 14, the Barthel index scores of the two groups increased, and the NIHSS score decreased compared to the preoperative values (Table 3). The Barthel index score of the observation group was higher than that of the control group, and the NIHSS score was lower than that of the control group (P < 0.05) (Table 4).

Comparison of complication rate during the hospital stay between two groups

Table 5 shows that there was no significant difference in the complication rates between the two groups (P > 0.05).

Comparison of prognosis within 6 mo between the two groups

Table 6 shows that both groups had no occurrence of class 1 case; the observation group had a significantly better prognosis than the control group (P < 0.05).

DISCUSSION

Minimally invasive puncture hematoma drainage surgery is commonly used in clinical practice. The operation is simple and can be completed under local anesthesia, which is suitable for application in frail and older patients or patients with serious diseases [6]. The operation causes minor trauma to the patient, which is conducive to the recovery of the patient. Needle drainage advocates earlier reduction of the compressive effect of the hematoma and less brain damage[7].

However, the hematoma clearance rate is low. Drainage of the hematoma requires time, and the nerve function damage caused by the hematoma compression cannot be completely relieved within a short time [8]. It was found that the operation time of the observation group was prolonged, and the intraoperative bleeding higher, but the hematoma clearance rate increased. Because neuroendoscopic surgery can treat accurate positioning of the hematoma, use the transparent outer tube to observe the distribution of the surrounding hematoma, so as to facilitate clinical observation as much as possible Limit hematoma removal[9].

Currently, neuroendoscopy is considered for the surgical treatment of hypertensive cerebral hemorrhage. The first indication is that the operation should be performed after 6 h of the episode as much as possible, and the operation time should be delayed as much as possible for patients who have been taking aspirin for a prolonged duration; second, it is suitable for patients with a hematoma volume of 30-90 mL, and is especially suitable for a deep hematoma. This operation is not suitable for patients...
Table 2 Comparison of surgical related indicators between two groups (mean ± SD)

<table>
<thead>
<tr>
<th>Groups</th>
<th>Cases</th>
<th>Operation time (min)</th>
<th>Volume of hemorrhage with introperative (mL)</th>
<th>Hematoma clearance rate (%)</th>
<th>48 h after surgery</th>
<th>72 h after surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>59</td>
<td>42.55 ± 9.14</td>
<td>22.36 ± 3.85</td>
<td>72.56 ± 7.02</td>
<td>89.35 ± 5.61</td>
<td>83.62 ± 4.18</td>
</tr>
<tr>
<td>Observation group</td>
<td>59</td>
<td>105.26 ± 28.35</td>
<td>45.36 ± 10.17</td>
<td>88.58 ± 4.69</td>
<td>94.47 ± 4.02</td>
<td>82.65 ± 5.24</td>
</tr>
<tr>
<td>t</td>
<td>16.171</td>
<td>0.000</td>
<td></td>
<td></td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.000</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Table 3 Comparison of cell factors between two groups (mean ± SD)

<table>
<thead>
<tr>
<th>Groups</th>
<th>Cases</th>
<th>TNF-α (µg/L)</th>
<th>IL-6 (ng/L)</th>
<th>IL-10 (ng/L)</th>
<th>SP (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Before surgery</td>
<td>14 d after surgery</td>
<td>Before surgery</td>
<td>14 d after surgery</td>
</tr>
<tr>
<td>Control group</td>
<td>59</td>
<td>65.38 ± 8.52</td>
<td>46.32 ± 4.11</td>
<td>57.25 ± 7.14</td>
<td>20.03 ± 4.36</td>
</tr>
<tr>
<td>Observation group</td>
<td>59</td>
<td>64.96 ± 7.86</td>
<td>40.25 ± 3.71</td>
<td>58.02 ± 7.63</td>
<td>14.88 ± 3.14</td>
</tr>
<tr>
<td>t</td>
<td>0.278</td>
<td>8.421</td>
<td>0.566</td>
<td>7.362</td>
<td>0.262</td>
</tr>
<tr>
<td>P value</td>
<td>0.781</td>
<td>0.000</td>
<td>0.572</td>
<td>0.000</td>
<td>0.793</td>
</tr>
</tbody>
</table>

*P < 0.05, compared between groups before surgery. TNF-α: Tumor necrosis factor-α; IL: Interleukin; SP: Serum P substances.

Table 4 Comparison of National Hospital Stroke Scale score and Barthel index between two groups (mean ± SD point)

<table>
<thead>
<tr>
<th>Groups</th>
<th>Cases</th>
<th>NIHSS score</th>
<th>Before surgery</th>
<th>14 d after surgery</th>
<th>Barthel index</th>
<th>Before surgery</th>
<th>14 d after surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>59</td>
<td>19.25 ± 4.77</td>
<td>8.12 ± 2.03</td>
<td>15.36 ± 4.74</td>
<td>54.15 ± 5.33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observation group</td>
<td>59</td>
<td>18.98 ± 5.02</td>
<td>6.98 ± 1.24</td>
<td>15.42 ± 5.02</td>
<td>66.05 ± 6.17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>t</td>
<td>0.299</td>
<td>3.681</td>
<td>0.067</td>
<td>11.211</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>0.765</td>
<td>0.000</td>
<td>0.947</td>
<td>0.000</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*P < 0.05, compared between groups before surgery. NIHSS: National Hospital Stroke Scale.

Table 5 Comparison of incidence of complications in hospital between two groups, n (%)

<table>
<thead>
<tr>
<th>Groups</th>
<th>Cases</th>
<th>Intracranial infection</th>
<th>Pulmonary infection</th>
<th>Recurrent postoperative hemorrhage</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>59</td>
<td>3 (5.08)</td>
<td>2 (3.39)</td>
<td>2 (3.39)</td>
<td>7 (11.86)</td>
</tr>
<tr>
<td>Observation group</td>
<td>59</td>
<td>1 (1.69)</td>
<td>1 (1.69)</td>
<td>1 (1.69)</td>
<td>3 (5.08)</td>
</tr>
<tr>
<td>χ²</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.748</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.186</td>
</tr>
</tbody>
</table>

with poor cardiopulmonary function or in those who cannot tolerate general anesthesia[10].

After treatment, the observation group increased significantly compared with the control group, whereas TNF-α, IL-6, IL-10 decreased significantly in the observation group. Thus, neuroendoscopic minimally invasive surgery for the treatment of hypertensive cerebral hemorrhage can significantly reduce the degree of inflammation in patients. On between group comparison, on postoperative day 14, the quality of life of patients improved significantly after neuroendoscopic minimally invasive surgery and the patients recovered. The effect of neurological deficit is more obvious. The
prognosis is better. Secondary brain damage caused by hematoma can cause serious damage to patients.

On the one hand, thrombin in the hematoma can cause inflammation in the body, affecting endothelial cells, neurons and glial cells and resulting in damage to the blood-brain barrier\[^{11}\]; on the other hand, white blood cells and microglia in the body are activated after cerebral hemorrhage, producing a large number of inflammatory factors, and further destroying the blood-brain barrier; thus, there is a vicious cycle created, further aggravating brain tissue damage\[^{12}\]. The endoscopic surgery produces less trauma, and the operation with the cannula does not damage the brain tissue, and the bleeding is arrested under electrocoagulation resulting in hemostasis in the hematoma cavity\[^{13}\]. Reducing the occurrence of postoperative bleeding and early and rapid removal of the hematoma is beneficial to patients in order for them to begin rehabilitation.

During the treatment, we summarized the following experiences: First, the incision should be mainly arc-shaped, and designed outside the bone window. At the same time, it is necessary to restore the bone flap to avoid a high tension of the incision and poor healing. Second, the outer sleeve should be inserted as much as possible once. Once the bottom of the hematoma cavity is reached, close attention should be paid to the removal of the hematoma. Third, due to the large number of accessories required for neuroendoscopy devices, strict attention should be paid to the implementation of aseptic procedures to reduce the chance of intracranial infection\[^{14}\]. The disadvantage of endoscopic surgery is that the operating space is small, and the technical requirements are high, especially when active bleeding occurs. Lens contamination caused by the active bleeding can cause the doctor’s vision to be blurred. Hemostasis is relatively difficult, suggesting that preoperative evaluation should be done, and craniotomy planning should be performed, if necessary\[^{15}\].

This study analyzed the advantages and disadvantages of the two surgical methods used in the surgical management of hypertensive intracerebral hemorrhage and selected an appropriate surgical treatment, for clinical reasons. The treatment plan provides a certain basis, but the number of patients enrolled in this study was small, and some of the included evaluation indicators have certain main factors. View ability may lead to bias in the results, and it is necessary to expand the sample size and formulate more reliable evaluation indicators for further demonstration\[^{16-20}\].

### CONCLUSION

In conclusion, neuroendoscopic minimally invasive surgery is more complicated than hard-channel minimally invasive puncture drainage in the treatment of hypertensive intracerebral hemorrhage, but has a more thorough hematoma clearance rate and a better short-term effect and long-term prognosis.

### ARTICLE HIGHLIGHTS

**Research background**

Surgical treatment is a common method for hypertensive cerebral hemorrhage. The traditional craniotomy has a large skull window and good effect on removing edema, which is helpful for patients to pass through the peak period of brain edema. However, patients with this operation should be carried out under general anesthesia, and the wound caused by this operation is large. Therefore, most patients need blood transfusion. Some patients may have stronger edema reaction after surgical treatment, which is not conducive to postoperative recovery of patients.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Cases</th>
<th>Class V</th>
<th>Class IV</th>
<th>Class III</th>
<th>Class II</th>
<th>Good prognosis rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>59</td>
<td>9 (15.25)</td>
<td>33 (55.93)</td>
<td>12 (20.34)</td>
<td>5 (8.47)</td>
<td>42 (71.19)</td>
</tr>
<tr>
<td>Observation group</td>
<td>59</td>
<td>16 (27.12)</td>
<td>35 (59.32)</td>
<td>6 (10.17)</td>
<td>2 (3.39)</td>
<td>51 (86.44)</td>
</tr>
</tbody>
</table>
Research motivation
Explore the application value of neuroendoscopic minimally invasive surgery in the treatment of hypertensive intracerebral hemorrhage.

Research objectives
The advantages and disadvantages of hard channel minimally invasive puncture drainage and neuroendoscopic minimally invasive surgery in hypertensive intracerebral hemorrhage were analyzed, which provided a basis for clinical rational selection of surgical treatment.

Research methods
A total of 118 patients with hypertensive cerebral hemorrhage were reviewed. The control group was treated with hard-channel minimally invasive puncture and drainage, and the observation group was treated with endoscopic minimally invasive surgery. The changes of serum P substances, inflammatory factors, National Hospital Stroke Scale (NIHSS) score and Barthel index were recorded, and the surgical related indexes and prognosis of the two groups were compared.

Research results
The operation time and intraoperative blood loss in the observation group were longer than those in the control group, with no advantages. Hematoma clearance rate and good prognosis rate at 48 h and 72 h after operation were higher than those in control group (P < 0.05); Complication rates in both groups not statistically significant (P > 0.05) The inflammatory cytokines, NIHSS score and Barthel index in the postoperative 14 d, observation groups were better than in the control group (P < 0.05).

Research conclusions
Neuroendoscopic minimally invasive surgery for hypertensive intracerebral hemorrhage is relatively complex, but hematoma removal is more complete and the effect is better.

Research perspectives
Minimally invasive neuroendoscopic surgery can be more widely used in the treatment of hypertensive cerebral hemorrhage.

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Retrospective Study

Ultrasonic assessment of cardiac function and disease severity in coronary heart disease

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Author contributions: Zhang JF and Du YH designed the experiment; Hu HY drafted the work, Han XQ collected the data; Zhang JF analyzed and interpreted the data; Zhang JF and Du YH wrote the article.

Institutional review board statement: This study was approved by the Second Affiliated Hospital of Xi'an Medical College Ethics Committee.

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

Conflict-of-interest statement: The authors declare that there is no conflict of interest between them.

Data sharing statement: No additional data are available.

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Abstract

BACKGROUND
Coronary heart disease (CHD) causes many adverse cardiovascular events and poses a threat to the patient’s health and quality of life.

AIM
To evaluate ultrasonography for evaluation of cardiac function and lesion degree in patients with CHD.

METHODS
A total of 106 patients with CHD (study group) and 106 healthy individuals (control group) in our hospital from March 2019 to September 2020 were selected for this study. All subjects were examined by ultrasound, and the mitral orifice’s early-to-late diastolic blood flow velocity ratio (E/A), left ventricular end-diastolic volume (LVDd), and left atrial diameter (LAD) were measured. Values were compared between the study group and healthy group, and the correlation between the ultrasonic parameters of patients with different cardiac function grades and the degree of CHD were assessed. In addition, the ultrasonic parameters of patients with different prognoses were compared after a follow-up for 6 mo.

RESULTS
E/A (1.46 ± 0.34) of the study group was smaller than that of the control group (1.88 ± 0.44), while LVDd (58.24 ± 5.05 mm) and LAD (43.31 ± 4.38 mm) were larger than those in the control group (48.15 ± 3.93 and 34.94 ± 2.81, respectively; P < 0.05). E/A for patients with grade III disease (1.41 ± 0.43) was smaller and their LVDd (60.04 ± 4.21 mm) and LAD (44.16 ± 2.79 mm) were larger than those in patients with grade II disease (1.71 ± 0.44) and grade I disease (1.98 ± 0.44), respectively; P < 0.05.

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± 0.48, 52.18 ± 3.67 mm, and 39.68 ± 2.37, respectively; \( P < 0.05 \)). Patients with grade IV disease had smaller E/A (1.08 ± 0.39) and larger LVDD (66.81 ± 5.39 mm) and LAD (48.81 ± 3.95 mm) than patients with grade II and III disease (\( P < 0.05 \)). In patients with moderate disease, E/A (1.14 ± 0.41) was smaller and LVDD (59.95 ± 4.14 mm) and LAD (45.15 ± 2.97 mm) were larger than in patients with mild disease (1.69 ± 0.50, 51.97 ± 3.88 and 38.81 ± 2.56 mm, respectively; \( P < 0.05 \)). In patients with severe disease, E/A (1.13 ± 0.36) was smaller and LVDD (67.70 ± 6.11 mm) and LAD (49.09 ± 4.05 mm) were larger than in patients with moderate disease (\( P < 0.05 \)). E/A was negatively correlated with cardiac function classification and disease severity, while LVDD and LAD were positively correlated with cardiac function classification and disease severity (\( P < 0.05 \)). E/A (1.83 ± 0.51) for patients with good prognosis was higher than that for those with poor prognosis (1.39 ± 0.32), while LVDD (49.60 ± 4.39 mm) and LAD (36.13 ± 3.05 mm) were lower (\( P < 0.05 \)).

CONCLUSION

The ultrasonic parameters of patients with CHD are abnormal, and differ significantly in patients with different cardiac function grades, lesion degree, and prognosis.

Key Words: Ultrasoundography; Left ventricular end-diastolic volume; Left atrial diameter; Coronary heart disease; Cardiac function

INTRODUCTION

Coronary heart disease (CHD), a clinical multiple cardiovascular disease mainly caused by coronary artery atherosclerosis[1], leads to vascular lumen obstruction or stenosis and, eventually, to myocardial hypoxia and ischemia. CHD causes many adverse cardiovascular events and, without timely intervention, poses a threat to the patient’s health and quality of life [2-4]. The incidence of CHD has recently increased, creating an urgent social and public health problem.

Early diagnosis and evaluation of CHD are important to guide clinical treatment and help improve prognosis of patients[5,6]. Ultrasound has been widely used in the diagnosis and treatment of cardiovascular diseases and has the advantage of being a simple, low-cost, noninvasive procedure. With the continuous development and improvement of ultrasonic diagnosis and treatment technology, it is readily tolerated by the majority of patients, and its use is increasing[7,8].

Therefore, this study sought to explore the usefulness of ultrasound in the evaluation of cardiac function and lesion degree in patients with CHD.

MATERIALS AND METHODS

Selection criteria

Inclusion criteria: Patients diagnosed with CHD after admission to our hospital from
March 2019 to September 2020 were enrolled. Patients were included if they met the diagnostic criteria for CHD according to the Chinese experts’ consensus on the diagnosis and treatment of CHD in elderly patients, if their cardiac function was classified as grade II–IV, and if they were compliant with the investigation and research instructions. Healthy individuals from the same period were selected as the control group. This study was approved by the Ethics Committee of our hospital. All patients provided signed informed consent.

**Exclusion criteria**: Patients with valvular disease, myocarditis, or cardiomyopathy; acute or previous myocardial infarction; persistent ventricular tachycardia or frequent premature heartbeats; secondary changes of the ST-T segment; prior treatment with spironolactone, diuretics, or valsartan; abnormal mental behavior, hearing loss, retinopathy, or unconsciousness; or a history of drug dependence or alcoholism.

**Methods**
All subjects were examined by ultrasound within 12 h of admission using the iE33 color Doppler ultrasound machine (Phillips) with a S5-1 probe and a probe frequency of 3–4 MHz. Dynamic echocardiography of the left ventricle was performed for five consecutive cardiac cycles on patients in the left recumbent position. Images of the aortic valve orifice, left ventricular outflow tract, and mitral orifice blood flow vein were collected, and measurements of the mitral orifice’s early-to-late diastolic blood flow velocity ratio (E/A), left ventricular end-diastolic volume (LVDd), and left atrial diameter (LAD) were recorded. Targeted treatment was provided according to the conditions of the patients with CHD.

**Observation index**
The ultrasonic parameters (E/A, LVDd and LAD) of the study and control groups were examined. In addition, patients from the study group were categorized by cardiac function and lesion degree, and the correlation between ultrasonic parameters and cardiac function and lesion degree was analyzed. The study group was followed up for 6 mo. The ultrasonic parameters were divided into the poor prognosis or good prognosis group based on whether the patients experienced adverse events. The correlation between the ultrasonic parameters and the patients’ prognoses was assessed.

**Statistical analysis**
The data were analyzed using SPSS version 22.0. The data are expressed as mean ± SD, and t tests were used for analysis. Numerical data are expressed as n (%), and the \( \chi^2 \) test was used. The correlation between ultrasonic parameters and the cardiac function grade and lesion degree was analyzed using the Spearman correlation. \( P < 0.05 \) indicated statistical significance.

**RESULTS**

**General data**
A total of 106 patients with CHD in our hospital from March 2019 to September 2020 were selected for the study group, and 106 healthy subjects from the same period were selected for the control group. The study group had 65 men and 41 women, aged 46–79 years (average: 62.41 ± 13.05 years). According to the New York Heart Association Functional Classification of cardiac function, there were 45, 37 and 24 cases of grade II, III and IV, respectively. According to the Gensini score, there were 43, 38 and 25 cases of mild (Gensini < 20), moderate (20 ≤ Gensini < 40), and severe (Gensini ≥ 40) CHD. The control group had 61 men and 45 women, aged 43–78 years (average: 64.19 ± 11.98 years). The sex, age and clinical data of the two groups were comparable (\( P > 0.05 \)) (Table 1).

**Comparison of ultrasonic parameters**
E/A in the study group (1.46 ± 0.34) was lower than that in the control group (1.88 ± 0.44). LVDd and LAD were significantly higher in the study group than in the control group (58.24 ± 5.05 and 43.31 ± 4.38 mm vs 48.15 ± 3.93 and 34.94 ± 2.81 mm, respectively; \( P < 0.05 \)) (Table 2).
### Table 1 Comparison of ultrasonic parameters between two groups (mean ± SD)

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>E/A</th>
<th>LVDd (mm)</th>
<th>LAD (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research group</td>
<td>106</td>
<td>1.46 ± 0.34</td>
<td>58.24 ± 5.05</td>
<td>43.31 ± 4.38</td>
</tr>
<tr>
<td>Control group</td>
<td>106</td>
<td>1.88 ± 0.44</td>
<td>48.15 ± 3.93</td>
<td>34.94 ± 2.81</td>
</tr>
<tr>
<td>t</td>
<td>7.776</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

E/A: Early-to-late diastolic flow velocity ratio; LVDd: Left ventricular end-diastolic volume; LAD: Left atrial diameter.

### Table 2 Comparison of ultrasonic parameters in patients with coronary heart disease with different cardiac function grades (mean ± SD)

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>E/A</th>
<th>LVDd (mm)</th>
<th>LAD (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade II</td>
<td>45</td>
<td>1.71 ± 0.48</td>
<td>52.18 ± 3.67</td>
<td>39.68 ± 2.37</td>
</tr>
<tr>
<td>Grade III</td>
<td>37</td>
<td>1.41 ± 0.43</td>
<td>60.04 ± 4.21</td>
<td>44.16 ± 2.79</td>
</tr>
<tr>
<td>Grade IV</td>
<td>24</td>
<td>1.08 ± 0.39</td>
<td>66.81 ± 5.39</td>
<td>48.81 ± 3.95</td>
</tr>
<tr>
<td>t/P value (Grade II vs III)</td>
<td>2.950/0.004</td>
<td>8.995/0.000</td>
<td>7.863/0.000</td>
<td></td>
</tr>
<tr>
<td>t/P value (Grade III vs IV)</td>
<td>3.035/0.004</td>
<td>5.490/0.000</td>
<td>5.391/0.000</td>
<td></td>
</tr>
</tbody>
</table>

E/A: Early-to-late diastolic blood flow velocity ratio; LVDd: Left ventricular end-diastolic volume; LAD: Left atrial diameter.

### Comparison of ultrasonic parameters in patients with different cardiac function grades

In patients with grade III cardiac function, E/A (1.41 ± 0.43) was smaller and the LVDd (60.04 ± 4.21 mm) and LAD (44.16 ± 2.79 mm) were greater than those of patients with grade II cardiac function (1.71 ± 0.48, 52.18 ± 3.67 mm, and 39.68 ± 2.37 mm, respectively; P < 0.05). The E/A of patients with grade IV cardiac function (1.08 ± 0.39) was lower than that of patients with grade III cardiac function (1.41 ± 0.43). The LVDd (66.81 ± 5.3mm) and LAD (48.81 ± 3.95mm) of patients with grade IV cardiac function was greater than those of patients with grade III cardiac function (60.04 ± 4.21mm and 44.16 ± 2.79 mm, respectively; P < 0.05) (Table 3).

### Comparison of ultrasonic parameters in patients with different severity of CHD

E/A of patients with moderate CHD (1.44 ± 0.41) was lower than that of patients with mild CHD (1.69 ± 0.50). Patients with moderate CHD had higher LVDd (59.95 ± 4.14 mm) and D (49.09 ± 4.05 mm) were greater in patients with severe CHD than in those with moderate CHD (59.95 ± 4.14 mm and 45.15 ± 2.97 mm, respectively; P < 0.05) (Table 4).

### Correlation between ultrasonic parameters and cardiac function grade and lesion degree of CHD

LVDd and LAD were positively correlated with grade of cardiac function and lesion degree (P < 0.05). There was a negative correlation between E/A and the grade of cardiac function and lesion degree (P < 0.05) (Table 4).

### Comparison of ultrasonic parameters in patients with different prognoses

Of the 106 patients in the study group, 11 experienced adverse cardiovascular events during follow-up and were categorized into the poor prognosis group, while the other 95 patients were categorized into the good prognosis group. E/A values for the good prognosis group (1.83 ± 0.51) were higher than those for the poor prognosis group (1.39 ± 0.32). LVDd (49.60 ± 4.39 mm) and LAD (36.13 ± 3.05 mm) were lower in the good prognosis group compared to those in the poor prognosis group (59.09 ± 5.67 mm and 45.10 ± 5.60 mm, respectively; P < 0.05) (Table 5).
Zhang JF et al. Ultrasonography in patients with CHD

Table 3 Comparison of ultrasonic parameters in patients with different degrees of coronary heart disease (mean ± SD)

<table>
<thead>
<tr>
<th>Group</th>
<th>Number</th>
<th>E/A</th>
<th>LVDd (mm)</th>
<th>LAD (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>43</td>
<td>1.69 ± 0.50</td>
<td>51.97 ± 3.88</td>
<td>38.81 ± 2.56</td>
</tr>
<tr>
<td>Moderate</td>
<td>38</td>
<td>1.44 ± 0.41</td>
<td>59.95 ± 4.14</td>
<td>45.15 ± 2.97</td>
</tr>
<tr>
<td>Severe</td>
<td>25</td>
<td>1.13 ± 0.36</td>
<td>67.70 ± 6.11</td>
<td>49.09 ± 4.05</td>
</tr>
</tbody>
</table>

$t$/P value (Grade II vs III): 2.441/0.017
$t$/P value (Grade III vs IV): 8.952/0.000

E/A: Early-to-late diastolic blood flow velocity ratio; LVDd: Left ventricular end-diastolic volume; LAD: Left atrial diameter.

Table 4 Correlation between ultrasonic parameters and cardiac function grade and lesion degree of coronary heart disease (n = 106)

<table>
<thead>
<tr>
<th>Project</th>
<th>E/A</th>
<th>LVDd</th>
<th>LA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac function classification</td>
<td>0.606</td>
<td>0.589</td>
<td>0.577</td>
</tr>
<tr>
<td>Degree of lesion</td>
<td>r</td>
<td>P value</td>
<td>P value</td>
</tr>
<tr>
<td></td>
<td>0.631</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>&lt; 0.001</td>
<td></td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

E/A: Early-to-late diastolic blood flow velocity ratio; LVDd: Left ventricular end-diastolic volume; LA: Left atrial diameter.

Table 5 Comparison of ultrasonic parameters in patients with coronary heart disease with different prognosis (mean ± SD)

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>E/A</th>
<th>LVDd (mm)</th>
<th>LAD (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good prognosis</td>
<td>95</td>
<td>1.83 ± 0.51</td>
<td>49.60 ± 4.39</td>
<td>36.13 ± 3.05</td>
</tr>
<tr>
<td>Poor prognosis</td>
<td>11</td>
<td>1.39 ± 0.32</td>
<td>59.09 ± 5.67</td>
<td>45.10 ± 5.60</td>
</tr>
<tr>
<td>$t$</td>
<td></td>
<td>2.791</td>
<td>6.579</td>
<td>8.333</td>
</tr>
<tr>
<td>$P$ value</td>
<td></td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

E/A: Early-to-late diastolic blood flow velocity ratio; LVDd: Left ventricular end-diastolic volume; LAD: Left atrial diameter.

DISCUSSION

CHD has a chronic progression. Most patients in the early stage of the disease have no obvious symptoms. However, when symptoms appear, most patients are diagnosed with serious coronary artery disease because of the strong compensatory function of the myocardium, leading to an adverse impact on prognosis[9,10]. Coronary angiography is the gold standard for clinical diagnosis of CHD because it can comprehensively and stereoscopically show entire vascular lesions, providing an imaging basis for disease diagnosis[11-13]. Since it is an invasive examination with a high cost and long procedural time, there are some limitations to its clinical application[14-17].

In the clinical diagnosis of CHD, ultrasound can quickly determine the velocity, direction and distribution of myocardial motion through the Doppler effect; accurately detect abnormal myocardial activity; and intuitively show the global and regional myocardial systolic function of the left ventricle. For these reasons, it provides an objective basis for the clinical evaluation of myocardial function and disease diagnosis [18]. Studies have confirmed that two-dimensional color Doppler ultrasound has a high diagnostic value for CHD and is a low-cost, simple, accurate and noninvasive method to evaluate cardiac function. Furthermore, studies have shown that carotid ultrasound can effectively identify the differences in intima media thickness of the carotid bifurcation, common carotid artery, and internal carotid artery between...
patients with CHD and healthy individuals, thereby allowing a differential diagnosis of CHD. Their results showed lower LVDd and LAD in the study group than in the control group, with significant differences in the E/A, LVDd and LAD between patients with CHD with different cardiac function grades and disease severity. There was a close correlation between ultrasonic parameters and heart disease severity, indicating that abnormalities in echocardiographic parameters were related to cardiac function in patients with CHD, and the severity of the lesions was aggravated as the cardiac function grade increased. The increase or decrease in E/A, LVDd and LAD was more significant, indicating that echocardiography can effectively identify the abnormal cardiac function of patients with CHD and evaluate the cardiac function and the degree of pathological changes, so as to guide the clinician to take targeted prevention and control measures that will ensure a successful intervention, rehabilitation of cardiac function, and good prognosis. The pathological basis of CHD is coronary atherosclerosis and plaque formation. A more serious lesion corresponds to a narrower coronary artery. Concurrently, coronary atherosclerosis and plaque formation cause coronary artery trunk and branch stenosis and blockage, which adversely affect myocardial oxygen and blood supply, cause myocardial tissue damage, and affect cardiac function. Consequently, changes in cardiac function are visible upon ultrasonic examination\[19,20\]. Some studies have shown that E/A is significantly decreased and LVDd and LAD are significantly increased in patients with CHD. There was a significant difference in E/A, LVDd and LAD between patients with different grades of CHD, with a negative correlation between E/A and disease severity and a positive correlation between LVDd or LAD and disease severity. The reason is that increases in LVDd and LAD are closely related to decreases in the left ventricular ejection fraction, left atrial volume emptying, and abnormal left atrial function. An abnormal decrease in E/A is closely related to mechanical dysfunction of the left atrium, an increase in left atrial volume load, a decrease in left ventricular filling, and abnormalities in left atrial diastolic function.

Based on the above findings, patients with CHD were treated with the corresponding treatment and followed up for 6 mo, during which they were divided into groups according to prognosis. The results showed higher E/A and lower LVDd and LAD values in the good prognosis group compared to those in the poor prognosis group. These findings suggest that ultrasonography is useful for evaluating the prognosis of patients with CHD. This may be due to the significant inhibition of ventricular remodeling, decrease in myocardial fibrosis and necrosis, increase in cardiomyocytes, and recovery of cardiac function in patients with CHD after effective treatment, resulting in improvement of the relevant parameters of ultrasonic examination. Consequently, patients with CHD can receive regular ultrasound examinations after treatment to clarify their cardiac function and guide the clinician to formulate further intervention programs to ensure a good prognosis.

CONCLUSION

Generally, the ultrasonic parameters of patients with CHD are abnormal. Patients with different cardiac function grades, lesion degree, and prognoses have significantly different parameters, as there is a close relationship between these parameters and CHD. Consequently, ultrasound can be used to evaluate the status and prognosis of heart disease and provide an objective reference for diagnosis and treatment.

ARTICLE HIGHLIGHTS

Research background
Coronary heart disease (CHD) is a clinical multiple cardiovascular disease that is mainly caused by coronary artery atherosclerosis. The incidence of CHD has recently increased, creating an urgent social and public health problem.

Research motivation
To provide a basis for the evaluation of cardiac function and disease severity in patients with CHD.
**Research objectives**

To evaluate the value of ultrasonography in the evaluation of cardiac function and lesion degree in patients with CHD.

**Research methods**

A total of 106 patients with CHD and 106 healthy individuals were selected for this study. All subjects were examined by ultrasound, and the mitral orifice’s early-to-late diastolic blood flow velocity ratio (E/A), left ventricular end-diastolic volume (LVDd) and left atrial diameter (LAD) were measured. Values were compared between the study group and healthy group, and the correlation between the ultrasonic parameters of patients with different cardiac function grades and the degree of CHD were assessed.

**Research results**

E/A of the study group was smaller than that of the control group (1.88±0.44), while LVDd and LAD were larger. E/A for patients with grade III disease was smaller and LVDd and LAD were larger than those in patients with grade II disease. Patients with grade IV disease had smaller E/A and larger LVDd than patients with grade II and III disease. E/A was negatively correlated with cardiac function classification and disease severity, while LVDd and LAD were positively correlated with cardiac function classification and disease severity.

**Research conclusions**

The ultrasonic parameters of patients with CHD are significantly different in patients with different cardiac function grade, lesion degree and prognosis. They can be used to evaluate the disease’s condition and prognosis, providing an objective reference for disease diagnosis and treatment.

**Research perspectives**

There is a close relationship between CHD and ultrasound parameters, which has a wider clinical application value.

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Retrospective Study

COVID-19 among African Americans and Hispanics: Does gastrointestinal symptoms impact the outcome?


Abstract

BACKGROUND

The coronavirus disease 2019 (COVID-19) disproportionately affected African Americans (AA) and Hispanics (HSP).
AIM
To analyze the significant effectors of outcome in African American patient population and make special emphasis on gastrointestinal (GI) symptoms, laboratory values and comorbidities

METHODS
We retrospectively evaluated the medical records of 386 COVID-19 positive patients admitted at Howard University Hospital between March and May 2020. We assessed the symptoms, including the GI manifestations, comorbidities, and mortality, using logistic regression analysis.

RESULTS
Of these 386 COVID-19 positive patients, 257 (63.7%) were AAs, 102 (25.3%) HSP, and 26 (6.45%) Whites. There were 257 (63.7%) AA, 102 (25.3%) HSP, 26 (6.45%) Whites. The mean age was 55.6 years (SD = 18.5). However, the mean age of HSP was the lowest (43.7 years vs 61.2 for Whites vs 60 for AAs). The mortality rate was highest among the AAs (20.6%) and lowest among HSP (6.9%). Patients with shortness of breath (SOB) (OR2 = 3.64, CI = 1.73-7.65) and elevated AST (OR2 = 8.01, CI = 3.79-16.9) had a high mortality rate. Cough and fever were common but unrelated to the outcome. Hypertension and diabetes mellitus were the most common comorbidities. Glucocorticoid treatment was associated with higher mortality (OR2 = 5.40, CI = 2.72-10.7). Diarrhea was prevalent (18.8%), and GI symptoms did not affect the outcome.

CONCLUSION
African Americans in our study had the highest mortality as they consisted of an older population and comorbidities. Age is the most important factor along with SOB in determining the mortality rate. Overall, elevated liver enzymes, ferritin, procalcitonin and C-reactive protein were associated with poor prognosis. GI symptoms did not affect the outcome. Glucocorticoids should be used judiciously, considering the poor outcomes associated with it. Attention should also be paid to monitor liver function during COVID-19, especially in AA and HSP patients with higher disease severity.

Key Words: COVID-19; Pandemic, Gastrointestinal manifestation; Liver; African Americans; Hispanics

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Core Tip: The Coronavirus disease 2019 (COVID-19) disproportionately affected African Americans and Hispanics. Understanding the transmission dynamics, a different array of symptoms and the impact of the presence of other chronic diseases in minority patients can provide important hints about the progression of the pandemic and treatment options, especially in areas where access to equal health services is limited, unequal and challenging for underserved populations is broad. This study presents the findings of a comprehensive analysis of COVID-19 patients in a Washington DC tertiary hospital that caters primarily to minority populations. The main objective of this study was to define major effectors of outcome in this patient population. We sought to determine clinical and gastrointestinal (GI) factors associated with differences in outcomes. Special emphasis was made on GI symptoms, laboratory values and comorbidities.

INTRODUCTION

A new cluster of pneumonia cases in China surfaced in December of 2019. On January 7, 2020, the agent causing this pneumonia was identified and named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) for SARS-CoV-2 instead of SARS-CoV-1 that prevailed in 2003[1]. The disease caused by this new virus, coronavirus disease (COVID-19), was recognized by the World Health Organization as a pandemic on March 11, 2020. Since its appearance, the virus has infected more than 70 million people and caused more than 1.5 million deaths worldwide, as of December 20, 2020 [2]. The pandemic has affected over 150 countries and significantly impacted all racial and socioeconomic segments of the population. COVID-19 affected more than 22 million people within the United States and caused the death of more than 373 thousand deaths as of January 10, 2021, by far one of the most affected areas in the world. The most affected states are California, Texas, Florida, Georgia, and New York [3].

The United States has a population of 328239523 and is one of the most diverse countries in the world, with 13.4% African Americans (AA) and 18.5% Hispanics (HISP). Health disparity is a significant issue in the United States, reflecting differences in access to healthcare, education, lifestyle, and socioeconomic status [4]. This minority population has been disproportionately affected by the pandemic [5]. For example, in Chicago, IL [6], the rates of COVID-19 positive cases as of September 21 are more excellent among Latinos and African Americans [30232 (47.8% of the total cases) cases and 13273 (27.3% of the total cases) cases respectively] in comparison to Whites [11092 cases (17.5% of the total cases)]. The same applies to mortality rates, with deaths from Latinos and African Americans are 33.1% and 42.7%, respectively, while Whites represent just 19.1% of the total deaths. This same scenario was reproduced in many other states, with reported cases and deaths in minorities much higher than their percentage within the general population.

The most common explanation for such disproportionate impact of COVID-19 in these minority populations might be the higher prevalence of chronic conditions or comorbidities when compared to Whites (European Americans) [7]. These populations are probably also living in conditions that promote breeding and incubation for infection and transmission of the virus. Apart from the clinical and environmental causes, there may be genetic/biological factors that may also play a role in predisposing them to more severe disease and more unsatisfactory outcomes. Understanding the transmission dynamics, a different array of symptoms and the impact of the presence of another chronic disease in minority patients can provide important hints about the progression of the pandemic and treatment options, especially in areas where access to equal health services is limited, unequal and challenging for underserved populations is broad [8,9].

This study presents the findings of a comprehensive analysis of COVID-19 patients in a Washington DC tertiary hospital that caters primarily to minority populations. The main objective of this study was to define significant outcome effectors in this patient population. Special emphasis was made on gastrointestinal (GI) symptoms, laboratory values and comorbidities.

MATERIALS AND METHODS

Patients’ selection

This retrospective study used data from 386 adult patients hospitalized for COVID-19 at Howard University Hospital. Demographic, clinical, and pathological features of these patients were collected. Using the medical record number for each patient, we searched all reports in the hospital system and analyzed all available charts and doctors’ notes to collect all relevant data for our study. Howard University Institutional Review Board approved this study. The main features, prognosis assessment and potential effectors relate to the outcome of patients were collected. This is a retrospective study covering patients from the first wave and for a period 6 mo (March
to August 2020) when protocols and management of patients were evolving with increasing clinical parameters being captured and ordered by treating physicians. Also, because our institution mainly caters to minorities, Caucasians were not well represented in our cohort.

**Collected data**

The following information was collected for all COVID-19 patients: Demographics (date of the report, age, gender, height, weight, body mass index), symptoms (fever, cough, shortness of breath, abdominal pain, anorexia, diarrhea, nausea, vomiting, fatigue), comorbidities (cardiac disease, diabetes mellitus, hypertension, immunocompromised status, alcohol consumption) and laboratory values: lymphocytes count (reference value: 0.9-3.2 × 10⁹), C-reactive protein (CRP, reference value: < 10 mg/dL), D-dimers (reference value: < 10 mg/dL), Ferritin (reference value: 20-400 ng/mL), Creatinine (reference value: 0.6-1.2 mg/dL), Alanine transaminase (ALT, reference value: 0-55 IU/L), Alkaline Phosphatase (ALP reference value: 0-50 IU/L), Aspartate Transaminase (AST, reference value: 0-50 IU/L), Albumin (reference value: 3.2-5.5 g/dL), Procalcitonin (reference value: < 0.50 ng/mL), treatment (Hydroxychloroquine, Glucocorticoid, Intubation and Mechanical ventilation) and outcome (alive or dead). For laboratory clinical values, reference lab values were used to determine normal from out-of-range values.

**Data synthesis and statistical analysis**

Patient demographics, symptoms, underlying comorbidities, treatment, and outcomes were compared among AA, EA, LAT, and other ethnic groups. Predictors of hospital mortality evaluated by using logistic and/or multiple logistic regression using four models to assess the effect of each risk factor with: (1) No adjustment (OR1); (2) Adjusted for gender, age, ethnicity, and center (OR2); (3) The previous (OR2) model, further adjusted for comorbidities (OR3); and (4) The previous (OR3) model, further adjusted for disease severity (OR4). Each OR and the associated 95% confidence interval for OR were calculated. The 95% confidence interval was investigated to see if it contains unity. Present of unity (i.e., OR=1) in any confidence interval means that the concerned risk factor is not statistically and significantly affects mortality. SPSS version 26 (SPSS Inc., Chicago, IL, United States) was used for this analysis.

**RESULTS**

**Adults over 50 years were predominantly affected by COVID-19, and age was considered as a significant effector of outcome**

Among the 386 patients, the mean age was 55.6 years. There were 257 AAs, 102 HSP (Latin Americans), and 26 Caucasians (CAU, European Americans), while 14 were other races. With respect to mortality, 20.6% (53 patients) AAs, 11.5% (3 patients) CAU and 6.9% (7 patients) HSP died (Table 1). The mean age for those who survived was 53.4 years old and 67.2 years old for the deceased. The mean age of the deceased among the AA was 68.4 years, HSP 51.1 years and CAU 84.6 years. Among deceased, the average length of hospital stay in days was highest in EA (25.5 d) followed by AA (11.1 d) and HSP (6.1 d). Using less than 35 years old as a reference, those within the groups of over 75 years old had 5.80 more risks to die in OR2 analysis (CI = 1.52-22.1), and those between 65 years old to 74 years old had 9.88 times more risk to die (OR2, CI = 2.62-37.17) (Table 2).

**Male mortality was higher despite equal infection rates in both genders**

Our cohort was homogeneously distributed for gender with 50.1% females and 49.9% males (Table 1). The male death rate was 19.1% (37 patients), while the females’ rate was 13.6% (26 patients, Table 2). For AA (140 males and 117 females), 21.4% of males and 19.7% of females died in the hospital. In contrast with Caucasians CAU (15 males and 11 females), none of the females died because of the infection and three males (20%) were deceased. For HSP (39 males and 63 females), 10.3% (4 patients) male patients and 4.8% (3 patients) females patients died (Table 1).

**Ethnicity did not influence in determining outcomes in our cohort**

The race was not associated with outcome. Using AA as a reference, overall CAU had less risk of dying (OR3 = 0.38, CI = 0.08-1.83) and HSP with 0.55 Less risk than comparing with AA (OR3, CI = 0.21-1.47) (Table 2). The African Americans in our
### Table 1 Overall baseline characteristics of the study population

<table>
<thead>
<tr>
<th>Indices</th>
<th>African Americans, n (%)</th>
<th>European- Americans, n (%)</th>
<th>Latin-Americans, n (%)</th>
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<td>Ashktorab H et al. COVID-19 and gastrointestinal symptoms among African Americans</td>
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<td>ALP (n = 317)</td>
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<td>Hydroxychloroquine (n = 371)</td>
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<td>Yes (n = 68)</td>
</tr>
<tr>
<td>Mechanical ventilation (n = 376)</td>
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</table>
study had the highest mortality as they consisted of an older population compared to the Hispanic and other ethnic groups. In other words, if controlling for age, sex, ethnicity, center and other potential confounding variables, age is the most crucial factor in determining the mortality rate.

**Body mass index was a minor effector of outcome**
In our cohort, 127 patients had a normal body mass index (BMI) (< 25), 111 were obese (BMI > 30), and 94 were overweight (25 < BMI < 30) (Tables 1 and 2). In the obese group, 19.8% died, followed by 19.1% in the overweight group and 15% in the normal BMI group. Among the AA patients, the death rate was high for normal weight (22.7%) compared to the obese (20.9%) and overweight (21.7%). There was no significant association between high BMI (overweight and/or obesity) and poor outcome (OR were not significant) for BMI.

**Fever and shortness of breath were more common in AA**
Shortness of breath, cough and fever were the most common symptoms in our cohort. Overall, 62% (237 patients) reported shortness of breath, followed by 59.7% (229 patients) cough, and 54.6% (209 patients) had a fever as their symptom (Table 1). There were race-based differences concerning the presentation of symptoms. Fever (58.2%) and shortness of breath (66.8%) were more commonly seen in AA when compared to CAU and HSP. Whereas cough was the most common presentation of the EA (76.9%) when compared to the AA (63.2%) and HSP (48.5%). While cough and fever were the most common symptoms, neither cough (OR 2 = 0.87 with a CI = 0.46-1.63) nor fever (OR2 = 1.07, CI = 0.58-1.96) were significant for poor outcome. However, shortness of breath was highly associated with mortality (OR2 = 3.64, CI = 1.73-7.65), even after adjusting for age, sex, and ethnicity (Table 2). In AAs, CAU and HSP, the above symptoms affected the outcome similarly as in the overall cohort.

**Diarrhea was the most prevalent GI symptom, and GI symptoms did not affect outcome**
Diarrhea (15.9%) was the most common GI symptom among the overall cohort, followed by nausea (13%), vomiting (11.3%), anorexia (26.4%), and abdominal pain (13.8%) (Table 1). This distribution of GI symptoms was the same within racial groups. Diarrhea was reported in 18.8%, 12%, and 9.8% in AAs, CAU and HSP, respectively.

**Hypertension and diabetes mellitus were the most prevalent chronic conditions**
Hypertension and diabetes mellitus was present in 51% and 37.4% of patients, respectively (Table 2). They were followed by cardiac disease in 19% of the cohort and immunocompromised status in 9.1%. All the ethnic groups have hypertension followed by diabetes mellitus as the most common pre-existing comorbidities. Only cardiac disease was significantly associated with poor outcomes in the crude calculation (OR = 1.86, 95%CI = 1.00-3.47). However, after we adjust for age, gender, race, this becomes not significant (OR = 0.96, 95%CI = 0.47-1.05) (Table 2).

**AST and ALT were the most altered in the liver test panel and are associated with poor outcomes**
AST was elevated in 147 patients (43.8%) (Table 2). ALT values were high in 98 patients (29.6%) and ALP in 60 patients (18.2%). The same trend was encountered in the race groups, with AST elevated in 45.3% and 40.2%, with an OR ratio of 7.90 (3.93-15.9) has the highest association with poor outcomes (Table 2). In OR2 analysis adjusted for age, gender, and ethnicity, elevated AST was associated with poor outcomes in a statistically significant manner. Elevated AST added 8 times more risk to the patients. Worth noting that AST is not specific to the liver. For the ALT enzyme, which is more liver-specific, the OR associating with death was 2.64 (1.36-5.01) after adjustment for age, race, and gender.

**Glucocorticoids treatment did not improve patients outcome**
Overall, 18% (68 patients) received glucocorticoids. Concerning outcome, 39% (27
<table>
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<tr>
<th>Age (n = 384), yr</th>
<th>Alive, n (%)</th>
<th>Dead, n (%)</th>
<th>OR1 (95%CI)</th>
<th>OR2 (95%CI)</th>
<th>OR3 (95%CI)</th>
<th>OR4 (95%CI)</th>
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<td>&lt; 35 (n = 66)</td>
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<td>48 (96)</td>
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<td>0.71 (0.094-5.50)</td>
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<td>1.85 (0.31-11.07)</td>
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<td>9.91 (2.09-46.81)</td>
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<td>35 (18.4)</td>
<td>1.30 (0.75-2.25)</td>
<td>0.79 (0.42-1.51)</td>
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<tr>
<td>Immune suppression (n = 369)</td>
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<td>No (n = 355)</td>
<td>282 (84.2)</td>
<td>53 (15.8)</td>
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<td>Yes (n = 34)</td>
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<td>9 (26.5)</td>
<td>1.91 (0.84-4.33)</td>
<td>2.19 (0.87-5.53)</td>
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<td>Presenting symptoms</td>
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<td>Fever (n = 383)</td>
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<td>No (n = 174)</td>
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<td>1.32 (0.76-2.29)</td>
<td>1.07 (0.58-1.96)</td>
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<tr>
<td>Cough (n = 380)</td>
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<tr>
<td>No (n = 151)</td>
<td>125 (82.8)</td>
<td>26 (17.2)</td>
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<td>Yes (n = 229)</td>
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<td>0.87 (0.46-1.63)</td>
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<td>Shortness of breath (n = 381)</td>
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<td>Yes (n = 237)</td>
<td>185 (78.1)</td>
<td>52 (21.9)</td>
<td>3.39 (1.70-6.75)</td>
<td>3.64 (1.73-7.65)</td>
<td>3.60 (1.71-7.56)</td>
<td>2.38 (1.07-4.09)</td>
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<td>Symptom</td>
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<td>Yes</td>
<td>Odds Ratio (95% CI)</td>
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<tr>
<td><strong>Fatigue</strong></td>
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<td>Yes (n = 93)</td>
<td>80 (86)</td>
<td>13 (14)</td>
<td>1.12 (0.52-2.42)</td>
<td>0.71 (0.30-1.67)</td>
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<tr>
<td><strong>Nausea</strong></td>
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<td>(n = 315)</td>
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<tr>
<td>Yes (n = 47)</td>
<td>42 (89.4)</td>
<td>5 (10.6)</td>
<td>0.61 (0.23-1.63)</td>
<td>0.86 (0.30-2.50)</td>
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<tr>
<td><strong>Vomiting</strong></td>
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<td>(n = 375)</td>
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<tr>
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<td>277 (83.4)</td>
<td>55 (16.6)</td>
<td>-</td>
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</tr>
<tr>
<td>Yes (n = 43)</td>
<td>39 (90.7)</td>
<td>4 (9.3)</td>
<td>0.51 (0.17-1.50)</td>
<td>0.631 (0.20-1.99)</td>
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<tr>
<td><strong>Abdominal pain</strong></td>
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</tr>
<tr>
<td>(n = 343)</td>
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<tr>
<td>No (n = 296)</td>
<td>248 (83.8)</td>
<td>48 (16.2)</td>
<td>-</td>
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<tr>
<td>Yes (n = 47)</td>
<td>44 (93.6)</td>
<td>3 (6.4)</td>
<td>0.35 (0.10-1.18)</td>
<td>0.50 (0.14-1.82)</td>
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<td><strong>Diarrhea</strong></td>
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<tr>
<td>No (n = 332)</td>
<td>277 (83.4)</td>
<td>55 (16.6)</td>
<td>-</td>
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<tr>
<td>Yes (n = 47)</td>
<td>39 (90.7)</td>
<td>4 (9.3)</td>
<td>0.51 (0.17-1.50)</td>
<td>0.631 (0.20-1.99)</td>
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<tr>
<td><strong>Abdominal pain</strong></td>
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</tr>
<tr>
<td>(n = 343)</td>
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<tr>
<td>No (n = 296)</td>
<td>248 (83.8)</td>
<td>48 (16.2)</td>
<td>-</td>
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<tr>
<td>Yes (n = 47)</td>
<td>44 (93.6)</td>
<td>3 (6.4)</td>
<td>0.35 (0.10-1.18)</td>
<td>0.50 (0.14-1.82)</td>
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<td><strong>Laboratory results</strong></td>
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<tr>
<td>(quartiles determined based on the entire study population; q1 always as reference)</td>
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<tr>
<td><strong>Lymphocyte count</strong> (n = 380)</td>
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<tr>
<td>Normal (n = 193)</td>
<td>177 (91.7)</td>
<td>16 (8.3)</td>
<td>-</td>
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<tr>
<td>Low (n = 163)</td>
<td>121 (74.2)</td>
<td>42 (25.8)</td>
<td>3.84 (2.06-7.14)</td>
<td>2.77 (1.41-5.45)</td>
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<tr>
<td>Elevated (n = 24)</td>
<td>19 (79.2)</td>
<td>5 (20.8)</td>
<td>2.91 (0.95-8.83)</td>
<td>3.27 (0.97-11.04)</td>
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<tr>
<td><strong>CRP</strong> (n = 295)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Normal (n = 99)</td>
<td>91 (919)</td>
<td>8 (8.1)</td>
<td>-</td>
<td></td>
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<tr>
<td>Elevated (n = 194)</td>
<td>149 (76.8)</td>
<td>45 (23.3)</td>
<td>3.43 (1.55-7.61)</td>
<td>3.19 (1.39-7.29)</td>
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<tr>
<td><strong>D-Dimer</strong> (n = 309)</td>
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</tr>
<tr>
<td>Normal (n = 39)</td>
<td>39 (100)</td>
<td>0 (0)</td>
<td>L. Reg. N/A: No death for normal D-dimer; Chi-square P = 0.001 highly significant</td>
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<tr>
<td>Elevated (n = 270)</td>
<td>212 (78.5)</td>
<td>58 (21.5)</td>
<td>-</td>
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<tr>
<td><strong>Procalcitonin</strong> (n = 276)</td>
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<td></td>
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</tr>
<tr>
<td>Normal (n = 163)</td>
<td>151 (92.6)</td>
<td>12 (7.4)</td>
<td>-</td>
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<tr>
<td>Elevated (n = 113)</td>
<td>67 (59.3)</td>
<td>46 (40.7)</td>
<td>8.63 (4.30-17.3)</td>
<td>8.27 (3.95-17.3)</td>
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<tr>
<td><strong>Ferritin</strong> (n = 273)</td>
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<tr>
<td>Normal (n = 98)</td>
<td>88 (89.8)</td>
<td>10 (10.2)</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated (n = 175)</td>
<td>131 (74.9)</td>
<td>44 (25.1)</td>
<td>2.95 (1.41-6.18)</td>
<td>2.69 (1.24-5.82)</td>
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<tr>
<td><strong>Hydroxychloroquine</strong> (n = 371)</td>
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<td></td>
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</tr>
<tr>
<td>No (n = 291)</td>
<td>249 (80.8)</td>
<td>42 (66.7)</td>
<td>-</td>
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<tr>
<td>Yes (n = 80)</td>
<td>59 (19.2)</td>
<td>21 (33.3)</td>
<td>2.11 (1.16, 3.83)</td>
<td>1.95 (0.98 - 3.79)</td>
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<tr>
<td><strong>ALP</strong> (n = 317)</td>
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<tr>
<td>Normal (n = 260)</td>
<td>221 (85)</td>
<td>39 (68.4)</td>
<td>-</td>
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<tr>
<td>Elevated (n = 57)</td>
<td>39 (15)</td>
<td>18 (31.6)</td>
<td>2.61 (1.36 - 5.03)</td>
<td>3.52 (1.65-7.51)</td>
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<tr>
<td><strong>AST</strong> (n = 332)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Normal (n = 185)</td>
<td>174 (94.1)</td>
<td>11 (5.9)</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Elevated \((n = 147)\) & 98 (66.7) & 49 (33.3) & 7.90 (3.93-15.9) & 8.01 (3.79-16.9) \\
ALT \((n = 329)\) & & & & \\
Normal \((n = 231)\) & 197 (85.3) & 34 (14.7) & - & - \\
Elevated \((n = 98)\) & 72 (73.5) & 26 (26.5) & 2.09 (1.17-3.73) & 2.64 (1.36-5.01) \\

**Interventions (no as reference)**

**Glucocorticoids \((n = 371)\)**

<table>
<thead>
<tr>
<th>Group ((n))</th>
<th>Deaths</th>
<th>Survivors</th>
<th>OR (1^\text{st})</th>
<th>OR (2^{nd})</th>
</tr>
</thead>
<tbody>
<tr>
<td>No ((n = 303))</td>
<td>267 (88.1)</td>
<td>36 (11.9)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Yes ((n = 68))</td>
<td>41 (60.3)</td>
<td>27 (39.7)</td>
<td>4.88 (2.68-8.87)</td>
<td>5.40 (2.72-10.7)</td>
</tr>
</tbody>
</table>

**Mechanical ventilation \((n = 376)\)**

<table>
<thead>
<tr>
<th>Group ((n))</th>
<th>Deaths</th>
<th>Survivors</th>
<th>OR (1^\text{st})</th>
<th>OR (2^{nd})</th>
</tr>
</thead>
<tbody>
<tr>
<td>No ((n = 320))</td>
<td>303 (94.7)</td>
<td>17 (5.3)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Yes ((n = 56))</td>
<td>17 (30.4)</td>
<td>39 (69.6)</td>
<td>40.8 (19.3-86.5)</td>
<td>35.2 (15.3-81.1)</td>
</tr>
</tbody>
</table>

OR1 = Crude, without any adjustment; OR2 = Adjusted for age, sex, ethnicity; OR3 = Multivariable, adjusted for age, sex, ethnicity, and other potential confounding variables (to be decided later). The final model suggest that Age, shortness of breath (SOB) and C-reactive protein (CRP) is significantly increase the risk of mortality. Baseline comorbidity, ethnicity and gender are not significant after controlling for SOB and CRP. BMI: Body mass index; CRP: C-reactive protein; ALP: Alkaline phosphatase; AST: Aspartate transaminase; ALT: Alanine transaminase.

patients) of those that received glucocorticoid died. Among AA, 20.2% received glucocorticoids, of these 45% of them died. Among CAU, 20% were on glucocorticoids (5 patients), and only one died. In HSP, 12.9% received glucocorticoids, and 3 of them died. In HSP, 12.9% received glucocorticoids, and 3 of them died. Among glucocorticoid-treated patients, there was an overall risk of 5.40 times more than those that did not receive them to die (OR2, CI = 2.72-10.7) (Table 2).

**Mechanical ventilation associated with poor outcome**

Overall, 14.9% (56 patients) received mechanical ventilation. The proportion of patients receiving mechanical ventilation was highest among the AA (18.7%) compared to CAU (8%) and HSP (7%) (Table 1). Patients on mechanical ventilation were 40 times more susceptible to poor outcomes. Even after controlling the analysis for age, sex and ethnicity, patients on mechanical ventilation were still 35 times (OR = 35.2, CI= 15.3-81.1) more prone to poor outcomes (Table 2).

**DISCUSSION**

The United States has one of the most diverse populations[10], exhibiting discrepancies in healthcare access, socioeconomic status, and wealth distribution, all of which lead to disparities in health outcomes across different groups, especially in minorities[11]. African Americans and Hispanics, who are known to carry a heavy burden of comorbidities compared to the general population, are likely to have these comorbidities exacerbated by the current COVID-19 pandemic and likely to exacerbate outcomes from the virus infection[12].

This study comprehensively analyzed features and effectors of COVID-19 patients hospitalized in a Tertiary Care University Hospital in Washington DC, which caters primarily to minorities. We found that elevated liver enzymes, procalcitonin, ferritin, CRP and D-dimers are robust markers of poor prognosis in minority patients receiving medical care for COVID-19. GI symptoms, although not indicative of outcome in COVID-19 patients, were prevalent in our cohort. Anorexia (26.4%), diarrhea (15.8%), abdominal pain (13.8%), nausea (13%) and vomiting (11.3%) were the main symptoms of the GI tract-associated symptoms. GI symptoms are likely important latent markers to manifest as the virus persists within the GI system, even after clearing the respiratory system.

In this cohort, the patients that died were more likely to be older than 50 years; this agrees with Center for Disease Control (CDC) reports for hospitalized patients in which 74.5% were older than 50 years[13]. Interestingly, Hispanics had the youngest patients’ group; the mean age was 43.2 for survivors, while the deceased was 51.1 years. Rodriguez-Diaz et al[14] reported similar findings with their Hispanics being less than 35 years. The high rate of young people within the HSP in this study is likely
a reflection of the occupation these patients are involved in, making them highly exposed to the virus and unlikely to benefit from the protections that remote working offers to others.

Both genders were equally represented in our cohort. Many studies, including a CDC report found in a study of 1482 patients (54.4% males)[13], report more males than female infections, generally explained by men’s likely higher exposures in many societies. Males had higher mortality in our cohort. This was explained by potential protective immune functions on the X chromosome[15] or protective effects hypothetically attributed to female hormones. This trend was reproduced in the 3 races included in this study (AA, CAU, and HSP). Worth noting that AA had the highest mortality rate in our cohort when compared to CAU and HSP. While this finding may be affected by sample sizes of the 3 groups, Doumas et al[16] have also reported that AA displays the worst outcome in the United States across different racial and ethnic groups.

Obesity has been described as a negative marker in COVID-19 patients’ outcomes, primarily because of obesity-associated pro-inflammation, excessive oxidative stress, impaired immunity, and a creator/trigger of metabolic syndrome[17,18]. Our findings showed that 20.2% were obese, 18.6% overweight and 14.8% regular BMI patients died. However, this trend of high BMI with death was not statistically significant. This contrasts with what was found by Malik et al'[9]'s meta-analysis of 10233 COVID-19 confirmed cases where they showed a significant association between obesity and COVID-19 severity and poor outcomes.

Shortness of breath was seen in 62%, cough in 59.7%, fever in 54.6% and fatigue (39.5%). Overall, in our cohort, although very common, these symptoms were not all related to outcome/severity or mortality.

Shortness of breath was significantly associated with higher mortality in the HSP group only. This contrasts with Li et al[20] who reported that in the Henan province in China, fatigue and expectoration were signs of severe COVID-19 infection and prognostic markers for outcome in their patients, and shortness of breath was prognostic only for males. Can et al[21] also reported similar presentations distribution in their COVID-19 patients that had fatigue (46.5%), cough (69.4%) and fever (41.4%).

The presence of GI symptoms points to the likelihood of the virus affecting different systems at once, even though others hypothesize that such non-respiratory symptoms are associated with inflammations triggered by infections of other systems besides the lungs. Angiotensin-converting enzyme 2 (ACE2) receptor, the target of the virus SPIKE protein and transmembrane protease serine 2 (TMPRSS2) that is needed for its cleavage and entry into the cells, was reported to be expressed in the GI system, and as such, we cannot rule out that GI symptoms may be the result of a direct virus effect on these systems. It is noteworthy that many patients who tested negative for the virus in the respiratory specimens continued to test positive for the virus RNA in their stools after they recovered from the disease[22]. It is possible that in the foreseeable future, many new disorders in the GI system, as well as neurological and cardiovascular systems, of which SARS-CoV-2 is an etiological element may occur among patients who recovered from COVID-19 infection.

Diabetes mellitus and hypertension, two of the most common chronic conditions in the United States were not significantly associated with higher mortality in our cohort. Cardiac disease in heart failure or coronary artery disease was present in 19% of our cohort and was significantly associated with higher mortality \( (P = 0.028) \). This contrasts with the Almeida-Petitto et al[23]'s report, where cardiovascular disease is related to outcome and diabetes mellitus and hypertension. When the analysis was done within the race groups in this study, none of the comorbidities were significant for AA, CAU or HSP.

Laboratory test values are essential markers for the general assessment of underlying determinants of observed symptoms and prognosis. In OR2 analysis, low lymphocyte elevated CRP, elevated procalcitonin, elevated ferritin and elevated AST and ALT were significantly associated with severe outcome and death in our cohort. These findings corroborate with Bastug et al[24]'s cohort, where they reported that D-dimer and CRP are significant predictors of mortality, but not AST, LDH, ferritin, or lymphocytes. COVID-19 induces systemic inflammation and a prothrombic state which translates to elevated CRP, procalcitonin, and D-dimer levels which are the worst prognostic factors[25].

Liver function test has been well documented in COVID-19 patients. In our cohort, elevated AST was highly significant for higher mortality. AST was found to be elevated in 147 patients (43.8%); ALT was found to be elevated in 98 patients (29.6%). None of our findings for the overall cohort were translated to the race group analyses. While elevated AST is associated with the highest OR for poor outcomes, not all AST
can be assigned to the liver. However, the more liver-specific ALT enzyme did associate with a higher OR of poor outcome, although not to the same magnitude as AST associated OR. These findings confirm that liver function alterations that might stem from viral-induced liver damage of triggered inflammation are related to severe outcomes. Wang et al.[27] described histological damage to the liver in a cohort of 156 patients. Their findings stated that infected hepatocytes displayed conspicuous mitochondrial swelling, endoplasmic reticulum dilatation, glycogen granule decrease, massive hepatic apoptosis, and some binuclear hepatocytes. These are hallmarks of typical lesions of viral infection origin. As stated above, for the GI system of recovered patients, liver health and status need to be monitored in millions of recovering patients to avoid a resurgence of new liver diseases linked to the sequels of the pandemic.

Treatments implemented in our hospital (21.1% with hydroxychloroquine and 18% with glucocorticoids) did not seem to have benefited our patients. Indeed, there was even higher mortality in those receiving them (hydroxychloroquine with \( P = 0.019 \), and glucocorticoids with \( P < 0.0001 \)). Similar findings were reported by Budhathoki et al.[28] who stated that using corticosteroids made the viral clearance duration and hospital stay longer in the treated group, real-time polymerase chain reaction took 3 d more to come negative when compared to the non-treated group. Patel et al.[29] also reported an adverse outcome risk using hydroxychloroquine and even worse when adding azithromycin. It is worth mentioning that the present cohort of our study corresponds to the first wave of COVID-19 patients where treatment protocols were still being developed and tried.

CONCLUSION

In conclusion, elevated liver enzymes, ferritin, CRP, and D-dimers are robust markers of poor prognosis. The African Americans in our study displayed the highest mortality as they consisted of an older population compared to the Hispanic group. GI symptoms did not correlate with the outcome; however, they may manifest essential features as the virus persists within the GI system, even after clearing from the respiratory system. Attention should also be paid to monitor liver function during COVID-19, especially in African Americans and Hispanic patients with higher disease severity. Our study showed that digestive symptoms and liver injury are not uncommon in patients with COVID-19. Increased attention should be paid to the care of African Americans and Hispanics’ unique group of patients.

ARTICLE HIGHLIGHTS

Research background
The coronavirus disease 2019 (COVID-19) disproportionately affected African Americans and Hispanics. The United States has one of the most diverse populations, exhibiting discrepancies in healthcare access, socioeconomic status, and wealth distribution, all of which lead to disparities in health outcomes across different groups, especially in minorities.

Research motivation
To evaluate the clinical manifestations, comorbidities, and laboratory parameters in COVID-19 patients and identify risk factors that may be related to poor prognosis.

Research objectives
To clarify whether clinical manifestations and laboratory parameters are related to the prognosis of COVID-19 positive African American (AA) patients.

Research methods
This study is a retrospective analysis. Patient demographics, symptoms, underlying comorbidities, treatment, and outcomes were compared among AA, Caucasians, Hispanics, and other ethnic groups. Predictors of hospital mortality evaluated by using logistic and/or multiple logistic regression. SPSS version 26 (SPSS Inc., Chicago, IL, United States) was used for this analysis.
Research results
A total of 386 COVID-19 positive patients, 257 (63.7%) were AAs, 102 (25.3%) Hispanics, and 26 (6.45%) Whites. The mortality rate was highest among the AAs (20.6%) and lowest among Hispanics (6.9%). Patients with shortness of breath (OR2 = 3.64, CI = 1.73-7.65) and elevated AST (OR2 = 8.01, CI = 3.79-16.9) elevated Procalcitonin (OR2 = 8.27, CI = 3.95-17.3), AST (OR2 = 8.01, CI = 3.79-16.9), ferritin (OR2 = 2.69, CI = 1.24-5.82), and Lymphopenia (OR2 = 2.77, CI = 1.41-5.45) had a high mortality rate. Glucocorticoid treatment was associated with higher mortality (OR2 = 5.40, CI = 2.72-10.7)

Research conclusions
The African Americans were the most affected population due to severe acute respiratory syndrome coronavirus 2 in our study with high mortality. Predictors of poor outcomes in our study are Age > 50, shortness of breath, increased liver enzymes, CRP, Ferritin, Procalcitonin. Injudicious use of glucocorticoids resulted in poor outcomes. The presence of gastrointestinal symptoms did not increase disease severity.

Research perspectives
In the future, we will continue to follow COVID-19 positive patients to analyze the causes of death and the risk factors that may lead to death. And we will devote ourselves to finding predictors related to the prognosis of minority patients with COVID-19.

ACKNOWLEDGEMENTS
We would like to thank all COVID-19 patients who participated in this study. We appreciate the work of all healthcare providers in this COVID-19 pandemic.

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Observational Study

Validated tool for early prediction of intensive care unit admission in COVID-19 patients

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Institutional review board statement: The study protocol was approved by the Ethics Committees of the Third People’s

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Abstract

BACKGROUND
The novel coronavirus disease 2019 (COVID-19) pandemic is a global threat caused by the severe acute respiratory syndrome coronavirus-2.

AIM
To develop and validate a risk stratification tool for the early prediction of intensive care unit (ICU) admission among COVID-19 patients at hospital admission.

METHODS
The training cohort included COVID-19 patients admitted to the Wuhan Third Hospital. We selected 13 of 65 baseline laboratory results to assess ICU admission risk, which were used to develop a risk prediction model with the random forest (RF) algorithm. A nomogram for the logistic regression model was built based on six selected variables. The predicted models were carefully calibrated, and the predictive performance was evaluated and compared with two previously published models.
The coronavirus disease 2019 (COVID-19) outbreak started in Wuhan, China in December 2019[1,2]. Since then, COVID-19 spread rapidly to pandemic proportions. This disease is caused by severe acute respiratory syndrome coronavirus 2. The disease is associated with symptoms of varying severity. While some patients remain asymptomatic, some exhibit more severe symptoms that rapidly progress to acute respiratory distress syndrome, metabolic acidosis, coagulopathy and septic shock[3,4]. Therefore, patients with severer forms of the disease often require intensive care unit (ICU) care.

The severity and prognosis of COVID-19 varies widely. The clinical characteristics of COVID-19 that impact the disease course can serve as a guide in clinical decision-making[5,6]. Currently, COVID-19 research has focused on the epidemiology and the clinical characteristics of patients[3,7]; however, very few studies have reported the early prediction of prognosis, especially in terms of disease course severity or probability of ICU admission.
Due to the rapidly expanding number of patients and the limited resources in the ICU, prediction models for COVID-19 are crucial in clinical decision-making and medical resource micro-allocation. However, although approximately 50 prognostic models have been built so far, including eight models to predict progression to severe or critical disease [8], only four of the models predicted ICU admission [9-12]. Among the four studies, only two calibrated their models, resulting in underestimation of the risk of poor outcomes and miscalibration risks during external validation [11,12]. Several prognostic predictive models mainly based on laboratory tests have been developed to predict disease progression to a severe or critical state, and the estimated C index of model performance was approximately 0.85 [13-15]. Similarly, one of these studies reported perfect calibration. However, the method to check calibration may have been suboptimal [8].

At the start of the pandemic, there was no antiviral agent or vaccine that existed to target this virus, and none of the existing antiretroviral treatments had been recommended for this disease. On October 22, 2020, remdesivir was approved by the Food and Drug Administration as a drug for treating hospitalized COVID-19 patients aged 12 years or more [16]. Since then, ledipasvir and paritaprevir, which have been approved by the Food and Drug Administration, have also been shown to have potential in the treatment of COVID-19. The United States Food and Drug Administration has granted Emergency Use Authorization for the use of two messenger RNA vaccines against COVID-19 [17]. However, even highly effective vaccines cannot keep the pandemic under check unless they cover a high percentage of the population. Therefore, it is necessary to stratify patients by illness severity risk or ICU admission risk so that patients who are at higher risk of requiring ICU admission can be identified; this can help reduce the burden of ICU usage, particularly in resource-limited settings. The development of a prognostic model is crucial to address the problem of micro-allocation of scarce healthcare resources in the face of a pandemic [18].

Therefore, the present study aimed to develop and validate a risk stratification tool for the early prediction of ICU admission among COVID-19-positive patients with reference to previously published literature and expert opinion together with data-driven methods. To this end, we externally validated the predicted model on another dataset, and its performance was carefully calibrated.

**MATERIALS AND METHODS**

**Study design and participants**

In this retrospective study, all patients with a positive COVID-19 diagnosis according to any one of the following diagnostic criteria were included in the present study: (1) Respiratory tract or blood specimens were positive for severe acute respiratory syndrome coronavirus 2 nucleic acids by real-time fluorescence reverse transcription-polymerase chain reaction; (2) Genetic sequencing of respiratory tract or blood specimens revealed that the material had high homology with severe acute respiratory syndrome coronavirus 2; and (3) Suspected cases with imaging features of pneumonia consistent with that described in the “Diagnosis and treatment plan for pneumonia infected with new coronavirus [trial version 5]” issued by the National Health Commission of China (this standard was limited to Hubei Province).

Consecutive patients diagnosed with COVID-19 in the Wuhan Third Hospital between December 2019 and March 2020 were included in the training cohort. There were 681 patients in the training cohort. The predictive model was built and internally validated using the above data. The features evaluated for the predictive model included baseline demographics and laboratory data of each patient obtained at their first examination after admission. All blood and urinary samples were processed within 2 h of collection. Figure 1 presents a flowchart illustrating the patients in the training and validation cohorts. The data for each cohort was obtained and analyzed retrospectively. Cases in need of ICU admission were defined according to the following criteria [19]: (1) Respiratory rate ≥ 30 times/min; (2) Pulse oximeter oxygen saturation ≤ 93% at rest; and (3) Partial pressure of arterial oxygen/fraction of inspired oxygen ≤ 300 mmHg.

**Prediction algorithm**

The proposed algorithm used in this study was built on the basis of the random forest (RF) algorithm [20], with modifications made to improve the selection of features (Figure 2). The number of trees was set to 480, and the number of variables selected at
Figure 1 The flowchart illustrating the patients in the training and validation cohorts. The data for each cohort was obtained and analyzed retrospectively. A: Patients in the training cohort; B: Patients in the validation cohort. COVID-19: Coronavirus disease 2019; ICU: Intensive care unit.

Figure 2 Feature selection. Thirteen predictors were selected in the information gain algorithm and were to train the random forest (RF) model. Six predictors with $P < 0.05$ were selected in the multivariate logistic regression (LR) analysis and were used to train the LR model. COVID-19: Coronavirus disease 2019; LASSO: Least absolute shrinkage and selection operator.

Feature selection consisted of the following two steps. First, the least absolute shrinkage and selection operator logistic regression (LR) and univariate LR were used to determine which variables were associated with disease prognosis. We performed a tenfold cross-validation of the training set to calculate the weight of least absolute shrinkage and selection operator penalty. Furthermore, physicians’ knowledge, together with previously published predictors significantly associated with COVID-19 severity[21] were also used to guide feature selection. Then, since each feature’s relative rank could reflect its relative significance[22-24], the information gain algorithm based on entropy and out-of-bag error assessment were used to screen the selected variables for training the RF model. Furthermore, we carried out stepwise multivariate regression analysis to screen the selected variables for training the LR model. We used variables with a $P < 0.05$ to build the model.
Figure 3 Importance of the variables included in the predictive model for coronavirus disease 2019 events based on the random forest algorithm. ALT: Alanine transaminase; AST: Aspartate aminotransferase; CK: Creatine kinase; Cr: Creatinine; CRP: C-reactive protein; GLU: Glucose; LAC: Lactate; LDH: Lactate dehydrogenase; NLR: Neutrophil-to-lymphocyte ratio; PCT: Procalcitonin; PLT: Platelet; TBil: Total bilirubin; WBC: White blood cell.

**Model construction**
A tree-based ensembled machine learning algorithm, RF, was used to build a risk prediction model based on 13 selected variables. GridsearchCV was performed to search the best parameter for the optimal model. A nomogram for the LR model was built based on six selected variables, which were then screened by multivariate logistic regression analysis. The models were developed in Python version 3.6.5. The reporting followed the TRIPOD statements [25].

**Performance evaluation**
Here, we comparatively assessed the predictive performances of scores yielded by the present and conventionally used models, as described below:

**Discrimination:** To evaluate discrimination, we used the area under the receiver operating characteristic curve, accuracy, specificity, sensitivity, box plots of predicted probabilities of ICU admission and corresponding discrimination slopes, defined as the differences between the mean predicted risks for ICU admission.

**Calibration:** The conventional Hosmer-Lemeshow statistic was avoided due to its shortcomings [26, 27]. Calibration of the predictive model was assessed by the visual representation of the relationship between the predicted and observed values [28]. We constructed calibration curves by plotting the predicted risk of ICU admission divided into 20 groups based on the model risk score against the observed ICU admission.

**Reclassification**
The net reclassification index (NRI), which has been devised to overcome the limitations of usual discrimination and calibration measures, was computed to compare our proposed algorithm to the other scores [29]. The NRI comparing risk score A of ICU admission to score B was defined as two times the difference between the proportion of no ICU admission and ICU admission groups, respectively, which deemed the risk of ICU admission to be higher according to score A than according to score B [30]. Positive values of the NRI indicated that score A had better discriminative ability than score B, whereas negative values indicated the opposite.

**Decision curve analysis**
A decision curve analysis (DCA) was used to estimate the clinical usefulness and net benefit of the intervention [31]. The decision curve [32] is a novel and clever graphical device used to assess the potential population impact of adopting a risk prediction instrument into clinical practice. It is grounded in a decision-theoretical framework that accounts for both the benefits of intervention and the costs of intervention to a patient who cannot benefit from the intervention.
Table 1 Baseline clinical and laboratory characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Training cohort, ( n = 681 )</th>
<th>Validation cohort, ( n = 296 )</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>63.0 (51.0-71.0)</td>
<td>49.0 (36.0-61.0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>338 (49.6%)</td>
<td>146 (49.3%)</td>
<td>0.985</td>
</tr>
<tr>
<td>BNP (ng/L)</td>
<td>27.9 (11.5-64.5)</td>
<td>37.6 (37.6-37.8)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>13.7 (2.5-53.6)</td>
<td>11.4 (5.0-26.2)</td>
<td>0.073</td>
</tr>
<tr>
<td>D-dimer (mg/L)</td>
<td>0.6 (0.3-1.4)</td>
<td>0.4 (0.3-0.5)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>37.4 (33.7-40.8)</td>
<td>43.0 (40.7-44.8)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>C3 (g/L)</td>
<td>1.1 (1.0-1.2)</td>
<td>1.1 (1.1-1.1)</td>
<td>0.382</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>27.0 (20.0-38.0)</td>
<td>26.3 (21.0-34.2)</td>
<td>0.230</td>
</tr>
<tr>
<td>APTT (s)</td>
<td>29.7 (26.5-33.5)</td>
<td>35.1 (32.4-37.8)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>K⁺ (mmol/L)</td>
<td>3.9 (3.6-4.3)</td>
<td>3.8 (3.6-4.0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>LYMPH (10⁹/L)</td>
<td>1.1 (0.8-1.5)</td>
<td>1.3 (1.0-1.7)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>IgA (g/L)</td>
<td>2.6 (2.0-3.3)</td>
<td>2.0 (2.0-2.0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>LDH (U/L)</td>
<td>214.0 (169.0-294.0)</td>
<td>224.0 (179.0-397.8)</td>
<td>0.001</td>
</tr>
<tr>
<td>Hgb (g/L)</td>
<td>126.0 (116.0-135.0)</td>
<td>137.0 (126.0-146.0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>GLU (mmol/L)</td>
<td>5.4 (4.7-6.8)</td>
<td>5.8 (5.3-6.6)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>NEUT (10⁹/L)</td>
<td>3.2 (2.4-4.4)</td>
<td>2.8 (2.0-3.6)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CK (U/L)</td>
<td>71.0 (46.0-133.0)</td>
<td>61.0 (61.0-61.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Cr (μmol/L)</td>
<td>65.9 (53.6-81.5)</td>
<td>63.0 (52.5-77.0)</td>
<td>0.033</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>24.0 (15.0-37.0)</td>
<td>24.0 (16.0-35.3)</td>
<td>0.465</td>
</tr>
<tr>
<td>PLT (10⁹/L)</td>
<td>192.0 (152.0-258.0)</td>
<td>184.0 (143.8-227.0)</td>
<td>0.002</td>
</tr>
<tr>
<td>PCT (ug/L)</td>
<td>0.05 (0.05-0.06)</td>
<td>0.04 (0.03-0.06)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>TBil (μmol/L)</td>
<td>8.9 (6.6-11.9)</td>
<td>10.2 (7.9-13.9)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>WBC (10⁹/L)</td>
<td>5.0 (3.9-6.3)</td>
<td>4.7 (3.7-5.8)</td>
<td>0.032</td>
</tr>
<tr>
<td>NLR</td>
<td>2.8 (1.9-4.5)</td>
<td>2.1 (1.4-3.2)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>LAC (mmol/L)</td>
<td>2.8 (2.3-3.4)</td>
<td>1.4 (1.1-1.5)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

ALT: Alanine aminotransferase; APTT: Activated partial thromboplastin time; AST: Aspartate aminotransferase; BNP: Brain natriuretic peptide; CK: Creatine kinase; Cr: Creatinine; CRP: C-reactive protein; GLU: Glucose; Hgb: Hemoglobin; IgA: Immunoglobulin A; LAC: Lactate; LDH: Lactate dehydrogenase; LYMPH: Lymphocyte; NEUT: Neutrophils; NLR: Neutrophil-to-lymphocyte ratio; PCT: Procalcitonin; PLT: Platelet; TBil: Total bilirubin; WBC: White blood cell.

**External validation**

A completely independent dataset was then used to externally validate the predictive performance of the algorithm developed herein. To this end, we randomly collected patients with COVID-19 that had been clinically confirmed by reverse transcription-polymerase chain reaction between January 19, 2020 and March 14, 2020, in Shenzhen Third People’s Hospital, which is a tertiary-care teaching hospital. Informed consents were obtained from all patients or from their families by telephone before their data were used in this study. All patient privacy data were protected under the confidentiality policy. Data were analyzed using the statistical software package R, version 3.4.3 (R Core Team, 2017) and EmpowerStats (X&Y solutions, Inc. Boston, Massachusetts).

**Model comparison**

The performance of the proposed predictive model was compared to other recently published models on the same external validation data. For convenience, the two published models were designated model A[33] and model B[34].
Statistical analysis
All participants’ baseline demographic and clinical characteristics were obtained at admission. Continuous variables were presented as means ± SD or medians (interquartile ranges), whereas categorical variables were presented using frequencies (percentages). Intergroup differences were analyzed with the χ² test, one-way analysis of variance and Kruskal-Wallis test for categorical variables, normal variables and continuous variables with skewed distribution, respectively. A P < 0.05 was considered statistically significant.

RESULTS

Study population
This study describes the development of an algorithm for the early prediction of ICU admission among COVID-19 patients at hospital admission. For developing the prediction model, we first used a training cohort consisting of 681 patients from Wuhan Third Hospital and analyzed their basic baseline demographic and laboratory data obtained at the first admission. We then calibrated the performance of this prediction tool using an entirely different sample set of 296 patients from Shenzhen Third People’s Hospital.

Table 1 presents a comparison of the baseline clinical and laboratory characteristics between the training and validation cohorts. The patients in the training cohort were older than those in the validation cohort (median age: 63.0 vs 49.0 years, P < 0.001), and the percentages of male gender were similar (49.6% vs 49.3%, P = 0.958). There was also some heterogeneity in laboratory results among the different patient groups. Table 1 presents all the patient characteristics.

Feature selection for the predictive model
We selected a total of 65 baseline clinical features for use in our prediction tool. Those with missing values were deleted (n = 18), and the remaining 47 features with complete data were used as potential predictors of critical illness requiring ICU admission. Twenty-three predictors with non-zero coefficients were selected in the least absolute shrinkage and selection operator LR model. Of these, those with P > 0.05 were excluded, and 19 predictors with P < 0.05 were selected for the univariate LR analysis (Table 2). After adjusting the model based on expert opinion, a total of 17 predictors were decided.

The information gain of each variable and its importance were calculated and ranked based on entropy and out-of-bag error. Figure 3 depicts the relative importance of each of the features. Variables were dropped from the bottom of the list, starting from the variable that was deemed least important and progressing in ascending order. The least classification error was obtained when gender, alanine transaminase, aspartate aminotransferase and white blood cell were dropped from the prediction model. Hence, these four features were removed. Figure 4 shows the relationship between the number of discarded variables and classification error. After all, a final of 13 predictors were selected. SHapley Additive exPlanations value was calculated to explain the output of the RF model (Figure 5). It connected optimal credit allocation with local explanations using the classic Shapley values from game theory and their related extensions [35]. In the next step, six predictors [neutrophil-to-lymphocyte ratio (NLR), age, lactate dehydrogenase, creatinine, glucose and albumin] with P < 0.05 were selected to build the multivariate LR model (Table 2). The personalized nomogram was then used to show the probability of ICU admission (Figure 6).

Internal validation performance
After feature selection, two predictive models, LR and RF, were built on the basis of the selected variables. For internal validation, the area under the receiver operating characteristic curve for the RF model was found to be 0.94, which was higher than that for the LR model at 0.91 (P = 0.111, DeLong’s test). The accuracy, sensitivity and specificity for the RF model were 91%, 88% and 93%, respectively, higher than those for the LR model (87%, 82%, and 89%, respectively) (Figure 7).

External validation performance
Moreover, we compared our results with those of previously published methods in the external validation dataset as well (Figure 7). The area under the receiver operating characteristic curves for the RF, LR, model A and model B models were 0.90, 0.86, 0.82
Table 2 Multivariate logistic regression models of risk severity in the training cohort

<table>
<thead>
<tr>
<th>Feature</th>
<th>Univariate logistic regression</th>
<th>Multivariate LR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95%CI)</td>
<td>P value</td>
</tr>
<tr>
<td>Age, yr</td>
<td>2.64 (2.06–3.37)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.68 (1.99-3.61)</td>
</tr>
<tr>
<td>BNP</td>
<td>1.53 (1.34-1.75)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CRP</td>
<td>2.01 (1.68-2.40)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>D-dimer</td>
<td>1.13 (1.06-1.20)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Albumin</td>
<td>0.37 (0.29-0.48)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>0.62 (0.46-0.83)</td>
<td>0.001</td>
</tr>
<tr>
<td>Hcv_ab</td>
<td>1.005 (0.999-1.011)</td>
<td>0.083</td>
</tr>
<tr>
<td>AST</td>
<td>1.50 (1.29-1.75)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CysC</td>
<td>1.32 (1.19-1.46)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>APTT</td>
<td>1.80 (1.45-2.23)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Cr</td>
<td>1.10 (1.05-1.16)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Myoglobin</td>
<td>1.64 (1.44-1.88)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CK</td>
<td>1.12 (1.05-1.20)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>PCT</td>
<td>1.008 (1.003-1.014)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Tp_ab</td>
<td>1.001 (0.999-1.003)</td>
<td>0.231</td>
</tr>
<tr>
<td>BUN</td>
<td>1.70 (1.44-1.99)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>PT</td>
<td>1.65 (1.36-1.99)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>LAC</td>
<td>0.81 (0.68-0.98)</td>
<td>0.012</td>
</tr>
<tr>
<td>LDH</td>
<td>2.36 (1.91-2.93)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hgb</td>
<td>0.69 (0.58-0.82)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>GLU</td>
<td>1.28 (1.15-1.44)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>HBeAg</td>
<td>1.010 (0.920-1.108)</td>
<td>0.156</td>
</tr>
<tr>
<td>HbsAg</td>
<td>0.999 (0.995-1.003)</td>
<td>0.577</td>
</tr>
<tr>
<td>NLR</td>
<td>1.90 (1.61-2.25)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>1.27 (1.06-1.51)</td>
<td>0.008</td>
</tr>
</tbody>
</table>

APTT: Activated partial thromboplastin time; AST: Aspartate transaminase; BNP: Brain natriuretic peptide; BUN: Blood urea nitrogen; CI: Confidence interval; CK: Creatine kinase; Cr: Creatinine; CRP: C-reactive protein; CysC: Cystatin C; GLU: Glucose; HBeAg: Hepatitis B e antigen; HbsAg: Hepatitis B surface antigen Hcv_ab: Hepatitis C virus antibody; Hgb: Hemoglobin; LAC: Lactate; LDH: Lactate dehydrogenase; LR: Logistic regression; NLR: Neutrophil-to-lymphocyte ratio; OR: Odds ratio; PCT: Procalcitonin; PT: prothrombin time; Tp_ab: Treponema pallidium antibody.

and 0.75, respectively. The DeLong’s test between these models was: \( P = 0.135 \) (RF vs LR), \( P = 0.004 \) (RF vs model A), \( P = 0.006 \) (RF vs model B), \( P = 0.333 \) (LR vs model A), \( P = 0.045 \) (LR vs model B) and \( P = 0.185 \) (model A vs model B). The accuracy for the RF, LR and model A models were 86%, 83% and 76%, respectively. The sensitivity was 82%, 79% and 82%, respectively. The specificity was 86%, 83% and 75%, respectively. Since model B showed the lowest performance in this validation set, only the predictive performance of LR, RF and model A were compared for the following experiments.

Figure 8A, 8C and 8E shows the observed risk of ICU admission vs model-predicted risk in groups based on the calculated model risk score. The overestimation and underestimation in the probability range of ICU admission risk were evident from the plots. Model A underestimated risk in patients with a predicted risk less than 30%. The RF and LR models show a perfect calibration. The RF risk score demonstrated an excellent ability to categorize patients in separate risk strata. Figure 8B, 8D and 8F shows the differences in the predicted probability values between ICU admission and no ICU admission using each of the prediction models. The discrimination slope for the RF, LR and model A models were 0.281, 0.246 and 0.143, respectively. The plots indicated a lack of fit for the model A.
Table 3 Reclassification

<table>
<thead>
<tr>
<th>Initial model</th>
<th>Updated model</th>
<th>Predicted probability according to initial model</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>&lt; 13%</td>
<td>13%-20%</td>
</tr>
<tr>
<td>Model A</td>
<td>RF</td>
<td>&lt; 13%</td>
<td>189</td>
</tr>
<tr>
<td></td>
<td></td>
<td>13%-20%</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 20%</td>
<td>2</td>
</tr>
<tr>
<td>LR</td>
<td>RF</td>
<td>&lt; 13%</td>
<td>208</td>
</tr>
<tr>
<td></td>
<td></td>
<td>13%-20%</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 20%</td>
<td>8</td>
</tr>
<tr>
<td>LR</td>
<td>RF</td>
<td>&lt; 13%</td>
<td>194</td>
</tr>
<tr>
<td></td>
<td></td>
<td>13%-20%</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 20%</td>
<td>0</td>
</tr>
</tbody>
</table>

CI: Confidence interval; LR: Logistic regression; NRI: Net Reclassification Index; RF: Random forest.

We further calculated the risk of each individual in the entire testing cohort and divided all patients into three groups based on the risk cut-off at 95% sensitivity and 95% specificity[36]. Then we computed the NRI with RF as the second model, and LR and model A as the first models. In this scenario, a positive NRI value would indicate that the RF model has better discriminative ability compared to the other models, while a negative value would indicate the converse. Table 3 summarizes the results of this analysis.

Finally, DCA was used to facilitate the comparison between different prediction models. As shown in Figure 9, the DCA graphically shows the clinical usefulness of each model based on a continuum of potential thresholds for major high risk and the standardized net benefit of using the model to stratify patients relative to assuming that there were no ICU admission patients. As shown from our results, the standardized net benefit yielded by the models developed in this study was larger across the major high-risk range compared with model A.

**DISCUSSION**

Due to the rapidly expanding number of patients and the limited resources in the ICU,
prediction models for patients with COVID-19 are crucial in clinical decision-making and medical resource micro-allocation. In the present study, a training cohort of 681 COVID-19 patients were recruited from Wuhan Third Hospital. A risk prediction model was successfully established to assess the chance of ICU admission based on the lab results obtained at the time of hospital admission. Furthermore, we performed an external validation on a total of 296 confirmed COVID-19 patients from Shenzhen Third People’s Hospital. Comparing with the recent published methods on the same validation data, our results revealed that the newly developed model (RF) exhibited relatively better discriminatory power, and the external verification was also satisfactory. In addition, our model showed a better discriminatory power in diverse populations from hospitals of different levels with varying death rates and varying
Huang HF et al. Early Prediction of ICU admission in COVID-19

![Figure 7 Performances of the newly developed prediction models and traditional scoring systems for internal and external validation. A: The receiver operating characteristic (ROC) curve for the random forest (RF) model and the logistic regression (LR) model; B: Receiver operating characteristic curve for models RF, LR, A and B; C: The performance matrix comparison for the RF model and the LR model; D: The performance matrix for models RF, LR and A. Internal validation: A and C. External validation: B and D. The performance matrix of RF, LR and model A models are shown in blue, orange and green, respectively. AUC: Area under the receiver operating characteristic curve.](image-url)

Baseline physical conditions, indicating that our models that were developed in the current study can be applied to a wide variety of settings.

Meanwhile, when creating a new prediction model, we recommend selecting predictors based on previous literature and expert opinion, rather than in a purely data-driven way[8]. In this case, we developed a mixed-knowledge feature selection process, including machine-selection and clinicians’ knowledge, together with previous published predictors[21]. Although the more information used during the developing step, the better performance the models would be, we would like to limit the number of the predictors while achieving similar performance in order to ease the user experience. Several studies have shown that lung imaging can help assess disease severity in COVID-19[37], which is one of the clinical diagnostic criteria. However, our predictive model was able to achieve good results by using only the biochemical indicators obtained on the first day of admission, thereby reducing the physical strain and economic burden on patients and governments.

Furthermore, based on the selected variables, two clinical predictive models were built. The LR model used only six of the selected variables but performed better than the other two published methods[33,34] on our external validated dataset. One step further, in order to improve the predictive ability of the model, a more sophisticated machine learning method, RF, was introduced in our model building step.

The predictive performance of the models built in the present study were carefully evaluated and calibrated. As we all know, poorly calibrated models will underestimate or overestimate the outcome of interest, while an excellent model will show strong calibration for different groups of patients. A model with adequate calibration by
Figure 8 The calibration and discrimination of model random forest, logistic regression and A in external validation dataset. A, C and E: The graph represents the relationship between observed (data markers represent the mean and the error bars represent the 95% confidence interval) and predicted risk of intensive care unit (ICU) admission using the models (orange line); B, D and F: The discrimination potentials of the random forest (RF), logistic regression (LR) and model A models. The values of the discrimination slope were 0.281, 0.246 and 0.143, respectively.

In our results, visual representation of the relationship between predicted and observed values were shown to evaluation calibration. Discrimination and calibration results show that the RF model demonstrated an excellent ability to categorize patients in separate risk strata and the values predicted by the model agree with the observed values, which indicated that both the RF and LR models performed better than other published methods, and the RF model performed the best. Furthermore, when comparing the performance of all the three models, the reclassification result revealed that the RF model resulted in the reclassification of a large number of patients, and a positive NRI value indicated that the RF model performed better than the other predicted risk strata will provide useful information for clinical decision making[28].
The following six variables were the most important in prediction of a risk of ICU admission among COVID-19 patients, in decreasing order of importance: NLR, age, lactate dehydrogenase, C-reactive protein, creatinine, D-dimer and albumin.

The NLR represents inflammation and is a known indicator of the systemic inflammatory response[38]. Yang et al.[38] stated that elevated NLR could be considered an independent biomarker of indicating poor clinical outcomes in the outcome following COVID-19. Age was the second most important factor in the model, and age has been very well known as an important biomarker of poor clinical outcomes in the context of COVID-19. Lactate dehydrogenase and C-reactive protein have also been found to be associated with poorer outcomes such as respiratory failure in COVID-19 patients[39]. These results are in agreement with the findings of our study.

Finally, the clinical model developed in this study may be able to assist medical professionals to identify high-risk patients at their first assessment in settings where medical resources are limited. Based on the results of the DCA, the standardized net benefit was the highest with the RF model across the major high-risk range. This model can aid doctors infer the likely course of COVID-19 at an early stage so that they can guide the patients toward more appropriate treatments. Therefore, patients that are more likely to develop a severe case of COVID-19 can get close attention and high-level treatments in advance.

The present study has some limitations. First, the participants included patients who tested positive for COVID-19 in Wuhan; therefore, studies across larger areas need to be carried out to further verify our findings. Second, any medications taken prior to hospital admission and the time interval between hospital admission and disease onset could have affected the data records. Third, we did not analyze some data points, e.g., the body mass index and viral load, which are potential risk factors of infection severity, in our study. Despite these limitations, our predictive models yielded good discriminatory power when we verified the models in a heterogeneous population. Fourth, some data that may be critical to a patient’s prognosis, such as mechanical ventilation data, were not collected in this study. However, in China, treatment for COVID-19 among all hospitals is carried out in line with the National Health Commission of China guidelines[26]. Here, we devised predictive models using patient information obtained from tests done at admission. In the future, research should include repeated measures data to identify whether any temporal changes in clinical indicators are better able to predict disease prognosis in COVID-19.
CONCLUSION

In the present study, we used the first day of laboratory results to build a model for the early prediction of the need for ICU admission among patients diagnosed with COVID-19 infection. Upon external verification, the discriminatory powers exhibited by our predictive models were relatively satisfactory. The models developed in this study can aid high-risk patients to achieve early intervention and provide guidance to ensure the rational allotment of medical resources.

ARTICLE HIGHLIGHTS

Research background
The novel coronavirus disease 2019 (COVID-19) pandemic is a global threat caused by the severe acute respiratory syndrome coronavirus-2.

Research motivation
The development of a prognostic model is crucial to address the problem of micro-allocation of scarce healthcare resources in the face of a pandemic.

Research objectives
To develop and validate a risk stratification tool for the early prediction of intensive care unit admission among COVID-19 patients at hospital admission.

Research methods
We selected 13 of 65 baseline laboratory results and developed a risk prediction model with the random forest algorithm. A nomogram for the logistic regression model was built based on six selected variables.

Research results
The accuracy, sensitivity and specificity for the random forest model were 91%, 88%, and 93%, respectively, higher than those for the logistic regression model. The area under the receiver operating characteristic curve of our model was much better than those of two other published methods (0.90 vs 0.82 and 0.75).

Research conclusions
Our model can identify intensive care unit admission risk in COVID-19 patients at admission, who can then receive prompt care, thus improving medical resource allocation.

Research perspectives
In the future, research should include repeated measures data to identify whether temporal changes in clinical indicators are better able to predict disease prognosis in COVID-19.

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Observational Study

Comparison of the impact of endoscopic retrograde cholangiopancreatography between pre-COVID-19 and current COVID-19 outbreaks in South Korea: Retrospective survey

Kook Hyun Kim, Sung Bum Kim

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Author contributions: Kim KH designed the research and wrote the paper; Kim SB analyzed the clinical data and reviewed the manuscript.

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Institutional review board statement: This study was approved by the Institutional Review Board of Yeungnam University Hospital (IRB No. 2020-12-042).

Informed consent statement: Written informed consent was waived owing to the retrospective nature of this study.

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

Data sharing statement: No additional data are available.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external experts.

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Abstract

BACKGROUND
The coronavirus disease 2019 (COVID-19) outbreak has markedly influenced the endoscopic patterns. Endoscopic retrograde cholangiopancreatography (ERCP) is an essential technique for pancreatobiliary disease but increases the risk of exposure to the virus-containing body fluid; however, the impact of COVID-19 on ERCP is unknown.

AIM
To compare the number of endoscopic activities and to analyze the clinical outcomes of ERCPs before and during the COVID-19 outbreak in Daegu, South Korea.

METHODS
This retrospective cohort study included patients aged ≥18 years who underwent ERCP between February 18 and March 28, 2020, at a tertiary hospital. ERCP indications and endoscopic details were compared with those from the same period in 2018 and 2019 as control groups.

RESULTS
Of the 269 ERCP procedures, 113 (42.0%) cases were performed as emergency procedures. The number of ERCP procedures in 2018 and 2019 decreased by 20.2% and 56.6%, respectively, compared with that in 2020 \( (P < 0.01) \); among the 113 emergency ERCPS, the observed numbers in 2018 \( (n = 42) \) and 2019 \( (n = 55) \) dramatically dropped by 61.9% and 70.9%, respectively, compared with that in 2020 \( (n = 16) \). Of the 16 cases in 2020, stent removal was performed in five, biliary stenting in five, sphincterotomy in five, and nasobiliary drainage in one. No case of ERCP-related infection in medical workers or other patients has been reported.
CONCLUSION
The COVID-19 outbreak significantly reduced the number of ERCPs; however, there is no difference in the indications and endoscopic interventions before and during the COVID-19 outbreak.

Key Words: Coronavirus disease 2019; Coronavirus; Endoscopic retrograde cholangiopancreatography; Emergency endoscopic retrograde cholangiopancreatography; Endoscopy

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INTRODUCTION
The coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has infected approximately 100 million people worldwide, with more than 2 million mortalities as of February 2021. The catastrophic viral transmission led to a pandemic in March 2020[1]. The advent of COVID-19 outbreak has revolutionized the pattern of endoscopies. However, little is known about the clinical impact associated with COVID-19 on endoscopic retrograde cholangiopancreatography (ERCP). We compared the change in the number of ERCP procedures, causes, and clinical outcomes of emergency ERCP before (2018, 2019) and during the COVID-19 (2020) outbreak at a tertiary referral hospital in South Korea.

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URL: https://www.wjgnet.com/2307-8960/full/v9/i28/8404.htm
DOI: https://dx.doi.org/10.12998/wjcc.v9.i28.8404

The advent of the coronavirus disease 2019 (COVID-19) outbreak has transformed the patterns of endoscopic activities. However, little is known about the clinical impact associated with COVID-19 on endoscopic retrograde cholangiopancreatography (ERCP). We compared the change in the number of ERCP procedures, causes, and clinical outcomes of emergency ERCP before (2018, 2019) and during the COVID-19 (2020) outbreak at a tertiary referral hospital in South Korea.

The coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has infected approximately 100 million people worldwide, with more than 2 million mortalities as of February 2021. The catastrophic viral transmission led to a pandemic in March 2020[1]. The advent of COVID-19 outbreak has revolutionized the pattern of endoscopies. However, little is known about the clinical changes associated with COVID-19 on endoscopic retrograde cholangiopancreatography (ERCP). SARS-CoV-2 infection is usually transmitted via aerosol droplets; however, there are emerging reports that SARS-CoV-2 can be spread via the gastrointestinal route[2-5]. Following the first identification of SARS-CoV-2 positivity on February 18, there was an alarming surge of COVID-19 at the end of February in Daegu, the third most densely populated city in South Korea. Statistics show that the cumulative number of COVID-19 cases had rapidly risen to 6600 within 1 mo[6].

Recently, endoscopic manipulation has been regarded as a potentially dormant reservoir for viral spread and aerosol formation during procedures[7-9]. Both protecting healthcare providers (HCPS) and limiting viral shedding in patients are of great importance in the endoscopy center[10]. Very recently, it has been reported that the sophisticated parts of the side-view scope can be a culprit of lethal bacterial colonization throughout procedures, thus requiring a series of laborious cleaning and disinfection processes[11]. Compared with other endoscopies such as colonoscopy and upper endoscopy, ERCPs are relatively time-sensitive procedures[12]. Most patients with pancreatobiliary disorders are referred to the emergency room (ER) from the clinics or medium-volume hospitals, mainly due to fever, abdominal pain, or jaundice. Most elective endoscopies were canceled or postponed due to the reinforced disease and infection control in our hospital, between February 18 and March 28, 2020, resulting in a substantial decrease in the number of endoscopic procedures, including ERCP[13]. The goal of this study was to compare and to analyze the change in the number of ERCP procedures, causes, and clinical outcomes of emergency ERCP before and during the COVID-19 outbreak in Daegu, the hardest-hit city in South Korea.
**MATERIALS AND METHODS**

**Study population and design**
This was a retrospective cohort study of patients aged ≥ 18 years who underwent ERCPs between February 18 and March 28, 2020, at a single tertiary referral hospital during the COVID-19 outbreak. These specific intervals are chosen based on the first SARS-CoV-2 confirmed date and the plateau date of the cumulative curve of the COVID-19 outbreak, in Daegu, South Korea. Baseline demographics, causes of ER visits, blood chemistry, and endoscopic findings relevant to ERCP were collected and compared with those in 2018 and 2019 (pre-COVID-19 era), which were labeled as control groups. In this study, the emergency ERCP group was defined as ERCP cases in which patients visited the ER and underwent ERCP within 24 h and did not include cases that were referred from the other departments due to bile leak, incidental bile duct stone, or sudden obstructive jaundice. Patients who underwent total gastrectomy were excluded. This study was approved by the Institutional Review Board of Yeungnam University Hospital (IRB No. 2020-12-042). Written informed consent was waived owing to the retrospective nature of this study.

**Endoscopic procedures**
All patients were sedated by administering midazolam (3-5 mg) and pethidine (25-50 mg) at the start of the procedure, and then propofol (10-100 mg) was administered intravenously by nurses during the procedure, with the endoscopists’ permission. All endoscopic procedures were performed using side-viewing endoscopes (TJF-240, Olympus Optical Corporation, Tokyo, Japan). When the side-viewing endoscope was not suitable, particularly for patients who underwent subtotal gastrectomy, such as Billroth II, it was changed to a forward-viewing endoscope. The use of either side-viewing or forward-viewing endoscopes in patients with surgically altered anatomy was determined by the endoscopist’s preference.

**COVID-19 quarantine and protective equipment**
Since the COVID-19 outbreak, all ER-visiting patients were subjected to the comprehensive COVID-19 quarantine process. They were directly guided through the walk-in screening tent at the ER entrance upon arrival, where the body temperature was checked, and patients were intensively questioned regarding any clinical presentation of respiratory symptoms and any chance of contact with patients with COVID-19. All ER patients underwent reverse transcription polymerase chain reaction (RT-PCR) for SARS-CoV-2 by swabbing the nose and throat. All emergency ERCPs were suspended until the RT-PCR results were identified, which took at least 6 h in our hospital. If the RT-PCR-based SARS-CoV-2 test was confirmed as positive, ERCP was delayed until the seroconversion of RT-PCR, except in urgent cases. If the RT-PCR test was negative, the patient was taken to the endoscopy center on the second floor, and ERCP was performed as usual. However, when the RT-PCR was pending, in urgent cases, the patient was fully covered with a negative pressure tent and taken to the endoscopy center through a designated pathway. Throughout the ERCP procedures, all doctors and nurses wore personal protective equipment (PPE), including an N95 mask, waterproof gown, goggles, surgical gloves, waterproof shoe covers, and facial shields [14,15]. Before the COVID-19 outbreak, to the best of my knowledge, there were no universal guidelines regarding the regulation of PPE and the sequential process of ERCP. In the pre-pandemic era, we usually used a disposable surgical gown, surgical mask, goggles, and disposable gloves during the ERCP procedure. The fluoroscopic units, endoscopic units, and patient’s bed were exhaustively cleaned and disinfected, and the ERCP room was ventilated for 30 min before and after the procedures.

**Statistical analyses**
The numbers, indications, and endoscopic findings of ERCP from February 18 to March 28, in 2018, 2019, and 2020 were compared and analyzed. Fisher’s exact test and one-way analysis of variance were used to compare categorical and continuous variables, respectively. Variables are described as means ± SD (ranges) and numbers (%). A P value less than 0.05 was considered statistically significant. Statistical analysis was performed using IBM SPSS version 21.0 (IBM Corp., Armonk, NY, USA).
RESULTS

From February 18 to March 28, 269 ERCP procedures were performed. Of these, 113 (42.0%) cases were considered an emergency, and the others (n = 156, 58.0%) were elective. The number of ERCP procedures performed in 2018 (n = 74) and 2019 (n = 136) decreased by 20.2% and 56.6%, respectively, compared with that of the same period in 2020 (n = 59), which showed a statistically significant difference (P < 0.01) (Figure 1).

Excluding 156 elective ERCPs, 113 emergency ERCPs were further analyzed to investigate clinical outcomes. Of the 113 cases, the observed numbers in 2018 (n = 42) and 2019 (n = 55) dramatically dropped by 61.9% and 70.9%, respectively, compared with that in 2020 (n = 16) (Figure 1). The mean ages were 73.0 ± 13.7 years (range, 33-91 years) and 72.1 ± 14.0 years (range, 41-99 years) in 2018 and 2019, respectively. In comparison, the mean age of 66.3 ± 13.4 years (range, 48-95 years) in 2020 was lower than that of the control groups, without statistical difference. In terms of sex distribution, there were 26 (61.9%) female individuals in 2018; however, the male individuals (n = 12, 75.0%) were predominant in 2020, with a statistical difference (P < 0.05) (Table 1).

Abdominal pain (n = 86, 76.1%) was the most common indication for emergency ERCP, followed by jaundice (n = 14, 12.4%) and fever (n = 13, 11.5%); however, no statistical difference was observed. The algorithm for all the ERCP procedures is shown in Figure 2. The distribution of endoscopic intervention was similar among the three groups (2018, 2019, and 2020). Endoscopic retrograde biliary drainage (ERBD) (n = 42, 37.2%) was the most commonly performed technique, followed by bile duct stone removal (n = 41, 36.3%), endoscopic sphincterotomy (EST) (n = 22, 19.5%) and endoscopic nasobiliary drainage (ENBD) (n = 4, 3.5%), showing no statistical difference. Of the 16 cases in 2020, stone removal was performed in five, ERBD in five, EST in five, and ENBD in one. Endoscopic diagnosis of the 113 cases demonstrated that bile duct stone removal was performed in 56 cases (49.6%), followed by probable spontaneous passage of stones (n = 22, 19.5%), pancreatobiliary malignancy (n = 17, 15.0%), and acute cholangitis due to stent occlusion (n = 9, 8.0%). Regardless of the time of the ERCP procedure, a similar pattern of endoscopic diagnosis was observed (P > 0.05). In terms of blood chemistry, such as hemoglobin, total bilirubin, alanine transaminase, aspartate transaminase, alkaline phosphatase, and gamma-glutamyl transpeptidase levels, no statistical difference was observed before and during the COVID-19 outbreak (Table 1).

Only one patient was RT-PCR negative before the ERCP procedure, and then ERCP was implemented with caution under the full PPE; however, he was later confirmed as SARS-CoV-2 positive after repeat RT-PCR test during the study period. Fortunately, no case of ERCP procedure-related SARS-CoV-2 infection in HCPs or to other patients was reported in our endoscopic center.

DISCUSSION

ERCP is a time-consuming and complicated; however, it is an essential technique for pancreatobiliary disease and is a common emergency procedure for common bile duct (CBD) stone removal or biliary decompression[12]. Delayed treatment may lead to the deterioration of cholangitis, organ failure, and septic conditions. With the rapid increase in COVID-19 cases in February 2020 in Daegu, the hardest-hit but later fully recovered city of South Korea, there were changes in the endoscopy section of a tertiary referral hospital. Since the first confirmed case of SARS-CoV-2 on February 18, 2020, SARS-CoV-2-positive cases were rapidly increased within the city. Due to the lack of experience and the highly contagious nature of the virus, all measures to stop the viral spread in and outside the hospital were prioritized. Initially, once the RT-PCR assay for SARS-CoV-2 was confirmed to be positive at the ER, the task force committee of the metropolitan city instructed the shutdown of the ER for 24 h as a preemptive measure, which was later modified. There are a few articles regarding the framework of endoscopic procedures, such as the reduction of the number of endoscopies following the lockdown order from the government[9,16,17]. However, little is known about the clinical impact of COVID-19 on ERCP procedures, despite the fact that many pancreatobiliary patients require urgent ERCP in the setting of COVID-19 pandemic.

Endoscopy can cause human-to-human viral transmission by producing massive aerosol droplets throughout the procedure, particularly during therapeutic interventions such as ERCP[12,18]. The ERCP providers should be aware that manipulation
Table 1 Comparison of the basic characteristics of emergency endoscopic retrograde cholangiopancreatography from February 18 to March 28 during 2020, before and during the Coronavirus Disease 2019 outbreak (n = 113)

<table>
<thead>
<tr>
<th>Variable</th>
<th>2018 (n = 42)</th>
<th>2019 (n = 55)</th>
<th>2020 (n = 16)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>16/26 (38.1/61.9)</td>
<td>28/27 (50.9/49.1)</td>
<td>12/4 (75.0/25.0)</td>
<td>0.041</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>73.0 ± 13.7 (33-91)</td>
<td>72.1 ± 14.0 (41-99)</td>
<td>66.3 ± 13.4 (48-95)</td>
<td>0.244</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>11.7 ± 1.8</td>
<td>13.7 ± 11.6</td>
<td>12.0 ± 2.8</td>
<td>0.487</td>
</tr>
<tr>
<td>Total bilirubin (mg/dL)</td>
<td>4.2 ± 4.4</td>
<td>5.7 ± 5.1</td>
<td>5.5 ± 7.4</td>
<td>0.388</td>
</tr>
<tr>
<td>AST (IU/L)</td>
<td>356.6 ± 543.4</td>
<td>290.8 ± 385.6</td>
<td>274.6 ± 336.8</td>
<td>0.722</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>253.9 ± 327.3</td>
<td>306.4 ± 406.7</td>
<td>234.7 ± 239.9</td>
<td>0.693</td>
</tr>
<tr>
<td>ALP (IU/L)</td>
<td>311.5 ± 286.5</td>
<td>372.8 ± 361.9</td>
<td>275.6 ± 196.0</td>
<td>0.408</td>
</tr>
<tr>
<td>GGT (IU/L)</td>
<td>328.9 ± 286.2</td>
<td>478.7 ± 476.6</td>
<td>464.1 ± 422.2</td>
<td>0.186</td>
</tr>
</tbody>
</table>

Values are presented as means ± SD (ranges) or numbers (%). ALT: Alanine transaminase; AST: Aspartate transaminase; ALP: Alkaline phosphatase; GGT: Gamma-glutamyl transpeptidase.

Figure 1 Comparison of all endoscopic retrograde cholangiopancreatography performed from February 18 to March 28, before and during the COVID-19 outbreak (n = 269) (P < 0.005). ERCP: endoscopic retrograde cholangiopancreatography.

of the scope can increase the risk of exposure to the virus-contaminated body fluids [16]. The presumed mechanism is as follows: First, the large-bore working channel can splash the body fluid during suction or irrigation. A tight suction cap can minimize fluid leakage through the working channel. Facial shields and PPEs are indispensable for preventing exposure to body fluids[12]. Second, repeated exchange of accessories through the endoscope can increase the risk of infection. The frequent exchange of therapeutic accessories (e.g., baskets, papillotome, retrieval balloon, dilating balloon catheter, and others) increases the possibility of exposure to viral secretions. Minimal accessory manipulation can reduce the contact with the contaminated fluid. In case of difficulties, two sessions of procedures are recommended to shorten each procedural time, thereby lowering the risk of viral contamination. Lastly, endoscopy can form aerosols by inducing sneeze, coughing, or belching with or without sedation. Owing to the features of side-view images, blind insertion of the duodenoscope is highly likely to irritate the oropharyngeal mucosa, causing profuse salivary secretion. In the clinical setting, endotracheal intubation under general anesthesia can lower the aerosol-forming process during the procedure; however, all ERCP procedures in South Korea are carried out under midazolam-/propofol-based sedation, and not under general anesthesia[19,20]. Given that ERCP can be a nidus of nosocomial viral propagation, it is strongly recommended that ERCP providers wear PPE for safety during the COVID-19 outbreak[8,21,22].

European countries and the United States experienced a drastic reduction in the number of endoscopies and a change in the pattern of endoscopies after the lockdown
We experienced a 20%-50% decrease in the number of ERCPs during the COVID-19 outbreak, compared with that in the equivalent period in 2018 and 2019, consistent with the report in Ireland[23]. How can we explain this decrease in the number of elective ERCP procedures? A few explanations can be provided for this phenomenon[17]. First, the main indications for elective ERCP were asymptomatic bile duct stones, interval ERBD change, ERBD removal, follow-up ERCP for remnant stones with inserted ERBD, or incidental jaundice due to potential pancreatobiliary malignancy. Most cases were canceled or postponed until the resolution of the viral upsurge, except malignancy-associated jaundice[12]. Given that East Asia, including South Korea, has a high prevalence of intra- or extrahepatic biliary cancer and, since the incidence of pancreatic cancer is steadily rising recently, the deferral of endoscopic intervention may cause a delay in the diagnosis or progression of the disease[16]. Unfortunately, follow-up data were not available in this study, and some might have been treated at other hospitals. Second, consultation ERCP cases from other departments, such as bile leaks, incidental CBD stones, postoperative bile duct stricture, or incidental obstructive jaundice, decreased. In addition, cancelation or postponement of major pancreatobiliary surgery, following the strict infection control policy of the hospital, might have contributed to the decrease in elective ERCP cases.

Meanwhile, emergency ERCPs dropped remarkably by more than 60% during the COVID-19 era, compared with that in the pre-COVID-19 era. A previous study demonstrated that the number of ERCPs fell by 36% in 2020, compared with that in 2019, which is similar to our study[23]. Unlike upper endoscopy and colonoscopy, pancreatobiliary disorders such as bile duct obstruction or associated cholangitis usually require urgent treatment. The decrease in the number of ERCP procedures performed during the COVID-19 outbreak was largely attributed to a reduction in emergency ERCP. The most common cause of ER visits was abdominal pain in all consecutive years. Interestingly, the number of abdominal pain episodes during the COVID-19 period dramatically decreased by approximately 70% compared with that in the pre-COVID-19 period, without statistical difference. There are several hypotheses for a notable reduction in the number of emergency ERCP procedures. First, a reduced referral from a medium-volume or primary care facility led to a decline in ER visits[23]. These patients might have been managed by either a percutaneous approach or a conservative approach, without a referral. Second,
extremely elderly or physically weak patients were advised to stay at home and to minimize ER visits to a tertiary hospital, if possible, due to their vulnerability to infection. A previous study reported a fatality rate of up to 62% [23]. Based on our data, the mean age in 2020 was, to some extent, lower than that of the non-COVID-19 period, without statistical difference. This might be due to the elderly’s refusal to visit the ER until obvious cholangitic symptoms developed. As mentioned in a previous study, the fear of leaving home and lockdown might have shunned the visit to the ER [23]. Third, a ban on social gatherings might have lowered alcohol-induced pancreatitis by abstinence of alcohol intake. Additionally, a lower chance of binge eating under home quarantine might have diminished gallstone-related complications such as acute cholecystitis, Mirizzi syndrome, secondly CBD stone, acute cholangitis, or biliary pancreatitis.

The endoscopic diagnosis was mostly consistent with the causes of emergency endoscopy in this study. Of the 16 cases in 2020, the most commonly performed endoscopic therapies were stone removal and stent placement, which showed a pattern similar to that in previous years. With the introduction of a simple and schematic algorithm from the ER door to the endoscopic center, no case of SARS-CoV-2 infection in other patients or medical personnel was reported in our center [21]. There was one case of mortality in a patient with severe biliary pancreatitis, in which an emergency ERCP was performed because of the impacted CBD stone. Despite aggressive treatment, however, he died due to multi-organ failure.

Our study has a few limitations. First, this was a single-center observational study with a limited number of patients during a short period. Large and long-term studies are required to determine changes in endoscopic activities. Second, follow-up data of elective ERCPs were lacking. There is a possibility that bile duct malignancy, such as hilar malignancy, might have affected the survival of elderly patients. Third, patients who visited the ER and underwent ERCP were labeled as emergency ERCP patients regardless of the situation; therefore, there is a possibility that non-emergency patients might have been included in this group, such as jaundiced patients without cholangitis or asymptomatic CBD stones, particularly in 2018 and 2019.

CONCLUSION
In conclusion, ERCP is a well-established and indispensable technique in the field of pancreatobiliary emergencies. The novel viral outbreak resulted in a significant reduction in the number of ERCP procedures performed, particularly emergency ERCPs, from February 18 to March 28, 2020. In practice, the ERCP procedure can function as a potential vector for viral transmission, which can be a threat to both HCPs and other patients. All emergency ERCP procedures were performed successfully and safely without causing infection in our endoscopy center. Nevertheless, a long-term follow-up is warranted to observe the clinical outcomes of ERCP procedures after the cessation of the COVID-19 outbreak.

ARTICLE HIGHLIGHTS
Research background
The coronavirus disease 2019 (COVID-19) outbreak has markedly influenced endoscopic patterns. Endoscopic retrograde cholangiopancreatography (ERCP) is an essential technique for pancreatobiliary disease but increases the risk of exposure to virus-containing body fluid; however, the impact of COVID-19 on ERCP is unknown.

Research motivation
Unlike upper endoscopy and colonoscopy, pancreatobiliary disorders such as bile duct obstruction or associated cholangitis usually require urgent treatment. However, endoscopy can cause human-to-human viral transmission by producing massive aerosol droplets throughout the procedure, particularly during therapeutic interventions such as ERCP. Due to the lack of experience and the highly contagious features of COVID-19, all measures to stop the viral spread in and outside the hospital were prioritized.
Research objectives
This study aimed to compare and to analyze the change in the number of ERCP procedures, causes, and clinical outcomes of emergency ERCP between pre-COVID-19 and during the COVID-19 outbreak in Daegu city, the worst-hit area in South Korea.

Research methods
This retrospective cohort study included patients aged ≥ 18 years who underwent ERCP between February 18 and March 28, 2020, at a tertiary hospital. Baseline demographics, causes of an ER visit, blood chemistry, ERCP indications, and endoscopic details relevant to ERCP were collected and compared with those from the same period in 2018 and 2019 as control groups.

Research results
The number of ERCP procedures in 2018 and 2019 decreased by 20.2% and 56.6%, respectively, compared with that in 2020 (P < 0.01); among the 113 emergency ERCPs, the observed numbers in 2018 (n = 42) and 2019 (n = 55) dramatically dropped by 61.9% and 70.9%, respectively, compared with that in 2020 (n = 16). No case of ERCP-related infection has been reported in medical providers or other patients.

Research conclusions
The COVID-19 outbreak significantly reduced the number of ERCPs; however, no difference was observed in the indications and endoscopic interventions before and during the COVID-19 outbreak.

Research perspectives
All emergency ERCP procedures were performed safely without causing any viral infection in our endoscopy center. However, a long-term follow-up is warranted to observe the clinical outcomes of ERCP procedures after the cessation of the COVID-19 outbreak.

REFERENCES


Kim KH et al. Impact of ERCP following COVID-19


Randomized Controlled Trial

Effect of family caregiver nursing education on patients with rheumatoid arthritis and its impact factors: A randomized controlled trial

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Clinical trial registration statement: Not applicable.

Informed consent statement: All study participants, or their legal guardian, provided informed consent.

Abstract

BACKGROUND
Rheumatoid arthritis (RA) is a common autoimmune disease. Nursing education for family caregivers is considered a workable and effective intervention, but the validity of this intervention in RA has not been reported.

AIM
To explore whether family caregiver nursing education (FCNE) works on patients with RA and the factors that influence FCNE.

METHODS
In this randomized controlled study, a sample of 158 pairs was included in the study with 80 in the intervention group and 78 in the control group. Baseline data of patients and caregivers was collected. The FCNE intervention was administered to caregivers, and inflammation level indicators, disease activity indicators, and mood disorder indicators of patients were followed up and analyzed.

RESULTS
Baseline characteristics of the intervention and the control groups had no significant difference. Indicators were significantly reduced in the intervention group compared to the control group. The FCNE intervention showed significant differences in stratification of relationship, education duration, and mood disorder indicators of patients were followed up and analyzed.

CONCLUSION
The effect of FCNE on RA is multifaceted, weakening inflammation level, alleviating disease activity and relieving mood disorder. Relationship between caregiver and patient, caregiver’s education level and patient’s age may act as impact factors of FCNE.
written consent prior to study enrollment.

**Conflict-of-interest statement:** The authors declare that they have no conflict of interest.

**Data sharing statement:** Technical appendix, statistical code and dataset available from the corresponding author at jinglijing0311@163.com. Participants gave informed consent for data sharing.

**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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**Core Tip:** Education for family caregivers is considered a workable and effective intervention, but the validity of this intervention in rheumatoid arthritis (RA) has not been reported. Therefore, we designed a health education program called family caregiver nursing education, a series of professional training courses for family caregivers that focused on care techniques of RA patients and main points of RA-related knowledge. We chose a total of nine characteristic indicators in terms of inflammation level, disease activity and mood disorder for a 6 mo intervention and follow-up to assess the effect of family caregiver nursing education on RA in multiple ways.

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## INTRODUCTION

Rheumatoid arthritis (RA) is a common autoimmune disease characterized by chronic inflammation[1]. A recent survey has been reported that the prevalence of RA in the United States population ranges from 0.5% to 0.8%, with rates as high as 1.7% for specific groups of older adults[2]. In China, RA is one of the top ten chronic diseases, and its prevalence has been recorded at 1.02%[3]. Patients not only suffer from reduced physical function but also frequently experience increased mental stress accompanied by depression and anxiety[4]. As RA patients are more likely to be diagnosed between the ages of 35 and 60[5] and the disease is persistent and difficult to eradicate, long-term care is a necessity. Family nursing can no longer be ignored in the care of patients, and family caregivers have become the mainstay of caregivers[6].

Family nursing is gradually emerging, and support for family caregivers is increasingly valued[7]. Nursing education for family caregivers is considered as a workable and effective intervention that directly improves their disease knowledge, physiological management abilities and psychological support skills to provide better care to patients[8]. Studies have shown this intervention plays an active role in the course of specific diseases including stroke[9], asthma[10] and kidney injury[11]. However, the effectiveness of care education for family caregivers of patients with RA has not been reported. In this study, we designed a health education program called family caregiver nursing education (FCNE), a series of professional training courses for family caregivers that focused on care techniques of RA patients and main points of RA-related knowledge. Indicators of inflammation level, disease activity and mood disorder were also collected and followed up to explore the effect of FCNE on patients with RA and its impact factors.

## MATERIALS AND METHODS

**Trial design and participants**

Participants included RA patients and their corresponding family caregivers, and the effect on patients was observed by implementing the intervention on caregivers. Patients were selected from those who were hospitalized in the immune-rheumatology department of a governmental and university-affiliated hospital from June 2017 to December 2018, on the basis of the 2010 revised RA classification criteria of the American Rheumatism Association, the European League Against Rheumatism and the 1987 American College of Rheumatology classification[12]. Each patient was
required to have a family carer, on the basis of being the primary caregiver and having lived with the patient for at least 5 years. All patients were not on stable systemic therapy for 1 year, and caregivers have never received training in RA. For this study, the questionnaire had five dimensions for the patient and fifteen for the caregiver for a total of twenty items. According to the Kendall working guidelines, the sample size of the questionnaire was at least five to ten times the number of variables. So we took eight times the number of variables and took into account a 25% margin of error. The sample size was calculated as \( N = (15 + 5) \times 8 \times (1 + 25\%) = 200 \). A total of 200 pairs of participants were recruited, among which 158 were included in the final analysis in either the intervention group \((n = 80)\) or the control group \((n = 78)\). Each pair of patients and family caregivers signed an informed consent form, and the study was approved by the hospital ethics committee. The flow diagram for study participants was shown in Figure 1.

**Randomization**

By using the computer assignment procedure in SPSS 21.0, sequential numbers were generated and placed in a sealed opaque box, and a separate researcher was arranged to randomly assign the selected participants to the intervention group or the control group. Until all the baseline questionnaires were completed, neither the researchers nor the participants were aware of the group assignment[13].

**Intervention**

All patients in both groups received rheumatoid routine primary care and were treated with a uniform regimen of DMARDs represented by methotrexate plus hormonal medication represented by prednisone acetate for 6 mo. In addition, the family caregivers of the intervention group received the FCNE for 6 mo. All interventions were unchanged during the trial.

The original content of FCNE came from literature reviews and consensus guidelines in National Guideline Clearinghouse[14]. A total of eight experienced rheumatologists and nurses then worked together to add, delete, adapt and revise the teaching content in conjunction with expert advice and to develop an appropriate teaching scheme based on the predetermined study period. The final items covered seven primary areas: psychological guidance, medication guidance, functional exercise, diet, clean skin care, care during the active phase of the lesion and care during the stable phase of the lesion. In addition, a brief supplementary course on the epidemiology, pathogenesis and clinical symptoms of RA was interspersed between the main items.

FCNE was carried out around five major approaches: group education, individual training, distribution of written materials, web-based information dissemination and appraisal system. A 45 min one-to-one training and a 1.5 h group training were conducted at regular intervals each month, for a total of six one-to-one training sessions and six group training sessions. Each group training was followed by a workshop on the content of the course and the distribution of the corresponding paper material. Electronic data were released through the network at irregular intervals. A week after each session, participants were followed up by telephone calls of 15 min each, through which researchers checked acceptance and implementation of the last session and arranged additional courses if required[15]. Every 2 wk after the training was completed, an examination was used to test and evaluate the effectiveness of the teaching. For subjects who failed the test, retraining and make-up examinations were conducted. Those who still failed the make-up examination were removed from the intervention group. Those with an attendance rate of less than 80% were also removed from the intervention group. All of the above assessments were randomly assigned to five independent researchers and completed using a double-blind method.

**Data collection and processing**

General information of patients and caregivers was collected from questionnaire or medical chart at baseline. Indicators of patients including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), tumor necrosis factor (TNF-α), tender joint counts out of 28 joints (TJC28), swollen joint counts out of 28 joints (SJC28), pain on visual analogue scale, provider global assessment by visual analogue scale (PGA), patient global assessment of disease activity by visual analogue scale (PtGA), health assessment questionnaire (HAQ), self-rating depression scale (SDS) and self-rating anxiety scale (SAS) were followed up at baseline, 1st month, 3rd month and 6th month when patients came for their routine visits. ∆CRP, ∆ESR, ∆TNF-α, clinical disease activity index (CDAI), simplified disease activity index (SDAI) and disease activity
score with 28-joint count (DAS28) were respectively calculated by the following formulas: ∆CRP = (baseline CRP - 6th mo CRP)/baseline CRP; ∆ESR = (baseline ESR - 6th mo ESR)/baseline ESR; ∆TNF-α = (baseline TNF-α - 6th mo TNF-α)/baseline TNF-α; CDAI = TJC28 + SJC28 + PGA + PtGA; SDAI = TJC28 + SJC28 + PGA + PtGA + CRP; DAS28 = 0.56√TJC28 + 0.28√SJC28 + 0.70LnESR + 0.014PtGA.

Outcome measures

General information: General information included the patient’s age, gender, presence of comorbidity (hypertension, coronary heart disease and diabetes), drug therapy and disease duration and the caregiver’s age, gender, work status, relationship with the patient and education duration (representing the education level).

Indicators of inflammation level: CRP, ESR and TNF-α were used to assess the biochemical level of inflammation; ∆CRP, ∆ESR and ∆TNF-α were used to assess the degree of decline in inflammatory indicators. CRP, ESR and TNF-α are considered to be the main pathophysiological factors in RA. Biomarkers in the blood become higher when inflammation is severe, while ∆CRP, ∆ESR and ∆TNF-α rise accordingly when inflammation subsides[16].

Indicators of disease activity: CDAI, SDAI, DAS28 and HAQ were used to evaluate the level of disease activity in RA. The specific formulas for CDAI, SDAI and DAS28 have been listed previously with TJC28, SJC28, PGA, PtGA, CRP and ESR. HAQ covers daily activities such as dressing, standing, eating, walking and hygiene. High values of these scores indicate deterioration in physical function[15].

Indicators of mood disorder: SDS and SAS were used to appraise the level of mental health and mood disorder. The SDS and SAS assess 20 symptoms of depression and anxiety, respectively, rated numerically on a scale for each item, with higher scores indicating a higher intensity of the symptom in question. SDS ≥ 50 is defined as depression, 50-59 as mild depression, 60-69 as moderate depression and 70 or more as severe depression. SAS ≥ 50 is defined as anxiety, 50-59 as mild anxiety, 60-69 as moderate anxiety and 70 or more as severe anxiety[17]. SDS and SAS have been used to test the psychological level of RA patients[18].
Statistical analysis
This study utilized SPSS 21.0 software to process the data. A total of 158 cases were ultimately included in the statistical analysis, including 80 cases in the intervention group and 78 cases in the control group. If the quantitative data were normally distributed, the mean ± SD were used to describe. If the data showed a skewed distribution, the median and interquartile range were applied. Frequency and percentage reports were used to describe the categorical data. Depending on the type of data analyzed, baseline data was analyzed using the t-test, the Mann-Whitney U test and the χ² test. For follow-up data, repeated measures analysis of variance (ANOVA) was used to analyze the difference, and Pearson correlation analysis was used to analyze the correlation. All the statistical analyses were considered significant at P < 0.05.

RESULTS

Baseline characteristics
In total, 80 pairs were included in the statistical analysis in the intervention group and 78 pairs in the control group. For family caregivers, the majority were women with full-time jobs. The mean age was 47.4-years-old, ranging from 28-years-old to 65-years-old. The median education duration was 9 years, which meant they had senior high school education or near university education. For patients, most were also female, and the mean age was 59.2-years-old distributed between 34-years-old and 86-years-old. Patients with the median disease duration of 5.5 years were mainly treated with DMARDs + glucocorticoid and had no comorbidity. In addition, indicators were counted to assess the patient’s initial condition. There was no significant difference in all general information and indicators between the intervention group and the control group at baseline. Specific values and statistical results of the characteristics were shown in Table 1.

Effect of FCNE on patients with RA
FCNE reduced indicators of inflammation level: All follow-up indicators of the intervention group and the control group were shown in Table 2. Repeated measures ANOVA was performed. Main effect of time and interaction effect of time × group were significant in all inflammation indicators (P < 0.001), meaning that they had a downward trend over time while time interacted with FCNE. Effect of group was also significant in CRP, ESR and TNF-α (P < 0.001, P = 0.001, P = 0.019, respectively), implying that FCNE promoted containment of inflammation and reduced indicators of inflammation level in RA.

FCNE reduced indicators of disease activity: Except that the repeated measures ANOVA result of HAQ did not show significant difference, effect of time and time × group was significant in CDAI, SDAI and DAS28 (P < 0.001), and effect of group was significant in CDAI, SDAI and DAS28 (P < 0.001, P < 0.001, P = 0.013, respectively), indicating that FCNE helped to curb disease progression and reduced indicators of disease activity in RA.

FCNE reduced indicators of mood disorder: According to the scoring criteria, at baseline, 77 people were depressed in the intervention group (56 mildly depressed and 21 moderately depressed) and 71 in the control group (41 mildly depressed, 26 moderately depressed and 4 severely depressed), with no significant difference; after 6 mo of follow-up, 10 people were depressed in the intervention group significantly lower than 39 in the control group (P < 0.001). Similarly, 54 people in the intervention group suffered from anxiety at baseline (32 with mild anxiety, 19 with moderate anxiety and 3 with severe anxiety) and 48 in the control group (26 with mild anxiety, 14 with moderate anxiety and 8 with severe anxiety), with no significant difference; after 6 mo of follow-up, 6 people in the intervention group suffered from anxiety significantly lower than 23 in the control group (P < 0.001). In addition, the repeated measures ANOVA result also showed that time, time × group and group effect of SDS and SAS was significant (P < 0.001). All these suggested that FCNE contributed to mental health and reduced indicators of mood disorder in RA.

Influencing factors of FCNE
Relationship between caregiver and patient: The intervention group was reclassified based on the relationship between caregiver and patient: 23 cases in son or daughter group, 30 cases in spouse group and 27 cases in other relationships group. Inflam-
<table>
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<th>Characteristics</th>
<th>Total, n = 158</th>
<th>IG, n = 80</th>
<th>CG, n = 78</th>
<th>t</th>
<th>z</th>
<th>$x^2$</th>
<th>P value</th>
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<td>19 (24.4)</td>
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<td>0.933</td>
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<td>Male</td>
<td>114 (72.2)</td>
<td>55 (68.8)</td>
<td>59 (75.6)</td>
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<td>16 (20.5)</td>
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<td>27 (33.8)</td>
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<td>9.0 (6.0)</td>
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<td>Male</td>
<td>25 (15.8)</td>
<td>12 (15.0)</td>
<td>13 (16.7)</td>
<td></td>
<td></td>
<td></td>
<td>0.774</td>
</tr>
<tr>
<td>Female</td>
<td>133 (84.2)</td>
<td>68 (85.0)</td>
<td>65 (83.3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comorbidity, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.118</td>
</tr>
<tr>
<td>Yes</td>
<td>28 (17.7)</td>
<td>15 (18.8)</td>
<td>13 (16.7)</td>
<td></td>
<td></td>
<td></td>
<td>0.732</td>
</tr>
<tr>
<td>No</td>
<td>130 (82.3)</td>
<td>65 (81.3)</td>
<td>65 (83.3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug therapy, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.076</td>
</tr>
<tr>
<td>DMARDs + GC</td>
<td>117 (74.1)</td>
<td>60 (75.0)</td>
<td>57 (73.1)</td>
<td></td>
<td></td>
<td></td>
<td>0.783</td>
</tr>
<tr>
<td>DMARDs + GC + biologics</td>
<td>41 (26.0)</td>
<td>20 (25.0)</td>
<td>21 (26.9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease duration (yr), mean (IQR)</td>
<td>5.5 (6.0)</td>
<td>5.0 (5.0)</td>
<td>6.5 (4.3)</td>
<td>-1.816</td>
<td></td>
<td></td>
<td>0.069</td>
</tr>
<tr>
<td>CRP (mg/L), mean ± SD</td>
<td>18.00 ± 5.52</td>
<td>17.74 ± 5.65</td>
<td>18.25 ± 5.41</td>
<td>-0.579</td>
<td></td>
<td></td>
<td>0.563</td>
</tr>
<tr>
<td>ESR (mm/h), mean ± SD</td>
<td>35.49 ± 5.33</td>
<td>35.61 ± 5.29</td>
<td>35.36 ± 5.41</td>
<td>0.298</td>
<td></td>
<td></td>
<td>0.766</td>
</tr>
<tr>
<td>TNF-α (pg/mL), mean ± SD</td>
<td>43.47 ± 9.58</td>
<td>43.93 ± 9.04</td>
<td>42.99 ± 10.15</td>
<td>0.618</td>
<td></td>
<td></td>
<td>0.537</td>
</tr>
<tr>
<td>CDAI, mean ± SD</td>
<td>20.00 ± 7.63</td>
<td>19.97 ± 7.29</td>
<td>20.04 ± 8.01</td>
<td>-0.060</td>
<td></td>
<td></td>
<td>0.952</td>
</tr>
<tr>
<td>SDAI, mean ± SD</td>
<td>38.00 ± 8.70</td>
<td>37.71 ± 8.67</td>
<td>38.29 ± 8.78</td>
<td>-0.420</td>
<td></td>
<td></td>
<td>0.675</td>
</tr>
<tr>
<td>DAS28, mean ± SD</td>
<td>4.92 ± 1.30</td>
<td>4.94 ± 1.29</td>
<td>4.89 ± 1.33</td>
<td>0.251</td>
<td></td>
<td></td>
<td>0.802</td>
</tr>
<tr>
<td>HAQ, mean (IQR)</td>
<td>1.12 (0.99)</td>
<td>1.21 (0.99)</td>
<td>1.11 (0.99)</td>
<td>-0.442</td>
<td></td>
<td></td>
<td>0.659</td>
</tr>
<tr>
<td>SDS, mean ± SD</td>
<td>57.87 ± 5.51</td>
<td>57.31 ± 4.77</td>
<td>58.45 ± 6.15</td>
<td>-1.300</td>
<td></td>
<td></td>
<td>0.196</td>
</tr>
<tr>
<td>SAS, mean ± SD</td>
<td>53.82 ± 9.68</td>
<td>54.43 ± 8.34</td>
<td>53.21 ± 10.91</td>
<td>0.791</td>
<td></td>
<td></td>
<td>0.430</td>
</tr>
</tbody>
</table>

IG: Intervention group; CG: Control group; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; TNF-α: Tumor necrosis factor; SDAI: Simplified disease activity index; DAS28: Disease activity score with 28-joint count; CDAI: Clinical disease activity index; HAQ: Health assessment questionnaire; SDS: Self-rating depression scale; SAS: Self-rating anxiety scale; SD: Standard deviation; IQR: Interquartile range; GC: Glucocorticoid.
Table 2 Indicators of the intervention group and the control group (mean ± SD)

<table>
<thead>
<tr>
<th>Indicators</th>
<th>IG, n = 80</th>
<th>CG, n = 78</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>1st mo</td>
</tr>
<tr>
<td>Inflammation level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>17.74 ± 5.65</td>
<td>15.05 ± 4.51</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>35.61 ± 5.29</td>
<td>31.57 ± 4.81</td>
</tr>
<tr>
<td>TNF-α (pg/mL)</td>
<td>43.93 ± 9.04</td>
<td>38.22 ± 8.05</td>
</tr>
<tr>
<td>Disease activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDAI</td>
<td>19.97 ± 7.29</td>
<td>20.00 ± 7.25</td>
</tr>
<tr>
<td>SDAI</td>
<td>37.71 ± 8.67</td>
<td>35.06 ± 8.11</td>
</tr>
<tr>
<td>DAS28</td>
<td>4.94 ± 1.29</td>
<td>4.56 ± 1.00</td>
</tr>
<tr>
<td>HAQ</td>
<td>1.39 ± 0.64</td>
<td>1.04 ± 0.59</td>
</tr>
<tr>
<td>Mood disorder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SDS</td>
<td>57.51 ± 4.77</td>
<td>46.60 ± 5.67</td>
</tr>
<tr>
<td>SAS</td>
<td>54.43 ± 8.34</td>
<td>49.81 ± 7.52</td>
</tr>
</tbody>
</table>

IG: Intervention group; CG: Control group; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; TNF-α: Tumor necrosis factor; SDAI: Simplified disease activity index; DAS28: Disease activity score with 28-joint count; CDAI: Clinical disease activity index; HAQ: Health assessment questionnaire; SDS: Self-rating depression scale; SAS: Self-rating anxiety scale.

...mission indicators of these three groups were shown in Table 3. For CRP, effect of relationship-group was significant (P = 0.033), and further pairwise comparisons revealed that spousal group had a significantly lower reduction in CRP than other relationships group (P = 0.012). For ESR, relationship-group effect was also significant (P = 0.041), and pairwise comparisons showed that ESR reduction of spousal group was significantly lower than that of other relationships group (P = 0.024), while son or daughter group had a significantly lower ESR reduction than other relationships group (P = 0.035). However, TNF-α did not show significant stratification. Both CRP and ESR results suggested a more efficient effect of FCNE for spousal relationship, resulting in a more pronounced reduction in inflammatory indicators. Relationship between caregiver and patient was an impact factor of FCNE.

Education duration of caregiver: The means of ∆CRP, ∆ESR and ∆TNF-α were 84.74% (SD = 14.32%), 31.01% (SD = 14.89%) and 32.03% (SD = 9.75%), respectively. The results of Pearson correlation analysis showed that ∆CRP (r = 0.516, P < 0.001), ∆ESR (r = 0.507, P < 0.001) and ∆TNF-α (r = 0.734, P < 0.001) were significantly and positively correlated with education duration. The longer the caregiver’s education duration, the higher the patient’s inflammation decline, and the better the effect of FCNE, which meant that caregiver’s education duration was an impact factor of FCNE.

Age of patient: The intervention group was reclassified by patient age: 42 cases in middle-aged group and 38 cases in elderly group (the World Health Organization defines 45 years to 59 years as middle-aged people and 60 years and above as elderly people). Disease activity and mood disorder indicators of these two groups were shown in Table 4. For disease activity indicators, except for no difference in HAQ stratification, effect of age-group in CDAI, SDAI and DAS28 was significant (P < 0.001). CDAI, SDAI and DAS28 were higher in the elderly group than in the middle-aged group at baseline, but the level of the elderly group was approaching that of the middle-aged group by the 6th month of follow-up. The degree of disease activity decline was more evident in the elderly group.

For mood disorder indicators, age-group effect for both SDS (P = 0.014) and SAS (P < 0.001) was significant, meaning that the middle-aged group with higher mood disorder scores before the intervention was close to or even lower than the elderly group after 6 mo of FCNE intervention. FCNE had a significant psychological improvement effect on the middle-aged group and a significant disease mitigation effect on the elderly group, showing that patient’s age was another impact factor of FCNE.
Table 3 Indicators of the intervention group grouped by relationship (mean ± SD)

<table>
<thead>
<tr>
<th>Indicators</th>
<th>Son or daughter, n = 23</th>
<th>Spouse, n = 30</th>
<th>Others, n = 27</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP (mg/L)</td>
<td>5.03 ± 4.43</td>
<td>5.45 ± 4.85</td>
<td>4.59 ± 4.10</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>38.50 ± 5.57</td>
<td>36.11 ± 4.36</td>
<td>32.54 ± 3.97</td>
</tr>
<tr>
<td>TNF-α (pg/mL</td>
<td>47.25 ± 40.65</td>
<td>33.57 ± 29.91</td>
<td>32.24 ± 28.84</td>
</tr>
</tbody>
</table>

CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; TNF-α: Tumor necrosis factor.

Table 4 Indicators of the intervention group grouped by patient’s age (mean ± SD)

<table>
<thead>
<tr>
<th>Indicators</th>
<th>Middle-aged people, n = 42</th>
<th>Elderly people, n = 38</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDAI</td>
<td>14.48 ± 4.04</td>
<td>18.13 ± 10.02</td>
</tr>
<tr>
<td>SDAI</td>
<td>32.88 ± 30.14</td>
<td>44.71 ± 38.04</td>
</tr>
<tr>
<td>DAS28</td>
<td>4.09 ± 0.75</td>
<td>3.84 ± 0.72</td>
</tr>
<tr>
<td>HAQ</td>
<td>1.34 ± 0.63</td>
<td>1.24 ± 0.66</td>
</tr>
<tr>
<td>SDS</td>
<td>60.90 ± 48.00</td>
<td>45.05 ± 30.45</td>
</tr>
<tr>
<td>SAS</td>
<td>60.90 ± 48.11</td>
<td>43.66 ± 42.11</td>
</tr>
</tbody>
</table>

CDAI: Clinical disease activity index; SDAI: Simplified disease activity index; DAS28: Disease activity score with 28-joint count; HAQ: Health assessment questionnaire; SDS: Self-rating depression scale; SAS: Self-rating anxiety scale.

**DISCUSSION**

Traditional nursing education for RA is aimed at patients. In addition to the patients themselves, to a certain extent, the quality of life for patients also depends on the support of their families[19]. A study has proven that the mood of caregivers also affected the disease progression of RA patients[20]. More studies on family interventions have been published in recent years, and the majority of these showed benefit to the identified patient[21]. But there is little research on nursing education or family nursing for RA patients. Therefore, we designed the FCNE. For the selection of outcome measures, we chose a total of nine characteristic indicators in terms of inflammation level, disease activity and mood disorder for a 6 mo intervention and follow-up. The aim was to assess the effect of FCNE on RA and its influencing factors in a holistic manner.

Initially, we selected biochemical indicators of inflammation for evaluation due to their importance in the pathogenesis of RA[22]. In addition to the two traditional indicators of CRP and ESR[23], we also included TNF-α, an emerging marker of RA [16]. The results found that the intervention group showed a significantly better reduction in all three indicators than the control group, which corroborated the reliability of TNF-α. Afterwards, we calculated and appraised the disease indexes for RA and found that FCNE had a distinct advantage for the reduction of CDAI, SDAI and DAS28 but did not show the same effect for HAQ, probably due to errors caused by small values with insignificant changes. More and more care models were proven to work for RA, and a nurse-led study found that nursing education by telephone was effective in improving medication adherence in RA patients[14]. As a rising approach, FCNE plays a positive role in the prognosis of diseases including lung cancer[24] and stroke[25]. FCNE enhances caregivers’ knowledge of the disease and improves nursing skills, which is conducive to providing better care to patients while identifying risk factors and complications in time to reduce injuries. It also provides a communication platform, bringing participants together for exchange and discussion, which not only allows them to obtain more practical experience but also benefits the release of
negative emotions\cite{25}.

According to surveys, the prevalence of depression in RA patients is between 14.8% and 48.0%, which is twice that of the general population\cite{26} and increases the mortality rate of RA patients to a certain extent\cite{27}. Relevant studies have shown that FCNE can reduce depression, anxiety and self-harm in certain patient populations, such as ischemic stroke patients\cite{28}, older patients\cite{29} and suicidal patients\cite{30}. In this study, the effect of FCNE on alleviating mood disorder and promoting mental health in RA patients was similarly confirmed. This role of FCNE may be achieved by facilitating family communication, relieving misunderstandings and conflicts and supporting the maintenance of an enabling environment characterized by understanding and cooperation\cite{31,32}. The effectiveness of mindfulness interventions for RA\cite{33} also supported this speculation.

After confirming the effect of FCNE on RA, we had a stratified study of the intervention group according to different factors to explore the possible influencing factors of FCNE. The results showed that inflammation reduction was further enhanced when the caregiver was a spouse and had an advanced education level. A cross-sectional study indicated that spouses took on a vital role as family caregivers but also carried more of the role load\cite{34}. Besides, we found that the initial disease activity was higher but declined faster in elderly people compared to middle-aged people. Interestingly, the initial mood disorder was more severe but resolved more rapidly in middle-aged people compared to elderly people. A survey revealed that younger caregivers were more likely to report adverse psychological symptoms\cite{35}. Thus, we considered that the relationship between caregiver and patient, caregiver’s education level and patient’s age operated as influencing factors affecting the efficacy of FCNE, which also suggests priorities for FCNE participants, such as giving preference to spouses or caregivers with high education level as they are likely to have better intervention outcomes.

In this study we were surprised to find that FCNE had a significant improvement in a number of indicators, particularly inflammatory indicators including TNF-α, which we hypothesize is related to FCNE improving adherence to drug treatment. Patients with positive adherence to medication may be better able to contain the disease and slow its progression\cite{36}. Several previous studies have confirmed the effectiveness of educational interventions tailored to RA, which are achieved by improving and maintaining patients’ medication adherence\cite{37,38}. Nurses are increasingly prominent in this process, assisting patients to improve adherence and self-management\cite{39}. Studies have shown that education by experienced rheumatology nurses can help promote patient behavior, including maintaining medication adherence\cite{40} and that FCNE, as a nurse-led intervention that takes into account patient needs and disease characteristics, can help increase patients’ confidence, motivation and skills to take their medication in the long term\cite{41}. Further research is needed on the specific mechanisms that improve indicators including biochemical levels of inflammation and more evidence related to improving adherence.

**Limitations**

This study has some limitations. Primarily, the sample was small, and it was a single center study. The conclusions have yet to be validated in a large sample and multicenter experiment. Furthermore, there was a slight improvement in some indicators in the control group, which we speculate may be related to the conventional treatment they received and remains to be demonstrated. Finally, based on follow-up data for all indicators, the effect of FCNE is most pronounced after 1 mo and especially between 3 and 6 mo, demonstrating its short-term impact. However, the lack of long-term follow-up has demonstrated its role in relation to the chronic effects.

**CONCLUSION**

The effect of FCNE on RA is multifaceted, weakening inflammation level, alleviating disease activity and relieving mood disorder. Relationship between caregiver and patient, caregiver’s education level and patient’s age may act as impact factors of FCNE.
ARTICLE HIGHLIGHTS

Research background
Rheumatoid arthritis (RA) is a common disease that requires long-term care, and nursing education for family caregivers is considered as a workable and effective intervention.

Research motivation
The effectiveness of care education for family caregivers of patients with RA has not been reported.

Research objectives
This study aimed to explore whether family caregiver nursing education (FCNE) works on patients with RA and the factors that influence FCNE.

Research methods
In this study, we designed a health education program called FCNE, a series of professional training courses for family caregivers that focused on care techniques of RA patients and main points of RA-related knowledge. The FCNE intervention was administered to caregivers, and inflammation level indicators, disease activity indicators and mood disorder indicators of patients were followed up and analyzed.

Research results
Indicators were significantly reduced in the intervention group compared to the control group. The intervention group showed significant differences in stratification of relationship, education duration and age.

Research conclusions
The effect of FCNE on RA is multifaceted, weakening inflammation level, alleviating disease activity and relieving mood disorder. Relationship between caregiver and patient, caregiver’s education level and patient’s age may act as impact factors of FCNE.

Research perspectives
This study indicates that FCNE is feasible and efficient for patients with RA. It also suggests priorities for FCNE participants, such as giving preference to spouses or caregivers with high education level as they are likely to have better intervention outcomes.

ACKNOWLEDGEMENTS
The authors would like to thank all participants for their contribution to the study.

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Dealing with hepatic artery traumas: A clinical literature review

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Author contributions: Dilek ON wrote the majority of paper, critically revised the manuscript, and also coordinated the writing and correspondence of the paper; Atar A collected data and performed analysis and interpretation of data.

Conflict-of-interest statement: The authors declare that there are no conflicts of interest in connection with this paper.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

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Abstract

BACKGROUND
The hepatic artery (HA) is one of the most threatened vascular structures during hepatopancreatobiliary (HPB) surgeries and interventional procedures. It can be affected by many clinical pictures, especially tumors, due to its anatomical position and neighborhood.

AIM
To reveal the evolution and recent developments in the management of HA traumas in the light of the literature.

METHODS
In this article, 100 years of MEDLINE (PubMed) literature and articles including cases and series of HA injuries were reviewed, and the types of injury occurrence, treatment, and related complications and their management were compiled.

RESULTS
The risk of HA injury increases during cholecystectomies and pancreatoduodenectomies, among the most common operations. HA anatomy shows anomalies in approximately 15%-25% of the cases, further increasing this risk. The incidence of HA injury is not precisely known. Approaches that have evolved in recent years in managing patients with HA injury (laceration, transection, ligation, resection) with severe morbidity and mortality risk are reviewed in light of the current literature.

CONCLUSION
In conclusion, complications and deaths due to HA injury are less common today. The risk of complications increases in patients with hemodynamic instability, jaundice, cholangitis, and sepsis. Revealing the variations in the preoperative radiological evaluation will reduce the risks. In cases where HA injury is detected, arterial flow continuity should be tried to maintain with primary anastomosis,
INTRODUCTION

The hepatic artery (HA) is one of the most threatened vascular structures during hepatopancreatobiliary (HPB) surgeries and interventional procedures. HA can be affected by many clinical pathologies, especially tumors, due to its anatomical position and neighborhood. HA injury was one of the deadliest complications in the 1940s. In Edgecombe and Gardner's studies, it was found that 40 HA ligations were reported until 1950, and mortality developed in 50%-75% of them. They reported that HA was ligated during artery aneurysm, bile duct tumor, stomach tumor, and pancreatic tumor surgeries[1,2]. Although significant improvements in complications and mortality rates due to HA injuries have been detected in recent years, it continues to cause severe morbidity and mortality[3].

It has been reported that almost all animals (rats, rabbits, pigs) who underwent artery ligation experimentally died[4,5]. In experimental studies with dogs, it was reported that dogs were much more resistant to HA ligation. Especially in dogs that were given antibiotics (penicillin), it was better tolerated[3-7]. The use of antibiotics reduces the damage to the liver. Unlike other animals, it has been found that dogs have too much collateral in their liver. If collaterals are ligated, the dogs die within 24 h[5]. In the same period, it was reported that humans' average survival is 9-10 d due to artery ligation[1,2].

HA anomalies can also increase the risk of injury. HA anomalies are seen in 15%-25% of the population[2,3,8]. The most common anomaly is the replaced right HA (rRHA) anomaly. In the studies conducted, there is a common belief that more HA lacerations occur in patients with abnormalities[3,9,10].

In autopsy studies, it has been stated that deaths seen as a result of HA injury are mainly due to liver necrosis. Necrosis that occurs in the liver is diffuse or patchy[2,3,11]. Better results are obtained today with a better understanding of liver physiology, antibiotics, and improved intensive care conditions.

In this study, we aimed to examine the problems related to HA injuries, ligations, and resections encountered during our HPB operations, the approaches we applied, and the prevention methods.

Key Words: Hepatic artery; Injury; Anomaly; Ligation; Resection; Reconstruction

Core Tip: The hepatic artery (HA) is one of the most threatened vascular structures during hepatopancreatobiliary surgeries and interventional procedures. Complications and deaths due to HA injury are less common today. The risk of complications increases in patients with hemodynamic instability, jaundice, and cholangitis. Revealing the variations in the preoperative radiological evaluation will reduce the risks. In cases where HA injury is detected, arterial flow continuity should be tried to be maintained with primary anastomosis, arterial transpositions, or grafts. In cases where bile duct injury develops, patients should be directed to hepatopancreatobiliary surgery centers, considering the possibility of accompanying HA injury. Large-scale and multicentric studies are needed to understand better the early and long-term results of HA ligation and determine preventive procedures.

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DOI: https://dx.doi.org/10.12998/wjcc.v9.i28.8425
MATERIALS AND METHODS
In this article, 100 years of MEDLINE (PubMed) literature was reviewed. A clinical approach algorithm was developed by reviewing articles, including cases and series of HA injuries. In the study, keywords containing "hepatic artery" and (trauma or injury or resection or ligation or avulsion or transection or reconstruction) and their various combinations were researched.

Articles on HA transection and reconstruction, a challenging stage of liver transplantation, were not included in the study. Planned ligation, resection, and reconstructions for HA aneurysms were also briefly discussed. HA embolization has found many more clinical applications with the developing technological applications, and more studies have been reported in recent years (Figure 1). Here, therapeutic HA embolization is also mentioned because of its similarity to liver damage seen in HA traumas.

RESULTS
It was found that there were 6314 articles as a result of the Medline research. While one to two articles were published annually in the first 50 years, this number has increased gradually in the last 50 years and reached 109-237 articles per year (Figure 1). There are 1555 articles with the keywords "hepatic artery injury" or "hepatic artery trauma" and 468 articles with the word "hepatic artery ligation". In the first half of the century, it was found that HA traumas were mostly applied with unintentional ligations during gallbladder and stomach surgeries and in patients who underwent planned ligation for HA aneurysm. Fifty-seven studies with the phrase "hepatic artery resection" were identified; most of them conducted in the last 20 years. "Hepatic artery embolization" was the subject of 406 studies, and most of them were published in the previous 2 decades.

DISCUSSION
HA can be affected by many pathological conditions, especially tumors, due to its anatomical position and neighborhood (Figure 2). It is one of the most threatened vascular structures during HPB surgeries. The risk of injury is higher during Laparoscopic cholecystectomy (LC), pancreaticoduodenectomy (PD), and bile duct surgeries, which are among the most commonly performed operations in the abdomen[3,10,12,13]. HA can rarely be injured during stab wounds. HA has become an essential tool for diagnosis and treatment, and injuries occur in various forms depending on interventional procedures[14]. The incidence of HA injury is not precisely known. There is minimal data on this subject in the literature.

HA injury patterns
HA is injured mainly during HPB surgeries (Figure 3). However, injury can also occur during interventional procedures and with penetrating tools or blunt abdominal injuries. HA injury may develop with laceration, transection, avulsion, and unintended ligation/resection. Arterial blood flow can also be impaired with planned embolization, ligation, and resection of HA. Damage and invasion of HA by pathological processes such as infections and tumors may be another form of trauma. However, such injuries and interruption of HA blood flow cause less liver damage with collaterals and compensation mechanisms that come into play when developing in a chronic process[10,11,14,15].

Liver damage
The degree of liver damage after HA trauma depends on many factors (Table 1)[6,7,15-17]. Some of these are; 1-artery anatomy, 2-location of injury/ligation, 3-tissue bacterioloogy, 4-portal vein capacity, 5-collateral system and variations, 6-hemodynamic stability and complications, and 7-duration of HA trauma. The location of the injury/ligation is one of the most critical factors. Naturally, the blood supply tries to be preserved by prehepatic, intrahepatic, and perihepatic collateral mechanisms. The size of the damage caused by HA injury/ligation may vary depending on the size of the dissection performed in or around the liver's hilum. Collaterals are more likely to be involved in injuries at the right gastric artery or gastroduodenal artery.
Table 1 Factors affecting the extent of liver damage in hepatic artery injury

<table>
<thead>
<tr>
<th>Factors affecting the extent of liver damage in hepatic artery injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artery anatomy</td>
</tr>
<tr>
<td>Location of injury</td>
</tr>
<tr>
<td>Portal vein capacity</td>
</tr>
<tr>
<td>Collateral system and variations</td>
</tr>
<tr>
<td>Hemodynamic stability</td>
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<td>Complications/comorbidities</td>
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<tr>
<td>Duration of HA trauma (injury invasion)</td>
</tr>
<tr>
<td>Dimensions of the operation/intervention</td>
</tr>
<tr>
<td>Cholangitis (sepsis)</td>
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<tr>
<td>Tissue bacteriology</td>
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<tr>
<td>Hyperbilirubinemia</td>
</tr>
</tbody>
</table>

HA: Hepatic artery.

Figure 1 One-hundred-year distribution of publications associated with hepatic artery trauma (PubMed).

level. However, where the injury/ligation site goes towards the periphery, the risk of developing damage increases[4,5]. Bacterial contamination also increases the risk of infection and sepsis in necrotic liver tissue. The risk of developing infection also increases in patients with endoscopic retrograde cholangiopancreatography or percutaneous transhepatic cholangiogram stents[18]. Studies in the literature have been mostly carried out for patients with malignancy, but there is no study on the outcome of HA injury and catheterization association.

Damage to the liver resulting from impaired hepatic artery blood flow for any reason has similar characteristics. The fact that HA injury is acute or chronic is another factor affecting the outcome. Many studies have been reported without reconstruction following resections in patients with the HA invasion by the tumor[19,20]. The collateral system, which occurs in cases where arterial occlusion develops slowly, is thought to reduce/prevent liver damage after resection. However, many factors such as the size of the operation, accompanying procedures, patient's comorbidity, hemodynamic stability, cholangitis (sepsis), jaundice, and liver residue may affect the degree of liver damage and the clinical picture[16,20,21].

Unintended HA injuries (transection, ligation, resection, etc.)
The frequency of vascular injury during LC was reported as 0.25%, and the frequency
Figure 2: Types of hepatic artery trauma. HA: Hepatic artery.

Figure 3: Schematic description of pathologies and procedures that can lead to hepatic artery injury in hepatopancreatobiliary surgery. HA: Hepatic artery; HPB: Hepatopancreatobiliary.

The incidence of HA injury during PD ranges from 0.1% to 4.4%. During resections in patients with chronic pancreatitis or locally advanced tumors, the risk of vascular injury increases due to intense adhesions and inflammation[12,20,24]. In large tumors,
the risk of trauma may increase due to the displacement of anatomical structures and tumor invasion. Gaujoux et al[24] performed angiographies in their PD series of 545 cases to investigate postoperative ischemic conditions. They performed reconstructions on four patients with HA trauma and detected thrombus in angiographies taken in the postoperative period. Although 2 of the patients with thrombus underwent stenting, 1 thrombectomy, and 1 surgical revision, 3 died from liver necrosis and abscesses. They reported that 3%-4% of the cases after PD might develop liver ischemia. Also, ischemic conditions may cause deaths whose cause cannot be determined after surgery[3,24].

HA anomalies are another factor that increases the risk of injury[20,25]. Intertwined anatomical relationships between the pancreas and regional vessels become more complicated with the anomaly, increasing vascular injury risk. According to Michel’s classification, a typical anatomical structure (Type 1) is present in 52%-80% of cases. In cadavers and clinical trials, HA anomaly was found in 15%-25% of the cases. Shukla et al[26] stated that HA variations might show in 55%-79% of patients.

The incidence of rRHA was reported in the literature as 6.7%-19%[8,9,19,25-27]. Rubio et al[28]’s series stated that 73% of HA injury occurs in anomaly arteries. Eshuis et al[9] detected rRHA (18.8%) in 143 cases in the PD series of 758 cases and found injuries in 13 of them. At the same time, 10 patients had severe morbidity, while 1 patient died.

Accessory left HA (aLHA) incidence varies between 3%-34.2%. LHA or aLHA injury is more likely to occur during the celiac region’s dissection for gastric cancer[29,30].

HA trauma (rupture, thrombus, embolus, aneurysm, fistula) may develop accidentally and dislocated coils and stents during the interventional procedures. Vascular occlusion may impair HA blood flow. Blocking of the celiac trunk with thrombus can also interrupt HA blood flow. Lacerations, avulsions, and transections may develop due to sharp or blunt traumas[14,31].

**Planned HA ligation, resection, or embolization**

Many procedures and clinical studies in which HA was linked due to liver-derived pathologies (hepatocellular carcinoma, cirrhosis, portal hypertension, hemangioma, liver trauma, hemobilia) have been described[22,32-36]. It is predicted that by ligating HA, the amount of blood coming to the liver will decrease by 35%, whereas 95% of the blood requirement of a metastatic tumor in the liver will be reduced[32]. This effect is observed more in hypervascular metastases (hypernephroma, leiomyosarcoma, carcinoid, papillary adenocarcinoma of the pancreas)[32]. In their 19-disease invasive hepatocellular carcinoma series by Elsanousi et al[34], 13 of the patients who underwent ligations of HA on the lesion side and extrahepatic collateral divisions (HALED) received a complete response. They also reported that there were no abscesses and necrosis in the liver. However, there is not enough literature on this subject, and prospective studies are needed.

HA ligation, resection, and reconstruction can also be performed in HA aneurysm, pseudoaneurysm, abdominal aortic dissections, and HELLP syndrome[1,27,38]. In a meta-analysis including 374 hilar cholangiocarcinoma cases with HA resections performed by Chen et al[39], they found that the rate of R0 resection was higher in those who had HA resection. They found that mortality and morbidity were higher in the group with HA resection. However, there was no statistically significant difference in terms of complications. They also reported that the group’s survival with R0 resection and HA resection was much better when combined with adjuvant chemotherapy. During Appleby or Whipple procedures performed in borderline pancreatic tumors, aggressive tumor resections and artery resections have been increasingly performed due to tumor invasion[12,20,24,40]. Kleive et al[20] performed planned HA resection in 22 (1.43%) cases in a pancreactectomy series of 1535 cases. They reported that complications developed in a total of 16 (73%) cases, 10 of them (45%) being severe (thrombosis, bleeding, stenosis, liver necrosis, bile leakage). In the PD series of 323 patients by Asano et al[19], they detected rRHA anomaly in 51 patients. They performed planned resections in eight of them, and they reported that accidental injury occurred in one. They found that liver abscess developed in only 1 case in the series without reconstruction. There was no statistical difference with other patients in terms of demographics.

When compared with the complications seen after HA trauma, it was determined that fewer complications developed after planned HA resections[19,20]. The reasons for this may be technological developments, use of antibiotics and improvements in intensive care conditions, less liver damage in hemodynamically stable patients, and the contribution of collateral networks that develop during the invasion of the HA.
Angiography, stenting, coiling, and embolization are increasingly preferred methods for diagnosing and treating patients with hemodynamically stable liver trauma. Blood supply of the liver may also be impaired in patients who have been embolized for treatment purposes (tumor, metastasis, hemangioma, aneurysm, postoperative bleeding, etc.) or due to HA trauma. Selective embolization is better tolerated. It has been reported in the literature that the procedure is generally well-tolerated, and serious complications such as liver necrosis, cholangitis, and liver abscess are much less common\[14,41,42\]. In the Transarterial chemoembolization series of 2300 sessions applied by Sakamoto et al\[42\] to 850 patients, it was reported that complications (4 liver necrosis, 5 liver abscesses, 7 cholecystitis, 20 biloma, 6 aneurysms, and others) developed in 4.4% ($n = 102$ procedures) of the applications. Minimally invasive intervention and preservation of hemodynamic stability may contribute to better results.

**Complications/concomitant procedures**

Brittain et al\[16\] described the striking color change in the right liver lobe as an ominous sign in a patient who developed RHA laceration during cholecystectomy in 1964. The dimension of the damage varies according to the surgical intervention and the size of the HA injury. While most isolated HA injuries heal without symptoms, 11%-76% of patients with both RHA and bile duct trauma have been reported to have ischemic damage to the liver\[3,12,15,43\]. HA adventitia can be damaged by excessive manipulation, traction, and compression, and the risk of developing pseudoaneurysm increases, especially in pancreatic fistula cases\[9,26\].

As a result of HA injury, liver abcess, liver failure, anastomosis opening, late liver atrophy, and bile duct stenosis are the most common complications\[3,9,35,41,44\]. In the HA injury series of 21 cases, Landen et al\[3\] detected in the PubMed screen complications: Liver necrosis/abscess ($n = 14$), liver failure ($n = 3$), and anastomotic dehiscence ($n = 6$) were reported in 16 patients (76%), 3 of which had artery variations. They also noted that 11 of the patients were re-operated, and five (24%) died.

Due to ischemia of the bile duct wall caused by HA injury, anastomotic leakage may occur in the early period, and biliary strictures may develop in the long term\[15,43\]. The mucosal damage due to ischemia in the bile duct mucosa heals with inflammation, and fibrosis also leads to biliary stenosis. Recurrent cholangitis and hepatolithiasis can also be seen in patients with biliary stricture. In an autopsy study, stenosis in the biliary tract was found in 7% of cadavers with open cholecystectomy\[10,45\].

Right lobe atrophy can also be seen as a result of RHA injury or ligation. Alves et al\[15\] reported that in a series of 55 cases of postcholecystectomy biliary strictures after HA injury, they detected right lobe atrophy in 12 patients and performed right hepatectomy and Roux-en-Y hepaticojejunostomy.

Left lobe atrophy mainly develops due to left HA injury. Due to the high incidence of aLHA injury (36%-43%), it is accepted that liver left atrophy is more common after radical gastric resections. LHA injury is less common following PD surgeries. However, aLHA and LHA injuries can be seen more during dissections for stomach tumors\[15,29\].

**Treatment/reconstruction**

Management changes according to the type of HA injury (Figure 4). Reconstruction should be done in unintended HA traumas encountered during surgery\[12,15,20,24\]. If possible, reconstruction should be performed in the same session. Primary reconstruction of the laceration area should be tried first. In cases where proper HA transection develops, continuity of blood flow can be achieved by transposing the gastroduodenal artery, left gastric artery, or splenic artery. Reconstruction can also be performed using an allogeneic prosthetic graft (polytetrafluoroethylene, Dacron) or autografts (saphenous vein, gonadal vein, inferior mesenteric vein, renal vein, gastroepiploic artery) for long distances\[12,45-48\]. Anastomoses to be made with a microscope will increase the success. HA reconstruction can be beneficial in early postoperative injuries since liver necrosis occurs within the first 4 d. Li et al\[12\] reported that liver ischemia could be resolved before liver necrosis and atrophy develop in patients who undergo reconstruction within 4 d. However, reconstruction may not always be possible.

In planned ligations and embolizations, there is no need for additional procedures. In cases where artery resection is performed due to tumor invasion, there are different approaches regarding whether reconstruction is performed or not\[12,15,20,45,47,48\]. Primary reconstruction should be performed in planned resections due to benign pathologies (pseudoaneurysm, aneurysm, etc.). There is no need for additional procedures and clinical follow-up of the patient in planned ligations and emboliz-
Management of HA trauma

Figure 4 Algorithmic approach in the management of hepatic artery traumas. HA: Hepatic artery.

atations. All patients with or without reconstruction should be closely monitored for liver ischemia and early diagnosis and management of potential complications (Figure 4).

In HA injuries caused by penetrating or blunt trauma, the patient's hemodynamic status and the presence of acute abdominal findings (perforation) determine the treatment approach to be performed. Embolization is the first procedure to be performed in hemodynamically stable patients who develop HA injury during perforating injuries or blunt traumas and invasive procedures[35]. It has also been reported that blood flow can be achieved, and bleeding can be controlled with an endovascular stent in selected cases[14,48]. In the series of 32 patients by Tzeng et al[14], they reported that initial hemostasis was achieved in 30 of the patients due to embolization applied to patients referred with liver trauma and HA injury. Cholecystitis development after embolization is rare and varies according to the location of the trauma. Cholecystitis is also seen very rarely in selective embolizations. The conservative approach is primarily recommended in cases with cholecystitis. Cholecystectomy is recommended in patients with gallbladder necrosis and emphysematous cholecystitis[42,49].

Problem-oriented approaches should be preferred in the management of complications. Antibiotics and percutaneous drainage procedures are recommended in cases with liver abscesses[41]. In liver necrosis cases and subsequent hepatic failure, early prostaglandin E1 administration, hemodiafiltration, and plasma exchange can help recover the liver[50]. However, liver transplantation remains the only option in patients with extensive necrosis and liver failure[3,51].

Primary reconstruction is recommended first for the injuries of rRHA, but there is no consensus on this issue[19,52]. There are many series that are not reconstructed in rRHA injuries or after resections (Table 2). Okada et al[52] think differently about rRHA resections. They reported that trying to protect the rRHA reduces the chances of R0 resection and concluded that resection should be performed when the tumor is adjacent to or very close to rRHA.

Reconstruction could not be performed considering the resection area's width, the possibility of local recurrence, the occlusion of the arteries due to the tumor invasion process, and the liver's collateral compensation system.

Protection

Some various applications and procedures can be made to protect and increase liver blood supply and oxygenation. In the preoperative period, revealing HA and SMA's anatomy by radiological imaging plays a key role in preventing injury, preventing unnecessary procedures, and confirming the indication. Turrini et al[53] reported a
Table 2 Selected and summarized hepatic artery injury, ligation, resection, or embolization series in the literature

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Cases, n</th>
<th>Etiology</th>
<th>Anomaly</th>
<th>HA injuries (laceration/transsection, ligation/embolization)</th>
<th>Treatment options ligation/embolization reconstruction</th>
<th>Morbidity, n</th>
<th>Mortality, 90-d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brittain et al [16]</td>
<td>5</td>
<td>Cholecystectomy</td>
<td>NA</td>
<td>5 injury/ligation</td>
<td>No reconstruction, drainage</td>
<td>1% LA 1%</td>
<td></td>
</tr>
<tr>
<td>Alves et al [15]</td>
<td>55</td>
<td>Postcholecystectomy biliary tract stricture series (Bismuth type 3-4-5)</td>
<td>20?</td>
<td>20 RHA/RHA injury?, 2 HA pseudoaneurism, 4 portal vein injury</td>
<td>43 HJ, 12 right Hx</td>
<td>1% LA, 12% atrophy NA</td>
<td></td>
</tr>
<tr>
<td>Stewart et al [10]</td>
<td>261</td>
<td>Biliary tract injury during LC</td>
<td>NA</td>
<td>84 RHA injury</td>
<td>4 Hx, HJ, drainage</td>
<td>12% LA, 9% LN, 17% bleeding, 7% hemobilia, …</td>
<td></td>
</tr>
<tr>
<td>Gaujoux et al [24]</td>
<td>545</td>
<td>PD series</td>
<td>NA</td>
<td>4 injury (Postoperative detection)</td>
<td>4 (Thrombectomy, stenting, reconstruction) 2 left Hx</td>
<td>2% LN, 4% thrombosis, 1% HJ</td>
<td></td>
</tr>
<tr>
<td>Tzeng et al [14]</td>
<td>32</td>
<td>Liver trauma (15) + Interventional HA injury (17)</td>
<td>NA</td>
<td>32 injury</td>
<td>32 Embolization (2 fail)</td>
<td>2% LA, drainage -</td>
<td></td>
</tr>
<tr>
<td>Li et al [12]</td>
<td>60</td>
<td>Biliary tract injury during LC</td>
<td>NA</td>
<td>8 RHA injury; 2 PHA injury</td>
<td>5 Reconstruction (2 fail)</td>
<td>3 LN, 3 Hx, 2 LA, 3 others 3%</td>
<td></td>
</tr>
<tr>
<td>Turrini et al [55]</td>
<td>471</td>
<td>PD series</td>
<td>47</td>
<td>1 injury? 2 planned resection</td>
<td>2 Reconstruction</td>
<td>- -</td>
<td></td>
</tr>
<tr>
<td>Eshuis et al [9]</td>
<td>758</td>
<td>PD series</td>
<td>143</td>
<td>8 planned resection, 5 injury</td>
<td>3 Reconstruction</td>
<td>3 PF, 4 DGE, 1 LA, 3 Rlp 2%</td>
<td></td>
</tr>
<tr>
<td>Okada et al [52]</td>
<td>380</td>
<td>PD series</td>
<td>25</td>
<td>6 prep embolization and planned resection</td>
<td>No-reconstruction</td>
<td>1 POPF -</td>
<td></td>
</tr>
<tr>
<td>El Amrani et al [27]</td>
<td>2278</td>
<td>Systematic analysis for PD (1950-2014)</td>
<td>440</td>
<td>49 injury; 6 embolization (preop)</td>
<td>18 Reconstruction</td>
<td>POPF 15%, DGE 39%, 0%-10%</td>
<td></td>
</tr>
<tr>
<td>Landen et al [5]</td>
<td>NA</td>
<td>Systematic review for PD (1990-2016)</td>
<td>3</td>
<td>21 injury (8 PHA, 3 RHA, 3 rRHA, 4 HA thrombosis, 3 HA injury)</td>
<td>5 Reconstruction (1 fail)</td>
<td>14 LA, 3 LF, 6 AL,11 Rlp 5 (24%)</td>
<td></td>
</tr>
<tr>
<td>Asano et al [19]</td>
<td>343</td>
<td>PD series</td>
<td>51</td>
<td>1 rRHA injury; 8 rRHA planned resection</td>
<td>No reconstruction; 1 drainage</td>
<td>1 LA -</td>
<td></td>
</tr>
<tr>
<td>Kleive et al [20]</td>
<td>1535</td>
<td>Pancreatectomy series</td>
<td>NA</td>
<td>14 injury (5 SMA, 5 RHA, 2 CHA, 2 Celiac trunk); 22 planned resection</td>
<td>Embolectomy, Hx, re-resection, drainage</td>
<td>4 thrombosis, 2 PPH, 1 POPF, 5 LN, 11 Rlp 2 injured; 1 planned</td>
<td></td>
</tr>
<tr>
<td>Elsanousi et al [34]</td>
<td>19</td>
<td>Invasive HCC series</td>
<td>NA</td>
<td>19 HALED</td>
<td>19 HALED 8 Ascites-controlled, 2 jaundice 1 Pulmonary embolism</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1Ligation for therapeutic purpose.

Three patients died of LA at postoperative 5-7-12 mo. AL: anastomotic leakage; CHA: common HA; DGE: delayed gastric emptying; EHBT: Extrahepatic bile tract; HJ: Hepp-Couinaud hepaticojejunostomy; Hx: Hepatectomy, HALED: Hepatic artery ligation and extrahepatic collateral division; LA: Liver abscess; LC: Laparoscopic cholecystectomy; LF: Liver failure, LHA: Left HA; LN: Liver necrosis; n: Number of cases in series; NA: Not available; PD: Pancreatectoduodenectomy; POPF: Postoperative pancreatic fistula; PHA: Proper hepatic artery; PPH: Post pancreatectomy haemorrhage; Rlp: Relaparotomy; rRHA: Replaced right hepatic artery; SMA: Superior mesenteric artery.

Preoperative radiological evaluation in which most of the radiologists reported that they saw the HA anomaly but did not reflect it in their reports. For this purpose, a detailed description of vascular formations in magnetic resonance angiography and computed tomography angiography will be instructive. Doppler ultrasonography may also contribute to the evaluation of arterial flow. It is even stated that deaths can be reduced by detecting embolism, thrombus, and stenosis (median arcuate ligament syndrome) with angiography performed in selected cases after surgery. Compliance
with the radiological evaluation guidelines recommended by The Society of Abdominal Radiology and the American Pancreatic Association can minimize postoperative liver blood supply disorders[20,24,25].

In recent years, studies on the definition of vascular structures in three dimensions using three-dimensional (3D) imaging and 3D printing technology have been started [54-56]. Detailed information about lesions, vascular anatomy, anomalies, the relationship with the lesion, and anatomical structures can be obtained, especially with the simulation studies to be performed in the preoperative period. In addition to revealing the pathologies and vascular anatomy with great accuracy, 3D imaging methods are also used to calculate the remnant liver volume (Figure 5). Training of residents with 3D imaging and 3D printing products and simulation applications for preoperative evaluation guide in determining the path to be followed in interventional procedures and surgeries. There are studies on the application of more radical and more protective procedures during surgery by obtaining specific models specific to patients and adapting them to the navigation systems to be applied[55,57].

It is vital to meet the oxygen demand of the liver. Twenty-five percent of the cardiac output (1250-1500 cc/min) goes to the liver. While 20%-25% of the blood coming to the liver is supplied by HA, 75%-80% of it is supplied by the portal vein. Forty percent to 50% of oxygen is provided by HA, and the portal vein provides 50%-60%. While the portal vein blood’s oxygen saturation is 50%-60%, the HA oxygen saturation is over 90%[3,58]. In case of interruption of HA flow, the deficiency is compensated by portal vein flow. In a patient with impaired hemodynamics, the portal vein’s oxygen parameters deteriorate further, and the liver’s oxygenation is disrupted. The presence of hypovolemia, dehydration, anemia, lung problems, pain, excessive sedation, limitation of movement, or heart problems will further increase the risks associated with artery ligation[44,58]. Struggle with shock and providing oxygenation are the first protective and therapeutic procedures.

Exposing the HA and SMA and controlling HA pulses by closing the flow before cutting the gastroduodenal artery are among the first procedures to be performed. The most important reasons for the development of HA trauma are careless dissection and inadvertent transection. The posterior approach in surgery (arteria is first) can prevent the rHA injury[59]. The development of portal vein injury with HA is frequently mortal[3,60].

The extent of liver tissue damage that will occur as a result of HA trauma in patients with obstructive jaundice is greater. This is due to the high bilirubin levels and increased bile acids in the blood, further aggravating ischemia in liver cells. The presence of sepsis also aggravates this situation. HA blood flow plays a vital role in the clearance of bacteria from the portal vein to the liver. Necrosis resulting from the cessation of current also facilitates bacterial colonization. In experimental studies, it has been shown that animals whose HA was ligated and given antibiotics had a higher survival chance[16].

Portal blood flow and collaterals also gain critical importance in cases of HA injury. Oxygenation of the portal vein and collaterals will play an essential role in preventing the development of necrosis and survival[16,21,61]. It has been demonstrated that there are 26 different collateral pathways around the liver[21]. The presence of collaterals can be demonstrated with enhanced computed tomography. The inferior phrenic artery, superior falciform ligament artery, right triangular ligament artery, and omental and subcapsular collaterals can significantly contribute to preventing necrosis [62]. Yoshida et al[63] found dense collaterals (communications) between the capsular arterial plexus and intrahepatic isolated hepatic arteries. There is also a blood supply between the right and left hepatic arteries through the hilar plate plexus. Hilar plate plexus also provides blood supply of the collateral network around the common bile duct confluence and contributes to healing the hepaticojejunostomy anastomosis[64].

In cases where the artery revision is not successful, it should be tried to make the hepaticojejunostomy anastomosis close to the hilar plate, considering that the blood supply may be better[12]. In cases where artery reconstruction cannot be performed, (subhepatic) drainage is also recommended[16].

Arterialization of the portal vein was applied as a salvage procedure to increase portal blood oxygenation in HA thrombosis after liver transplantation. It has been applied from time to time in borderline pancreatic tumors and selected cases. It can be applied when HA repair is not possible or after resections[65,66]. The anastomosis can be performed in many places included in the portal system. The anastomosis can be made with autologous or synthetic (Gore-Tex, polytetrafluoroethylene graft) grafts or between arteries and veins (e.g., iliac artery-middle colic vein / superior mesenteric vein, colic artery branches, and ileocolic vein, etc.). It should be preferred to do it with a microscope/loop. It can also be done using the transected HA stump. In cases where
the arterial flow rate is high, portal hypertension clinics may develop. In such cases, the anastomosis may need to be closed by interventional methods (embolization, coiling)\[65,66\].

Control and follow-up of transaminases in the early postoperative period can provide important clues. In the case of high transaminases (> 2000 U/L), additional radiological imaging methods are recommended to investigate the extent of the ischemic condition and to perform reconstruction in cases with HA trauma\[67\]. Serum transaminases controlled serially in the early period in the follow-up of patients with or suspected HA trauma might be instructive about the extent of the damage and prognosis. In the 2894 PD series conducted in 25 years by John Hopkins, it was emphasized that there might be a serious relationship between the increase in serum transaminases and clinical progression and prognosis. In this study, it has been shown that if the serum transaminases peak level rises from < 500 U/L to 2000 U/L and above, the mortality may increase from 0.9% to 29%\[67\]. They also reported that almost all patients could recover if transaminases remained below 1000 U/L. In the same series, mortality was reported to be 7%, 3%, and 0.9% in patients with low albumin (< 2.5 g/dL), medium (2.6-3.5 g/dL), and high (> 3.5 g/dL), respectively.

It has been reported in experienced centers that HA trauma will be extremely rare. In the PD series of 434 cases by Kulkarni et al\[47\], they reported only 2 HA trauma. In the PD series of 1535 cases published in Oslo, Sweden, it was reported that only 8 patients (0.52%) had HA trauma\[20\].

Since HA trauma may develop in some of the patients who develop bile duct trauma\[12,13,10\], it is more appropriate to perform the intervention in experienced centers for patients who are planned to undergo reoperation for revision purposes.

The weaknesses of our study are the scarcity of clinical series in the literature and the fact that there are studies mostly in the form of case reports. Another point is that prospective studies on HA trauma are limited to experimental and subjects only, and these studies cannot be performed in humans. More comprehensive data can be obtained with the follow-up and evaluation of HA traumas encountered with multicentric study protocols.

**CONCLUSION**

Complications and deaths due to HA trauma are less common today. Repair should be attempted in all cases where HA trauma is detected (during surgery and early postoperative period). Arterial flow can be maintained with primary anastomosis, arterial transpositions, or grafts.

Liver failure, liver abscess, anastomotic opening, and bile duct stricture are the most common complications. The risk of complications increases in patients with...
hemodynamic instability, jaundice, cholangitis, and sepsis. The cause of death is often liver necrosis, sepsis, and liver failure. Antibiotic use and drainage reduce the risks.

To be protected from HA trauma, performing adequate radiological evaluation before the operation, revealing the variations, and determining the appropriate approach plan will minimize the risks.

HA trauma is a much less common complication, especially in HPB surgery centers. Considering the possibility of accompanying HA trauma in cases where bile duct trauma develops, the patient should be directed to HPB surgery centers if possible.

Large-scale and multicentric studies are needed to understand better the early and long-term consequences of HA trauma and develop preventive procedures.

**ARTICLE HIGHLIGHTS**

**Research background**
The hepatic artery (HA) has been used more and more for diagnosis and treatment in recent years. Besides, HA is one of the most threatened vascular structures during hepatopancreatobiliary (HPB) surgeries and interventional procedures. The incidence of HA injury is not precisely known.

**Research motivation**
There are many studies reporting that more than half of the cases died in the case of HA trauma or involuntary ligation until the last 3-4 decades. There is still a risk of serious morbidity and mortality as a result of injury to the HA during an increasing number of interventional procedures and HPB surgeries in recent years. There is a need for algorithmic approaches to HA-related problems and their solutions, which can be encountered for many different reasons.

**Research objectives**
Most of the studies related to HA in the literature are in the form of case reports. There are no algorithms developed for solving HA problems that surgeons, internists, gastroenterologists, hepatologists, and interventional radiologists often encounter sporadically. There is no consensus established for the solution of the problems encountered. Since there are no experimental studies in humans, there is a need for the analysis of data from case reports and a limited number of clinical series.

**Research methods**
The authors have reviewed 100 years of MEDLINE (PubMed) literature. The clinical approach algorithm was tried to define by reviewing the papers, including cases and series of HA injuries. The study researched keywords containing "hepatic artery" AND (trauma OR injury OR resection OR ligation OR avulsion OR transection OR reconstruction) and their various combinations. Approaches that have evolved in recent years in managing patients with HA injury (laceration, transection, ligation, resection) with severe morbidity and mortality risk are reviewed in the light of current literature.

**Research results**
The authors found 6314 articles as a result of the MEDLINE research. While one to two articles were published annually in the first 50 years, this number has increased gradually in the last 50 years and reached 109-237 articles per year. There are 1555 articles with the keywords "hepatic artery injury" or "hepatic artery trauma" and 468 articles with the word "hepatic artery ligation". In the first half of the century, we detected that HA traumas were applied mainly with unintentional ligations during gallbladder and stomach surgeries and patients who underwent planned ligation for HA aneurysm. We have identified 57 studies with the word "HA resection", and "HA embolization" was the subject of 406 studies; most of them have been published in the previous 2 decades. Articles on HA transection and reconstruction, a challenging stage of liver transplantation, ligation, resection, and reconstructions for HA aneurysms were also discussed. HA embolization has found many more clinical applications with the developing technological applications, and more studies have been reported in recent years. Here, HA pathologies, therapeutic procedures, and also HA embolization will be shortly described in the paper.
Research conclusions
With the technological developments in the last 2-3 decades and their contribution to diagnosis and treatment, positive developments have been identified in the prevention and management of HA trauma and related complications. The risk of HA injury increases during cholecystectomies and pancreateoduodenectomies, among the most common operations. HA anatomy shows anomalies in approximately 15%-25% of the cases, further increasing this risk. Complications and deaths due to HA injury are less common today. The risk of complications increases in patients with hemodynamic instability, jaundice, and cholangitis. Revealing the variations in the preoperative radiological evaluation will reduce the risks. In cases where HA injury is detected, arterial flow continuity should be tried to maintain with primary anastomosis, arterial transpositions, or grafts. In cases where bile duct injury develops, patients should be directed to HPB surgery centers, considering the possibility of accompanying HA injury.

Research perspectives
Due to the high risks it contains, the inability to conduct prospective studies in humans remains a problem. However, experimental studies in animals are needed regarding identified pathological processes. Besides, large-scale and multicentric clinical prospective studies are needed to understand better the early and long-term results of HA ligation and determine preventive procedures.

REFERENCES


Clinical considerations for critically ill COVID-19 cancer patients: A systematic review

Chidambaram Ramasamy, Ajay Kumar Mishra, Kevin John John, Amos Lal

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Abstract

BACKGROUND
The World Health Organization (WHO) on March 11, 2020, had declared the novel coronavirus disease 2019 (COVID-19) outbreak a global pandemic. The COVID-19 infection continues to be a pandemic and is currently causing overwhelming challenges to healthcare across the nations. Cancer patients represent a unique population vulnerable to COVID-19 infection due to their advanced age, intrinsic frailty, medical comorbidities, immunosuppression, and frequent health care visits for their underlying disease. Robust analysis of COVID-19 infection among cancer patients is crucial to aid in the optimal management of these patients.

AIM
To identify contributors of worse outcomes in patients with malignancy and COVID-19 and to describe the role of critical care.

METHODS
In this review, we summarized the information from seminal articles on the presentation and management of patients with COVID-19 and malignancy that were published before December 10, 2020. We searched the Pub Med and Medline database for “COVID-19” and “Cancer”, “Malignancy”. Studies published in English, including adults with malignancy and COVID-19 infection, were eligible to be included in this review. Studies on patients that provided details on malignancy, clinical presentation, management, and outcome were included. Various details of malignancy that were included are the site of cancer, histopathological type, stage, chemotherapy, and immunotherapy. Details of COVID-19
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Infection that were obtained are clinical presentation, the modality of testing, imaging, management, and outcome. Critical care details that were obtained were the type of the organ dysfunction and the requirement of organ support measures, requirement of noninvasive, invasive ventilation, management of vasopressor support, and outcome. Articles that did not have patient details, opinions, letters, and articles not published in English were excluded. All articles were reviewed by 2 independent clinicians. Articles were screened for the above terminologies by independent clinicians.

RESULTS

We identified two thousand one hundred eighty-six articles, among which fifty-five were studies that had included patient details pertaining to COVID-19 and cancer (Figure 1). Among these, eighteen studies were eligible and were included in this review as shown in Table 1. A total of 5199 cancer patients were reported. The mean age of patients across all the studies was 64.3 years with male predominance was noted in 12 studies. The clinical presentation and diagnosis of these patients were similar to the general population. Most commonly reported malignancies with COVID-19 infection were hematological in 44% of patients, followed by thoracic malignancy in 11% of patients. The mean number of cancer patients with COVID-19 requiring critical care was 16%. The mean mortality reported was 27.4%. Among the studies that reported the presence of organ dysfunction, respiratory failure was reported in 52% of patients, of which 11.7% required mechanical ventilation. 72% of COVID-19 cancer patients required hospitalization across all the studies. The factors which are associated with the worse outcome from COVID-19 infections among the cancer patients were male gender, age ≥ 65 years, presence of higher comorbidity burden based on Charlson comorbidity index and cumulative illness reporting scale > 6, and smoking history.

CONCLUSION

The majority of the cancer patients required intensive care due to respiratory failure and the need for mechanical ventilation. Appropriate contingency planning for these patients in terms of goals of care and judicious resource allocation in the resource-poor regions is the key. The factors associated with worse outcomes from COVID-19 infections were independent of oncological features such as tumor stage, disease status, or current provision of active antitumor therapy and it could be continued with caution.

KEY WORDS: COVID-19; Cancer; Critical care; Mortality; Pandemic

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**Core Tip:** Based on the analyses of 18 studies from major national and international cancer registries, it is evident that among symptomatic coronavirus disease 2019 (COVID-19) cancer patients, approximately one in six patients required intensive level of care, and one in four patients had a fatal outcome. It is crucial to identify factors associated with the worse outcome as it helps to provide prognostic enrichment while discussing the goals of care in this specific patient population. Appropriate contingency planning for these patients in terms of goals of care and judicious resource allocation in the resource-poor regions is the key. Later studies showed an absence of association between mortality from COVID-19 infection and active cytotoxic or noncytotoxic chemotherapy and it could be continued with caution.

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**URL:** https://www.wjgnet.com/2307-8960/full/v9/i28/8441.htm

**DOI:** https://dx.doi.org/10.12998/wjcc.v9.i28.8441
INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection causes a wide range of illnesses ranging from mild flu-like symptoms to severe respiratory failure leading to death. The novel coronavirus disease 2019 (COVID-19) infection continues to be a pandemic and is currently causing overwhelming challenges to healthcare across the nations. As of December 28th, more than 80 million cases have been diagnosed worldwide with 18 million cases reported from the United States of America[1]. Cancer patients represent a uniquely vulnerable population due to their advanced age, intrinsic frailty, medical comorbidities, immunosuppression, and frequent health care visits for their underlying disease. Existing data suggest that patients with hematological malignancies are more susceptible to SARS-CoV-2 infection[2-5]. The literature on COVID-19 infection in patients with cancer is limited. Robust analysis of outcomes of COVID-19 disease among cancer patients is crucial to aid in the optimal management of these patients during this continuously evolving pandemic. The impact of medical management, the role of critical care, and the multidisciplinary approach in treating patients with malignancy and COVID-19 infection are mostly unknown. In this review, we aimed to study the important epidemiological parameters and predictors of the requirement of acute critical care in patients with malignancy and COVID-19. We also aimed to study the various outcomes as reported in the literature in this subgroup of patients.

MATERIALS AND METHODS

In this review, we summarized the information from seminal articles on the presentation and management of patients with COVID-19 and malignancy that were published before December 10, 2020. We searched the Pub Med and, Medline database for “COVID-19” and “Cancer”, “Malignancy”. Studies published in English, including adults with malignancy and COVID-19 infection, were eligible to be included in this review. Studies on patients that provided details on malignancy, clinical presentation, management, and outcome were included. Various details of malignancy that were included are the site of cancer, histopathological type, stage, chemotherapy, and immunotherapy. Details of COVID-19 infection that were obtained are clinical presentation, the modality of testing, imaging, management, and outcome. Critical care details that were obtained were the type of the organ dysfunction and the requirement of organ support measures, requirement of noninvasive, invasive ventilation, management of vasopressor support, and outcome. Articles that did not have patient details, opinions, letters, and articles not published in English were excluded. All articles were reviewed by 2 independent clinicians. Articles were screened for the above terminologies by independent clinicians.

RESULTS

Studies from major national and international cancer registries and large single-center retrospective studies were included and interpreted. We identified two thousand one hundred eighty-six articles, among which fifty-five were studies that had included patient details on COVID-19 and cancer (Figure 1). Among these, eighteen studies were eligible and were included in this review as shown in Table 1. Eight of these studies were prospective in nature. These studies included patients from around eleven countries, from all over the world and five of these studies were multinational as shown in Figure 2. A total of five thousand one hundred ninety-nine patients were reported in the above studies. The mean age of patients across all the studies was 64.3 years. Male predominance among the study participants was noted in twelve (67%) studies.

The four most common presenting symptoms of COVID-19 were fever (64%), cough (61%), fatigue or malaise (43%), and dyspnea (41%) and were similar to the general population[6]. The diagnosis was uniformly established with reverse transcriptase-polymerase chain reaction and/or radiological finding suggestive of COVID-19 infection (100%)[7,8]. However, the diagnosis which was solely based on the clinical symptoms were excluded in these studies due to the high risk of bias. Most commonly reported malignancies with COVID-19 infection were hematological in 44% of patients, followed by thoracic in 11%, gastrointestinal, and breast cancer 10% each (Figure 3).
### Table 1 Study demographic details

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Country</th>
<th>Study type</th>
<th>Mean age (yr)</th>
<th>Gender</th>
<th>COVID-19 diagnosis</th>
<th>No. of patients</th>
<th>ICU admission rates</th>
<th>Mortality rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garassino et al[13] (TERAVOLT)</td>
<td>Multinational (8 countries)</td>
<td>Observational-cross sectional</td>
<td>68</td>
<td>M: 141 (70%); F: 59 (30%)</td>
<td>RT-PCR, or imaging</td>
<td>200</td>
<td>13 (9%)</td>
<td>33%</td>
</tr>
<tr>
<td>Passamonti et al[2]</td>
<td>Italy</td>
<td>Retrospective</td>
<td>66.8</td>
<td>M: 340 (63%); F: 196 (37%)</td>
<td>RT-PCR</td>
<td>536</td>
<td>82 (15%)</td>
<td>37%</td>
</tr>
<tr>
<td>García-Suárez et al[3]</td>
<td>Spain</td>
<td>Prospective observational cohort study</td>
<td>72</td>
<td>M: 413 (60%); F: 277 (40)</td>
<td>RT-PCR</td>
<td>697</td>
<td>55 (8%)</td>
<td>33%</td>
</tr>
<tr>
<td>Lee et al[8]</td>
<td>United Kingdom (UKCCMP)</td>
<td>Prospective-observational</td>
<td>69</td>
<td>M: 449 (56%); F:349 (44%)</td>
<td>RT-PCR</td>
<td>800</td>
<td>53 (7%)</td>
<td>28%</td>
</tr>
<tr>
<td>Mato et al[9]</td>
<td>United States and Europe</td>
<td>Retrospective cohort</td>
<td>70.5</td>
<td>M: 125 (63%); F: 73 (37%)</td>
<td>RT-PCR</td>
<td>198</td>
<td>70 (35%)</td>
<td>33%</td>
</tr>
<tr>
<td>Fürstenau et al[5]</td>
<td>Europe and Israel</td>
<td>Randomized control trial</td>
<td>61</td>
<td>M: 4 (57%); F:3 (43%)</td>
<td>RT-PCR</td>
<td>7</td>
<td>2 (29%)</td>
<td>29%</td>
</tr>
<tr>
<td>He et al[4]</td>
<td>China</td>
<td>Case control study</td>
<td>35</td>
<td>M: 7 (56%); F: 6 (44%)</td>
<td>RT-PCR or imaging</td>
<td>13</td>
<td>NA</td>
<td>61%</td>
</tr>
<tr>
<td>Fattizzo et al[30]</td>
<td>Italy</td>
<td>Case series</td>
<td>77</td>
<td>M: 10 (63%); F: 6 (37%)</td>
<td>RT-PCR</td>
<td>16</td>
<td>2 (12%)</td>
<td>31%</td>
</tr>
<tr>
<td>de Joorde et al[14]</td>
<td>Netherlands</td>
<td>Observational cohort study</td>
<td>70</td>
<td>M: 187 (53%); F: 164 (47%)</td>
<td>RT-PCR or imaging</td>
<td>351</td>
<td>NA</td>
<td>32%</td>
</tr>
<tr>
<td>Pinato et al[24]</td>
<td>Europe, United Kingdom, Italy, Spain</td>
<td>Retrospective observational</td>
<td>69.3</td>
<td>M: 127 (62%); F:77 (38%)</td>
<td>RT-PCR</td>
<td>204</td>
<td>36 (18%)</td>
<td>29%</td>
</tr>
<tr>
<td>Kuderer et al[6] (CCC19)</td>
<td>United States, Canada, Spain</td>
<td>Retrospective</td>
<td>66</td>
<td>M: 468 (50%); F: 460 (50%)</td>
<td>RT-PCR</td>
<td>928</td>
<td>132 (14%)</td>
<td>13%</td>
</tr>
<tr>
<td>Robilotti et al[21]</td>
<td>United Sates</td>
<td>Retrospective</td>
<td>NA</td>
<td>M: 212 (50%); F: 211 (50%)</td>
<td>RT-PCR</td>
<td>423</td>
<td>NA</td>
<td>12%</td>
</tr>
<tr>
<td>Ramaswamy et al[11]</td>
<td>India</td>
<td>Prospective observational</td>
<td>42</td>
<td>M: 124 (54%); F: 106 (46%)</td>
<td>RT-PCR</td>
<td>230</td>
<td>8 (3%)</td>
<td>10%</td>
</tr>
<tr>
<td>Nichetti et al[12]</td>
<td>Italy</td>
<td>Prospective observational</td>
<td>61</td>
<td>M: 4 (36%); F: 7 (64%)</td>
<td>RT-PCR</td>
<td>11</td>
<td>1 (9%)</td>
<td>55%</td>
</tr>
<tr>
<td>Kuderer et al[6]</td>
<td>Canada</td>
<td>Prospective observational</td>
<td>73</td>
<td>M: 127 (50%); F: 150 (50%)</td>
<td>RT-PCR</td>
<td>252</td>
<td>71 (28%)</td>
<td>13%</td>
</tr>
<tr>
<td>Lara et al[17]</td>
<td>United States</td>
<td>Retrospective</td>
<td>64</td>
<td>F: 121 (100%)</td>
<td>RT-PCR</td>
<td>121</td>
<td>20 (16%)</td>
<td>14%</td>
</tr>
<tr>
<td>Zhang et al[16]</td>
<td>China</td>
<td>Retrospective</td>
<td>66</td>
<td>M: 60 (56%); F: 47 (44%)</td>
<td>RT-PCR or imaging</td>
<td>107</td>
<td>NA</td>
<td>22%</td>
</tr>
<tr>
<td>Dai et al[15]</td>
<td>China</td>
<td>Case control study</td>
<td>64</td>
<td>M: 57 (55%); F: 48 (46%)</td>
<td>RT-PCR or imaging</td>
<td>105</td>
<td>20 (19%)</td>
<td>11%</td>
</tr>
</tbody>
</table>

1Percentage in decimals were rounded to the nearest whole number. RT-PCR: Reverse transcriptase polymerase chain reaction; M: Male; F: Female; UKCCMP: The United Kingdom Coronavirus Cancer Monitoring Project; CCC19: Coronavirus disease 2019 and Cancer Consortium; COVID-19: Coronavirus disease 2019; ICU: Intensive care unit; NA: Not available.

Fourteen (78%) studies reported the requirement of inpatient critical care management among patients and all of these studies reported mortality (100%). The mean number of cancer patients with COVID-19 requiring critical care was 16% with the minimum and maximum being 3% and 35% respectively. The mean mortality reported was 27.4%, with the minimum and maximum being 10% and 61.5%
respectively. The description of the various patterns of organ dysfunction was not uniform. The presence of acute hypoxic respiratory failure and requirement of mechanical ventilation was reported in 9 (50%) of the studies. Renal dysfunction, shock, and cardiac injury were reported in only 4 (22%), 2 (11%), 2 (11%) of the studies. Among the studies that reported the presence of organ dysfunction, respiratory failure was reported in 52% of patients, of which 11.7% required mechanical ventilation. The presence of renal dysfunction, shock, and cardiac injury was noted in 8%, 14.5%, and 4.3% respectively. The requirement of hospitalization was reported in 9 (50%) of the studies, with around 72% of patients requiring hospitalization across all the studies. There were significant differences in the study design, data collection, and measured outcomes among the studies which made the comparison of data difficult.

**DISCUSSION**

In this review, we summarized the role of intensive care in patients with COVID-19 and active malignancy. We identified that only very few studies discussed the medical management of sick patients with COVID-19 in the background of active malignancy. We identified that overall, 16% of COVID-19 cancer patients were admitted to the intensive care unit [the specific reasons for intensive care unit (ICU) admission were
Figure 3 Pie chart showing the reported coronavirus disease 2019 infections among various types of cancers.

not available due to lack of data granularity]. The commonest cause of admission to ICU was an acute hypoxic respiratory failure which is also the cardinal presentation of a typical symptomatic COVID-19 patient[8,9]. The reported intensive care unit admission rates among COVID-19 patients with chronic lymphomatous leukemia was 35% which was higher than 7% and 14% reported by the United Kingdom Coronavirus Cancer Monitoring Project (UKCCMP) and the COVID-19 and Cancer Consortium (CCC19) respectively[6,8,9]. The differences in the ICU admission rates among those patients may be multifactorial. These could be related to the intrinsic immune defect secondary to chronic lymphomatous leukemia, cultural and geographical differences in the practice and ICU admission criteria, and differences in the predisposing factors such as age and comorbidities. Most of the literature that we reviewed lacked detailed information about advance care directives. Variation of in-hospital mortality and ICU mortality at least in part can be attributed to do-not-intubate/do-not-resuscitate status for at least some of these patients.

COVID-19 and malignancy

The real burden of COVID-19 among cancer patients was unknown as the studies were done mostly in symptomatic patients requiring treatment. Asymptomatic cancer patients were not routinely tested for COVID-19 due to resource limitations during the initial phase of the pandemic. This is hypothesis-generating and further incites the discussion about how frequently should cancer patients be treated in the absence of symptoms if at all[10,11].

During the initial stages of the COVID-19 outbreak, due to the high risks of infection and limited medical resources, prioritization of certain anticancer treatments over others, temporary chemotherapy discontinuation was routinely practiced in Europe[12]. Initial data showed that chemotherapy was associated with fatal outcomes from COVID-19 infections among the cancer patients but later this association was not confirmed by later studies from national registries[8,13,14]. The United Kingdom cancer registry reported that 172 patients (22% of analyzed subjects) received interruption in their anti-cancer treatment due to potential fear from immunosuppression. They found active chemotherapy has no significant impact on mortality from COVID-19 infection (27% mortality observed on active chemotherapy patients vs 29% on non-chemotherapy patients; P = 0.467) after adjusting for age, comorbidities[8]. The absence of association between mortality and active cytotoxic or noncytotoxic chemotherapy, recent surgery within 4 wk suggests curative surgical resection, adjuvant chemotherapy, and maintenance chemotherapy could be continued during the pandemic with extreme caution[15-17]. Randomized clinical trials are necessary to confirm this hypothesis.

Interestingly, it was reported that thoracic malignancy and chronic lymphomatous leukemia patients with COVID-19 treated with tyrosine kinase inhibitors were less likely to develop severe COVID-19 infection requiring hospitalization, the requirement
of oxygen support, and mechanical ventilation[9,13]. However, tyrosine kinase inhibitor does not appear to impact survival[9]. It is hypothesized that tyrosine kinase inhibitors modulate the immune response by blocking pro-inflammatory and chemoattractant cytokines in the lungs thereby mitigating hyperinflammatory immune response. Randomized clinical trials of tyrosine kinase inhibitor for the treatment of COVID-19 are ongoing and will provide more definitive evidence of the effect of these drugs in COVID-19 (NCT04375397 and NCT04380688)[9,18].

**Role of critical care in patients with malignancy and COVID-19**

Outcomes from SARS-CoV-2 are influenced by ceilings of medical care. In cancer patients, escalation beyond ward-based care requires careful case-by-case evaluation. The decision to provide organ support to acutely ill cancer patients is made even harder in the context of a global pandemic, where saturation of clinical services imposes an often difficult prioritization of critical care resources in favor of younger and less co-morbid critically ill patients[3,6,19].

Dutch Oncology COVID-19 Consortium (DOCC) encouraged early discussion of advanced care planning and treatment strategies (do not intubate) among the vulnerable populations during the ongoing pandemic. They reported more than 80% of patients who had fatal outcomes with COVID-19 had previously discussed with their care team regarding goals of care and had opted for non-heroic measures in acute decompensation from a respiratory failure point of view (do not intubate or do not resuscitate)[14]. In the Netherlands, based on DOCC registry, cancer patients with COVID-19 infections were mainly admitted to the intensive care unit solely for mechanical ventilation. They provided most of the supportive care other than the mechanical ventilation, outside the intensive care unit. Their mortality rate of 32.4% of analyzed patients was comparable to the other national registries[4,6,8,13].

**COVID-19 and mortality**

The overall reported mortality among the COVID-19 cancer patients ranges from 12% to 37% which is higher than the general population. UKCCMP, a registry spanning the United Kingdom reported a mortality rate of 28% based on the analysis of 800 cancer patients which was similar to the other European studies [teravolt study group (33%), Italian hematology alliance (37%) and Spain cancer registry (33%)][2,3,8,13]. Whereas the COVID-19 and CCC19, a multi-institution registry mainly from North America reported a mortality rate of 13% based on analysis of 928 patients[6]. This was similar to two single-center retrospective analyses from large healthcare systems in New York City, one at Mount Sinai (11%), another (12%) from analysis of 423 COVID-19 cancer patients at Memorial Sloan Kettering Cancer Center[20,21].

Overall, 7% to 35% of patients were treated in the intensive care unit. The mortality rates seen were as high as 50%[22]. The most common reported reason for the requirement of intensive care unit admission was acute hypoxic respiratory failure needing non-invasive or invasive mechanical ventilation[23]. The reason for intensive care unit admission was not included in most of the analyses and lack of granularity on the data point remains to be the constraint associated with retrospective studies [24]. Information condensed in studies such as above and our extensive review helps to provide prognostic enrichment while discussing the goals of care in this specific patient population.

**Contributors of worse outcome in patients with malignancy and COVID-19**

The factors which are associated with the worse outcome from COVID-19 infections among the cancer patients were male gender, age ≥ 65 years, presence of higher comorbidity burden based on Charlson comorbidity index and cumulative illness reporting scale > 6, and smoking history (Figure 4). These factors are significantly associated with the patient’s mortality independent of oncological features such as tumor stage, disease status, or current provision of active oncantic cancer therapy[14,24]. The higher levels of inflammatory markers such as CRP, D-dimer, ferritin, and procalcitonin were associated with severe and critical COVID-19 infections[8,16].

Some of the observations reported in the studies have a biological basis in the pathogenesis of SARS-CoV-2 infection. Male gender and history of smoking are associated with the worse outcome from COVID-19 infection. In the general population, evidence regarding the history of smoking and the risk of COVID-19 infection is equivocal[25,26]. Based on the previous human and animal studies, it has been reported that angiotensin-converting enzyme2 (ACE2) receptor expression is increased among smokers which facilitates the viral entry to cells. The angiotensin-converting enzyme 2 converts biologically active angiotensin II to angiotensin (1-9)
Figure 4 Contributors of worse outcome of among cancer patients with coronavirus disease 2019 infection. 1Higher levels of C-reactive protein, D-dimer, ferritin and procalcitonin.

thereby acting as a physiological counter renin-angiotensin-aldosterone system activation. The binding of the virus to the ACE2 receptor leads to its downregulation and reduced clearance of angiotensin II. It has been postulated that acute lung injury secondary to the viral infection could be due to increased levels of unbound angiotensin II and downregulation of ACE2[27].

The SARS-CoV-2 virus also depends on the proteolytic effects of transmembrane serine protease 2 (TMPRSS2)[28]. TMPRSS2 mediated cleavage of viral glycoprotein S results in the fusion of the virus with the host cell membrane. The alveolar expression of TMPRSS2 is androgen-dependent and prostate-specific[29]. The observed gender differences with a worse outcome of COVID-19 could be due to biological differences in the expression of the enzyme in addition to the difference in exposures to the virus (for example high-risk jobs, professional exposure, cigarette smoking).

Passamonti et al[2] and García-Suárez et al[3] based on the descriptive analysis reported that 50% to 62% of severe and critical COVID-19 infections among hematologic cancer when compared to 26% to 43% among solid tumors vs 15% among non-cancer. In their analysis, they found that non-survivors had significantly higher baseline D-dimer levels at disease onset than survivors (0.6 mg/L vs 1.3 mg/L, P = 0.03).

Among the COVID-19 hematological malignancy patients, the lower levels of hemoglobin, lymphocyte, and platelet concentrations possibly due to the effect of hematologic therapies or attributable to COVID-19 infection itself which may predict worse outcomes[4].

Strengths and limitations

Our review is timely and has certain strengths such as; it included studies with patients having COVID-19 in the background of active malignancy from major national and international cancer registries. We also attempted to identify the predictors of morbidity, worse clinical outcomes, and the role of intensive care therapy in these patients.

At the same time, our study acknowledges several limitations. There are regional and geographical differences in the threshold for testing COVID-19 infection which may add to the selection bias of not testing the asymptomatic cancer patients. Studies included in this review were retrospective and lack overall granularity of information such as details on the severity of disease, details of malignancy, and details of medical treatment, details of comorbidities, drug interactions, and outcome. Details of COVID-19 infection on the management of malignancy and vice versa were also not uniformly addressed. Details of treatment of COVID-19, duration of therapy, length of hospital stay, the long-term outcome were not uniformly available, especially at the beginning of the pandemic. Details of intensive care treatment including mode of ventilation, vasopressors of choice, renal replacement therapies, the role of sedatives and
paralytics on this subgroup of populations were also not discussed. Studies with larger sample size and longer-term follow-up are needed. These limitations may also serve as hypothesis-generating questions for future studies.

CONCLUSION
As COVID-19 infection continues to affect the outcome of patients with malignancy on treatment, treating physicians need to be aware of the potential differences and contributors to outcome in patients with malignancy and COVID-19. Patients with hematological cancer and lung cancer are more vulnerable to complications of COVID-19 infections[13,14]. Superimposed bacterial infections seem to play an important role in outcomes among the hematological cancer population[4]. Limiting the exposure to novel coronavirus and prioritizing the vaccinations for these vulnerable populations should be considered. So far there is a paucity of focused data with regards to the efficacy and timing of vaccination among active cancer patients getting chemotherapy.

In this review, we identified that in the setting of active malignancy cytotoxic treatments can be continued with caution[8]. Interestingly, cancer patients treated with tyrosine kinase inhibitors were less likely to develop severe forms of COVID-19 infection. Two randomized control trials are ongoing to provide more definitive evidence. Another interesting finding was that majority of the cancer patients required intensive care due to respiratory failure and the need for mechanical ventilation. Appropriate contingency planning for these patients in terms of goals of care and judicious resource allocation in the resource-poor regions is the key.

ARTICLE HIGHLIGHTS

Research background
Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome-coronavirus 2 has led to an unprecedented global public health crisis. Patients with cancers are particularly susceptible to morbidity and mortality from COVID-19 infection due to their medical risk factors, immune dysfunction, and frequent health care visits for their underlying disease.

Research motivation
To analyze the characteristics of COVID-19 infection among cancer patients which would help treating physicians in optimal management of COVID-19 cancer patients.

Research objectives
In this review article, authors intend to describe the role of critical care in COVID-19 cancer patients and to analyze the various factors which determine the outcome in patients with malignancy and COVID-19.

Research methods
Authors searched the PubMed and, Medline database for “COVID-19” and “Cancer”, “Malignancy”. Studies published in English, including adults with malignancy and COVID-19 infection, were eligible to be included in this review. We identified two thousand one hundred eighty-six articles, among which eighteen studies were eligible and were included in this review.

Research results
A total of 5199 cancer patients were reported. Male predominance was noted in 12 studies. Most reported malignancies with COVID-19 infection were hematological in 44% of patients, followed by thoracic malignancy in 11% of patients. The mean number of cancer patients with COVID-19 requiring critical care was 16%. The mean mortality reported was 27.4%. 72% of COVID-19 cancer patients required hospitalization across all the studies. Majority of the cancer patients required intensive care due to respiratory failure and the need for mechanical ventilation. Male gender, age ≥ 65 years, presence of higher comorbidity burden and smoking history are associated with the worse outcome from COVID-19 infections among the cancer patients. These factors are significantly associated with the patient’s worse outcome independent of oncological features such as tumor stage, disease status, or current provision of active...
Criticality III COVID-19 cancer patients

Research conclusions
Among symptomatic COVID-19 cancer patients, approximately one in six patients required intensive level of care, and one in four patients had a fatal outcome. It is crucial to identify factors associated with the worse outcome as it helps to provide prognostic enrichment while discussing the goals of care in this specific patient population. Appropriate contingency planning for these patients in terms of goals of care and judicious resource allocation in the resource-poor regions is the key.

Research perspectives
In this review, we identified that in the setting of active malignancy cytotoxic treatments can be continued with caution. Cancer patients treated with tyrosine kinase inhibitors were less likely to develop severe forms of COVID-19 infection. Two randomized control trials are ongoing to provide more definitive evidence.

REFERENCES


Atypical granular cell tumor of the urinary bladder: A case report

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Author contributions: Wei MZ designed and drafted the article, and final approval of the version submitted; Yan ZJ was responsible for data acquisition, article drafting, and final approval of the version submitted; Jiang JH was responsible for data acquisition, critical revision of the article, and final approval of the version submitted; Jia XL was responsible for critical revision of the article, and final approval of the version submitted.

Informed consent statement: This case report was approved by the institutional ethical committee in our hospital, and written informed consent was obtained from the patient.

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

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Abstract

BACKGROUND
Granular cell tumor (GCT) is a neurogenic tumor mainly occurring in the head and neck. GCT in the genitourinary system is extremely rare and only sporadic cases of urinary bladder GCT have been reported. Most urinary bladder GCT cases are benign and only two malignant cases have been reported. Due to its rarity, no consensus criteria for the treatment of urinary bladder GCT are available at present.

CASE SUMMARY
A 62-year-old Chinese woman was found to have a urinary bladder tumor without any clinical manifestations on physical examination. Cystoscopy revealed a semispherical shaped lesion measuring approximately 4.0 cm in diameter at the junction of the left wall and roof of the bladder, which was covered with normal bladder mucosa. Computed tomography scan demonstrated a high-density lesion on the left wall of the bladder, measuring approximately 2.9 cm × 2.4 cm with clear boundaries. Contrast-enhanced pelvic magnetic resonance imaging revealed a space-occupying lesion on the left wall of the bladder (non-mucosal origin/external pressure), which was preliminarily suspected to be a desmoplastic fibroma or leiomyoma. In the context of the above findings, a pre-operative diagnosis of bladder leiomyoma was made. The patient consequently underwent a laparoscopic partial cystectomy. The resected bladder mass looked yellowish and well-demarcated, measuring 4.0 cm × 3.5 cm and infiltrated the muscular layer. The diagnosis of urinary bladder GCT was finally made by postoperative pathology, with positive immunohistochemical S-100 staining and negative pancytokeratin. The patient has been followed for 6 mo so far, with no tumor recurrence detected.

CONCLUSION
This case highlights the biological feature and differential diagnosis of urinary bladder GCT at the pathological and molecular levels. Transurethral resection of the bladder tumor and partial cystectomy are recommended in most urinary bladder GCT cases, while radical cystectomy is recommended in malignant cases.
Key Words: Granular cell tumor; Bladder; Partial cystectomy; Immunohistochemistry; Case report

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Core Tip: ATP6AP1, ATP6AP2, BRD7 and GFRA2 gene mutations can potentially induce the progression of urinary bladder granular cell tumor. Characteristic biomarkers such as S-100, SOX10, CD56, pancytokeratin and HBM45 are essential for the diagnosis and differential diagnosis. Partial cystectomy is the treatment of choice to minimize recurrence and improve disease-free survival in benign cases. A relatively conservative transurethral resection of the bladder tumor can also be an alternative option according to the location of the primary tumor or at the patient's request. For malignant bladder granular cell tumors, radical surgical intervention with pelvic lymph node dissection is necessary.

INTRODUCTION

Granular cell tumor (GCT) is a neurogenic tumor usually occurring in head and neck regions. GCT of the genitourinary system such as urinary bladder is extremely rare. As only sporadic cases of bladder GCT have been reported, there are no explicit criteria for the treatment of this disease. Most bladder GCT cases are benign, and only two malignant cases have been reported, and distant metastasis of GCT from the primary organ to the bladder should not be neglected[1,2]. It is usually difficult to distinguish GCT from other neurogenic tumors by simply depending on radiologic and pathological findings without immunohistochemical (IHC) staining. In this article, we report a case of GCT occurring in the urinary bladder, and hope that it can help better understand this rare disease entity in the bladder.

CASE PRESENTATION

Chief complaints
A 62-year-old Chinese woman was found to have a "hypoechoic bladder space" without any specific complaints during a pelvic ultrasound examination at the local community health service center.

History of present illness
The patient had no presenting symptoms.

History of past illness
She had diabetes mellitus and left kidney agenesis.

Physical examination
On initial physical examination, her temperature was 36.7°C, blood pressure was 133/85 mmHg, heart rate was 84 bpm, and respiratory rate was 16 breaths/min. The clinical urological examination revealed no characteristic signs.

Laboratory examinations
Routine blood, urine and stool tests were within the normal range, and microscopy for bacteria and fungi showed negative results. Laboratory tests showed high-sensitivity C-reactive protein of 17.97 mg/L (RR: 0.00-5.00 mg/L) and rheumatoid factor (RF) of 34.70 IU/mL (RR: < 20 IU/mL). Other biochemical and coagulation indicators were...
within the normal ranges. Tumor markers such as CA199, CA125, CEA and AFP which were used for routine screening for metastatic tumor from other primary organs such as the gastrointestinal tract, ovary, liver were not remarkable.

**Imaging examinations**

Cystoscopy revealed a semispherical shaped lesion measuring approximately 4.0 cm in diameter at the junction of the left wall and roof of the bladder, which was covered with normal bladder mucosa (Figure 1). An initial pelvic computed tomography (CT) scan revealed a high-density lesion on the left wall of the bladder, measuring was approximately 2.9 cm × 2.4 cm with clear boundaries, with a mean CT value of 44HU (Figure 2). Contrast-enhanced magnetic resonance imaging (MRI) revealed a space-occupying lesion (SOL) on the left wall of the bladder, the SOL did not originate from urothelium of the bladder wall but tended to generate externally into the bladder cavity (Figure 3), which was preliminarily suspected to be a desmoplastic fibroma or leiomyoma. MRI T1WI phase (Figure 3A) and T2WI (Figure 3B) sequences revealed round equalized signals; T1WI + fat suppression + enhanced sequences showed obvious enhancement (Figure 3C); the DWI phase revealed limited diffusion (Figure 3D).

**FINAL DIAGNOSIS**

Postoperative pathology of the resected specimen confirmed the diagnosis of bladder GCT, with positive IHC S-100 staining and negative pancytokeratin.

**TREATMENT**

Based on the imaging findings and biochemical indicators, a pre-operative diagnosis of bladder leiomyoma was made, for which a laparoscopic partial cystectomy (Figure 4A and B) was successfully performed with an intraoperative blood loss of approximately 20 mL. The resected solid mass looked yellowish and well-demarcated, measuring approximately 4.0 cm × 3.5 cm, without obvious adhesion to the surrounding tissues under gross appearance. Frozen section examination of the specimen suggested the diagnosis of mesenchymal neurogenic or myogenic tumor with negative margins. Post-operative pathologic study demonstrated the diagnosis of atypical GCT, which infiltrated the muscular layer of the bladder with enlarged tumor cells and scattered pleomorphic cells. The nuclei were obvious and vacuolar, with an increased nuclei/cytoplasm ratio, nuclear mitosis 0-1/10HPF, and no necrotic lesions (Figure 5A). IHC showed positive expression of S-100 protein (Figure 5B), negative pancytokeratin, positive neuron-specific enolase (NSE), and weak positivity of both Ki-67 (5%) and CD-68.

**OUTCOME AND FOLLOW-UP**

The patient underwent positron emission tomography-CT (18F-fluorodeoxyglucose) three weeks after surgery, and showed multiple enlarged lymph nodes and increased fluorodeoxyglucose metabolism in the retroperitoneal and bilateral iliac vascular region, devoid of tumor metastasis. The patient did not receive adjuvant therapy, and was followed up with cystoscopy and CT scan of the urinary system every 3 mo. During a follow-up period of 6 mo, no evidence of recurrence or lymph node enlargement was detected.

**DISCUSSION**

GCT is a neurogenic tumor, first described as a myoblast mass of the tongue by Abrikosoff in 1926[3]. GCTs commonly occur in the oral cavity, digestive tract, skin, and subcutaneous tissue, and most cases occur in women aged 40-60 years. Genitourinary GCT is extremely rare, and only about 20 cases of urinary bladder GCT have been reported to date[2]. Distant metastasis of GCT from the primary organ should not be neglected.
Figure 1 Pre-operative cystoscopy examination. A semispherical-shaped lesion, measuring approximately 4.0 cm in diameter at the junction of the left wall and roof of the urinary bladder and covered with normal bladder mucosa.

Figure 2 Pre-operative pelvic computed tomography scan. The orange arrow indicates a high-density lesion on the left wall of the bladder, measuring approximately 2.9 cm × 2.4 cm with clear boundaries, with a mean computed tomography value of 44HU.

Based on the currently available case reports, gross hematuria appears to be the most common clinical manifestation of urinary bladder GCT[4,5]. However, the patient in our case report did not present any apparent manifestations except the imaging findings, which were consistent with the pre-operative cystoscopic findings of undamaged mucosa of the solid mass.

GCT cells are larger than typical tumor cells, presenting as scattered polymorphic cells with polygonal and hyperchromatic nuclei and nuclear vacuoles[3]. GCT is mainly derived from Schwann cells and consists of large polymorphic cells containing a large granular cytoplasm. It is usually difficult to distinguish GCT from other neurogenic tumors and depends on cellular morphology and radiology. For instance, a schwannoma is completely composed of differentiated neoplastic Schwann cells, and a ganglioneuroma is mainly composed of mature Schwannian stroma and mature ganglion cells[6-8]. GCT often presents with atypical histological features, including spindling, increased mitotic features (> 2/10 HPF), nuclear pleomorphism, prominent nucleoli, a high nuclear/cytoplasm ratio, and necrosis[9].

The positive rate of Ki67 is usually less than 1% in benign GCT and ≥ 10% in malignant GCT. The GCT in our report was neurogenic, consistent with most reports [3,10-13], but the positive rate of Ki67 was 5%, which indirectly suggests that this may be the first reported case of atypical GCT of the bladder. The IHC profile of GCT is strongly positive for S-100 protein, SOX10, and CD68 but negative for pancytokeratin, which is partially consistent with the findings in the present case. Additionally, CD56, CD57, NSE, inhibin, calretinin, TFE3, PGP9.5, and vimentin are commonly positive in GCT[2]. It should be noted that malignant GCT tends to be misdiagnosed as melanoma due to positive IHC staining of S-100 and SOX10 in both cancers. However, HMB45 staining is positive in melanoma and negative in GCT[2,9].
Figure 3 Pre-operative contrast-enhanced pelvic magnetic resonance imaging. The orange arrow indicates a space-occupying lesion seen on the left wall of the bladder, originating from the bladder wall mucous membrane. It tended to infiltrate peripheral tissue, which was preliminarily suspected to be a desmoplastic fibroma or leiomyoma. A-D: It shows an oval structure that is isointense on T1WI (A) and T2WI (B) sequences; T1WI + fat suppression + enhanced sequence reveals noticeable enhancement (C); DWI sequence revealed limited diffusion (D).

Figure 4 Figures of laparoscopic partial cystectomy. The round solid neoplasm of the bladder was resected under laparoscopic assistance (orange arrows). A: Incising the bladder wall to expose the neoplasm; B: Resecting the neoplasm along the boundaries.

The most recent studies have suggested that ATP6AP1 and ATP6AP2 gene mutations may lead to GCT cell proliferation by decreasing the lysosomal activities and that BRD7 and GFRA2 proteins of the RTK signaling pathway are highly expressed in malignant GCT[14-16].
Yoshida et al.[17] reported that most urinary bladder GCT cases were pathologically diagnosed as benign tumors. However, although malignant cases are rare, local recurrence caused by incomplete resection of the primary tumor has been reported in sporadic cases, and accurate intra-operative biopsy is, therefore, necessary[17]. Given this context and based on the research of Abbas and other scholars in combination with the evaluation of the curative effect in our case, a preliminary consensus can still be reached that transurethral resection of bladder tumor (TURBt) or partial cystectomy may be the most common treatment for benign GCT of the bladder depending on the different positions of the tumor, and the prognosis is relatively optimistic[3]. One of the biological characteristics of GCT is its tendency to infiltrate tissues; if a GCT in other organs is not completely resected, it is likely to recur and continue to grow again. Sun et al.[2] reported that recurrence occurred in more than 50% of cases of benign bladder GCT after the initial TURBt treatment and a full follow-up period. Repeated TURBt of the lesion after diagnosis can reduce the possibility of recurrence. Compared with partial cystectomy, TURBt after the first recurrence may be associated with a higher recurrence rate[2]. Therefore, for both primary and recurrent benign bladder GCT cases, partial cystectomy can better ensure a negative incisal margin and reduce the possibility of recurrence. Extended radical bladder resection is often necessary for recurrent malignant GCT bladder tumors with a ureteral obstruction or more extensive tissue invasion. It is reported that radical cystectomy combined with bilateral pelvic lymphadenectomy can improve disease-free survival (DFS) and significantly improve the prognosis of malignant bladder GCT[2]. There is no clear evidence that patients with malignant bladder GCT should receive chemotherapy or radiotherapy. The current literature on malignant GCT derived from various body systems shows that the 5- and 10-year survival rates are 74% and 65%, respectively; the recurrence rate within 3-37 mo after pathological diagnosis is 32%-41%, and the metastasis rate is 11%-62%[18-20]. Therefore, the high risk of poor prognosis of malignant bladder GCT should not be ignored. After laparoscopic partial cystectomy in our case, the final pathological diagnosis was atypical GCT, suggesting the possibility of its malignant differentiation. Although this may indicate the malignant potency of the tumor, depending on the current consensus and promising follow-up result in our case, we finally performed a partial cystectomy instead of radical cystectomy to achieve better survival.
Furthermore, the enlargement of lymph nodes in the retroperitoneal and bilateral iliac vascular regions was detected by a positron emission tomography (PET) scan 3 wk after surgery; nevertheless, the routine CT scan during follow-up revealed no recurrence or apparent lymph node enlargement. In view of the above, we attribute the disparity of reports regarding the lymph nodes on PET and CT scans to the irritable inflammatory reaction. Although no recurrence has been detected within the 6-mo follow-up period, further close follow-up is necessary and radical resection may be required.

Significantly, the patient had left kidney agenesis and diabetes mellitus. Unilateral renal agenesis is usually accompanied by another ectopic kidney, nontrenal anomalies, and evidence of renal injury [21,22], such as contralateral renal hypertrophy, branchio-renal syndrome (commonly associated with hearing abnormalities), renal malfunction, and Müllerian defects [23] (e.g., uterine didelphys or vaginal duplication), which are common in girls. Unfortunately, depending on the illustrations of current reports, there is no relation between GCT and unilateral renal agenesis. In our case, the patient had a normal contralateral kidney size, which was not accompanied by hearing abnormality, renal injury (e.g., hypertension or proteinuria), abnormal serum creatinine or glomerular filtration rate; however, uterine didelphys was observed. We will continue to perform urinalysis in this patient during every follow-up to monitor the contralateral kidney function.

CONCLUSION

Bladder GCT is uncommon, and malignant GCT is extremely rare. IHC characteristics such as S-100, SOX10, CD56, HBM45, and pancytokeratin are essential for diagnosis. In addition, ATP6AP1, ATP6AP2, BRD7, and GFRA2 gene mutations cannot be neglected in terms of further diagnosis and targeting therapy. For benign bladder GCT, partial cystectomy is the treatment of choice because it can minimize recurrence and improve DFS. A relatively conservative TURBt can also be selected depending on the primary tumor location or upon the patient’s request. For malignant bladder GCT, radical surgical resection with pelvic lymph node dissection is necessary. The primary purposes of this case report were to attract more attention to this rare disease, help understand the disease, and promote more research on specific biomarkers for the diagnosis and treatment of bladder GCT.

REFERENCES


Hepatocyte nuclear factor 1B mutation in a Chinese family with renal cysts and diabetes syndrome: A case report

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Abstract

BACKGROUND
Renal cysts and diabetes (RCAD) syndrome is an autosomal dominant diabetic renal disease. Precise molecular diagnosis of RCAD syndrome has proven valuable for understanding its mechanism and personalized therapy.

CASE SUMMARY
A RCAD patient and her family were studied to investigate potential responsible genes by the whole exome sequencing (WES). Candidate pathogenic variants were validated by Sanger sequencing. The clinical characteristics of RCAD patient were collected from medical records. Unlike those typical RCAD patients, we observed renal manifestation and prediabetes phenotype, but not reproductive organ phenotype and hypomagnesaemia. A novel 7-bp deletion mutation in exon 4 of the hepatocyte nuclear factor 1B, NM_000458: c.882_888del (p.V294fs), was identified by WES and confirmed by Sanger sequencing.

CONCLUSION
This novel mutation identified in a Chinese family with RCAD syndrome might be the molecular pathogenic basis of this disorder.

Key Words: Renal cysts and diabetes; Hepatocyte nuclear factor 1B; Exome sequencing; Novel mutation; Autosomal dominant disorder; Case report

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INTRODUCTION

Renal cysts and diabetes (RCAD) syndrome (OMIM: 137920) is an autosomal dominant diabetic renal disease resulting from abnormal renal development. Highly variable phenotypes of the renal disease include renal cysts, glomerular tufts, aberrant nephrogenesis, primitive tubules, irregular collecting systems, oligomeganephronia, enlarged renal pelvices, abnormal calyces, small kidney, single kidney, horseshoe kidney, and hyperuricemic nephropathy[1]. The diabetic phenotypes of this disorder usually occur earlier than age 25 years and patients are thus diagnosed as having maturity-onset diabetes of the young type 5 (MODY5)[2]. Nevertheless, typical diabetic phenotypes may not occur in some cases.

At the molecular level, the RCAD syndrome is related to mutations of hepatocyte nuclear factor 1B gene (HNF1B). To date, more than 400 mutations of HNF1B gene have been identified in RCAD patients, and de novo mutations are encountered in up to 30%-50% of cases[3]. These mutations include missenses, nonsenses, frame shifts, splice site mutations, small indels, and large deletions. In fact, HNF1B-associated syndrome is much complicated, as this gene encodes a transcription factor of the homeodomain-containing superfamily that is expressed in multiple organs[4]. Most RCAD patients often present with renal cysts and renal function decline that precede the diabetes. Besides the phenotypes of diabetes and renal presentation, RCAD patients may also have anomalies of the organs such as the genital tract, including vaginal aplasia, rudimentary uterus, bicornuate uterus, epididymal cysts, and atresia of the vas deferens[5]. Thus, heterogeneous presentation of the multisystem phenotype is often found in HNF1B-associated syndrome. For example, a case study suggests that lack of HNF1B expression is related to chromophobe renal cell carcinoma, a rare renal cancer[6]. Notably, diabetes and renal cysts are not always present in HNF1B-mutated patients. Moreover, the phenotype of HNF1B mutant carriers is highly variable within and between families[7]. Recently, the clinical characteristics of HNF1B-related disorders in 33 patients were reported in a Japanese population[8]. Analysis of genotype-phenotype correlation showed that some clinical characteristics were significantly different between patients with heterozygous variant of HNF1B and those harboring a deletion of HNF1B. However, RCAD patients in the Chinese population are rarely reported. Here we report a frame shift mutation of HNF1B gene in a Chinese family with RCAD syndrome that has never been described previously.

CASE PRESENTATION

Chief complaints

A 24-year-old Chinese Han woman was admitted to our department of nephrology for sudden back pain and frequent micturition.

History of present illness

The patient also suffered from a temporary fever with the highest temperature of 41
History of past illness
The patient was hospitalized in the department of urology at our hospital 2 years ago, and diagnosed with bilateral multiple renal cysts. She was the sole child of her parents and denied the genetic history of kidney diseases.

Personal and family history
The patient denied a family history of kidney diseases.

Physical examination
The patient’s temperature was 41 °C, heart rate was 98 bpm, respiratory rate was 20 breaths per minute, and blood pressure was 110/76 mmHg.

Laboratory examinations
Laboratory test showed elevated levels of serum creatinine and uric acid (Table 1). Routine blood test showed normal white blood cell, neutrophil, and lymphocyte counts. Routine urine tests showed elevated levels of uric leukocytes and red cells, but without urine protein. The liver enzyme and magnesium levels were normal. Notably, the patient’s plasma glucose level was 6.88 mmol/L.

Imaging examinations
In order to confirm the previous diagnosis, abdominal ultrasound examination and computed tomography were performed. Result showed bilateral slight renal atrophy with hyperechogenicity and multiple renal cysts (Figure 1A and B). The diameter of the largest cysts in the left and right kidneys was 2.4 cm and 2.0 cm, respectively. No obvious structural anomalies were observed in other abdominal organs including the liver, spleen, pancreas, and gallbladder.

MULTIDISCIPLINARY EXPERT CONSULTATION
To further analyze the renal disease, histopathology study of renal biopsy was performed. A total of six glomeruli were observed, with one glomerulus having ischemic sclerosis. The volume of the ischemic glomerulus was increased, while the mesangial cells and matrix showed slight hyperplasia. The morphology of podocytes and the basal lamina was normal. There was no obvious positive signal of Congo red staining and Masson staining. Granular degeneration of renal tubular epithelial cells with focal tubular atrophy was observed. The cystic structure with serous substances was visible in three tubular lumens (Figure 1C and D). Mild to moderate intimal and medial thickening was observed in arcuate and interlobular arteries. All the immunological staining including IgA, IgG, IgM, complement C3, C4, C1q, κ, and λ was negative. Electron microscopy showed renal interstitial fibrosis, tubular basement membrane shrinkage, matrix collagen fibrosis, and lymphatic and monocyte infiltration.

As her serum glucose level was higher than normal, we wondered whether islet function was impaired. Thus, the release of insulin and C-peptide was measured by oral glucose tolerance test. As shown in Figure 2, the concentration of serum glucose constantly increased until 2 h after oral administration of glucose, which indicated a deficiency of insulin. However, autoantibody against diabetes was negative.

Blood samples were collected from this patient and her parents for genomic DNA extraction using the CWBIO Blood Genomic DNA Mini Kit (CWBIO, Beijing, China). Whole exome sequencing (WES) was performed by Chigene (Beijing) Translational Medical Research Center Co. Ltd (Beijing, China).

The sequence analysis revealed a novel heterozygous small deletion mutation, NM_000458: c.882_888del (p.V294fs), in exon 4 of the HNF1B gene. Sanger sequencing was performed to validate the identified variation (Figure 3A). The mutation was excluded from the Single Nucleotide Polymorphism database and the Human Genetic Variation Database. This de novo mutation was not found in her parents. The mutation was located in the DNA-binding domain of HNF1B, which contained about 60 amino acid residues and was highly conserved among species (Figure 3B). This variant can be classified as “pathogenic” (PS2+, PM2+, PM4) according to the American College of Medical Genetics and Genomics (ACMG) standards and guidelines[9]. After identifying the mutation in HNF1B gene, we also calculated the HNF1B score based on
Table 1 Laboratory data at presentation

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<td>Serum creatinine, umol/L</td>
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<td>56.9</td>
<td>69</td>
<td>45-105</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73m²)</td>
<td>59↓</td>
<td>110</td>
<td>110</td>
<td>&gt; 90</td>
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<tr>
<td>Serum uric acid, umol/L</td>
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<td>362.5</td>
<td>378.6</td>
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<tr>
<td>Cystatin-C, mg/L</td>
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<td>0.89</td>
<td>0.79</td>
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<td>PTH, pg/mL</td>
<td>79.40↑</td>
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<td>60</td>
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Blood values in result column indicate the abnormal values out of the reference range. WBC: White blood cell; NEUT%: Neutrophil ratio; LYMP%: Lymphocyte ratio; HGB: Hemoglobin; RBC: Red blood cell; UPE: Urinary protein excretion; PTH: Parathyroid hormone; IAA: Insulin autoantibody; GADA: Glutamic acid decarboxylase antibody; ICA: Islet cell antibody.
those items including antenatal discovery, family history, and the involved organs including the kidney, pancreas, liver, and genital tract. This tool provides a more rational approach to select patients for \(\text{HNF1B} \) screening\[10\]. The \(\text{HNF1B} \) score of this patient was 8, just the same as the optimal cutoff threshold for the negative predictive value.

**FINAL DIAGNOSIS**

The final diagnosis of the presented case was RCAD syndrome.

**TREATMENT**

The patient received metformin to control blood sugar, and renin-angiotensin-aldosterone system blockade to delay the progression of kidney disease. She was recommended to have a high-quality protein, low-salt (< 6 g/d) diabetes diet.

**OUTCOME AND FOLLOW-UP**

After 2 year of follow-up, the patient's blood glucose and renal function were relatively stable.
DISCUSSION

We report a novel small deletion mutation in exon 4 of the HNF1B gene in a RCAD patient from a Chinese family. As RCAD syndrome is an autosomal dominant disorder, the de novo mutation might occur at the somatic level, as the genotypes of parents are normal.

HNF1B is a developmentally regulated transcription factor required for tissue-specific gene expression in mouse epithelial cells[11]. It activates or represses transcription of target genes through binding of its specific domain. A previous study showed that mice with renal-specific inactivation of HNF1B developed polycystic kidney disease, and renal cyst formation was accompanied by a drastic defect in the transcriptional activation of UMOD, Pkd1, and Pkd2 genes[12]. Recently, cell experiment also showed that ablation of HNF1B in proximal tubule cells led to a shift from oxidative phosphorylation to glycolysis[13]. Such evidence suggests that the HNF1B gene is vital for mouse renal development and function. In humans, mutations of the HNF1B gene are found in patients with inherited and sporadic malformations of the kidney and genitourinary tract. Recently, the mutant spectrum of HNF1B gene was analyzed in a Japanese population and their finding of genotype-phenotype correlation was interesting[8]. The clinical characteristics of HNF1B-associated syndrome include renal phenotype, diabetes, pancreatic phenotype, and reproductive organ phenotype[8]. A study in 2018 found that kidney anomalies including bilateral cystic dysplasia and bilateral hyperechogenic kidneys were the most frequent[14]. In addition, more than one-third of the patients with HNF1B mutations developed moderate to severe chronic kidney disease. Our patient was diagnosed as having bilateral multiple renal cysts at the age of 22 years. Her renal manifestation included multiple renal cysts and hyperechogenicity. Histopathology study of renal biopsy confirmed the kidney anomalies in glomeruli and tubules. Analysis of HNF1B score suggested that her molecular basis of the disease might be associated with mutation of HNF1B gene.

The second frequent clinical characteristic of HNF1B-associated syndrome is diabetes. More than half of the patients with HNF1B mutations presented diabetes or prediabetes. Although no obvious structural anomalies were observed in other abdominal organs including the liver, spleen, pancreas, and gallbladder, a functional
Figure 3 Mutation analysis of the renal cysts and diabetes patient. A: Sanger sequencing of the renal cysts and diabetes patient (upper panel) and her parents (lower panel). Black arrow indicates the mutation position; B: The amino acid sequence of the DNA-binding domain of HNF1B is highly conserved among species.

test showed that the patient’s islet function was impaired, which suggested the existence of diabetes. This is also in line with the fact that RCAD patients often present with renal phenotype preceding the diabetes, as diabetes in these cases usually appears in the second and third decades of life[15]. Another characteristic of HNF1B-associated syndrome is hypomagnesaemia. However, this was absent in our patient. Comparing all the clinical characteristics of our patient with those in literature, we speculated that the patient was just at the early stage of RCAD syndrome.

Currently, more than 400 mutations of HNF1B gene have been recorded in the ClinVar database. Among the records in the ClinVar, 303 records of mutation are classified as “pathogenic” and “likely pathogenic”. As this gene encodes a transcription factor highly conserved among species, small indels and point mutations of HNF1B gene are found to be pathogenic. Nevertheless, copy number variations (CNVs) including microdeletion and microduplication of HNF1B gene can also be pathogenic. Fu et al[16] found that CNVs of HNF1B region were revealed by chromosome microarray analysis testing in fetal multicystic dysplastic kidneys. The encoded protein has three domains. The N-terminal domain (8-173) contains a dimerization sequence and an acidic region that may mediate the formation of HNF-1B homodimers or heterodimers with the related protein HNF-1[17]. The homeodomain (240-305) is the DNA-binding domain involved in the transcriptional regulation of key eukaryotic developmental processes, and its crystal structure has already been determined[18]. The C-terminal domain (314-550) is responsible for the activation of transcription. The homeodomain is the most conservative region (Figure 3). The 7-bp deletion mutation of HNF1B gene leads to a frame shift mutation and the mutated protein lacks the C-terminal domain. Based on the gene function and the genotype-phenotype correlation in this family, the mutation was classified as “pathogenic” according to the ACMG guidelines. Moreover, point mutations of this motif are also classified as “pathogenic” in the ClinVar database.

Here, we summarize the previously reported HNF1B mutations in the Chinese population (Table 2). Most studies of the mutations in HNF1B gene in the Chinese population are concerned with MODY5. For example, Wang et al[19] found a substitution of S36F in an MODY family. Amazingly, the phenotype of mutation carriers in this family was different: One had early onset diabetes, renal function impairment, and renal cyst, while the other had impaired glucose tolerance only. Similarly, a case report by Wang et al[20] showed that a missense mutation (c.1007A>G, p.H336R) in
the \textit{HNF1B} gene was found in a Chinese family of MODY with diabetic kidney disease. However, in these cases, the diabetes phenotype occurred earlier than renal phenotype. These findings suggest that the phenotype of \textit{HNF1B}-related disorders might be relative to ethnic region.

**CONCLUSION**

A novel deletion mutation of \textit{HNF1B} gene (NM_000458: c.882_888del, p.V294fs) was identified in a Chinese family with RCAD syndrome by using WES and Sanger sequencing. Considering the gene function and the genotype-phenotype correlation, mutation location, and its conservativeness, this mutation is considered to play a pathogenic role in the development of RCAD syndrome.

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Ultrasound features of primary non-Hodgkin’s lymphoma of the palatine tonsil: A case report

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Author contributions: Jiang R drafted the manuscript; Zhang HM was responsible for data analysis and manuscript preparation; Wang LY and Cui XW revised the manuscript; Pian LP supervised the work; all authors issued final approval for the version to be submitted.

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Abstract

BACKGROUND
Lymphomas are the second most common malignancy of the head and neck. In this region, the vast majority of extranodal lymphomas are located in the palatine tonsil, accounting for about 51%. Tonsillar lymphomas are aggressive tumors with intermediate- or high-grade histology. We here report a case of primary non-Hodgkin's lymphoma of the palatine tonsil and analyze its ultrasound features.

CASE SUMMARY
A 40-year-old man presented with right palatine tonsil swelling for 2 mo after a cold, accompanied by dysphagia, snoring, and suffocation. He had no sore throat, fever, or history of upper respiratory tract infection or tuberculosis. The patient was generally in good health and denied other diseases. He was diagnosed with acute tonsillitis initially and treated with antibiotics for 7 d. However, there was no improvement with the treatment. Tonsil biopsy and ultrasound-guided biopsy of the biggest lymph node of the right neck showed the typical pathology of non-Hodgkin lymphoma.

CONCLUSION
Primary lymphoma of the tonsils is rare, and its diagnosis is challenging. Ultrasound is a useful modality in diagnosing oropharyngeal diseases, and can clearly show the features of this tumor, but the final diagnosis should be established by histology.

Key Words: Ultrasound; Primary non-Hodgkin’s lymphoma; Palatine tonsil; Case report
Primary lymphoma involving the tonsils is a rare malignancy. We report a 40-year-old man presenting with right palatine tonsil swelling for 2 mo confirmed as a tonsillar lymphoma. Ultrasound can clearly show the features of primary non-Hodgkin’s lymphoma of the tonsils and could be a useful imaging modality in diagnosing oropharyngeal diseases.

**INTRODUCTION**

Lymphomas of the head and neck arise from lymph nodes as well as extranodal sites. Waldeyer’s ring is the most common anatomical site for extraneous lymphoma in this region (35%-65% of all head and neck lymphomas). Within the Waldeyer’s ring, more than 50% of lymphomas arise in the palatine tonsil[1,2]. Patients with tonsillar lymphomas may present with unilateral tonsil enlargement, sore throat, dysphagia, and/or lump in the throat and/or neck[3]. A few patients have fever, emaciation, night sweat, or other systemic symptoms. Diagnosis is challenging because of the unremarkable clinical presentation. Ultrasound is a commonly used modality in the detection of superficial organs, and has advantages including real time and absence of ionizing radiation. We here report a case of primary lymphoma of the palatine tonsil and analyze the ultrasound features for diagnosis.

**CASE PRESENTATION**

**Chief complaints**

A 40-year-old man presented with right palatine tonsil swelling for 2 mo.

**History of present illness**

The patient presented with right palatine tonsil swelling for 2 mo after a cold, accompanied by dysphagia, sleep snoring, and suffocation. He had no sore throat, fever, or history of upper respiratory tract infection or tuberculosis. He was diagnosed with acute tonsillitis initially and treated with antibiotics for 7 d. However, there was no improvement with the treatment.

**History of past illness**

The patient was generally in good health and denied other diseases.

**Personal and family history**

The patient did not have any addictions or any significant family history.

**Physical examination**

Physical examination revealed right-sided tonsillar enlargement (grade III) with surface ulceration, but without pharyngeal portion hyperemia. Several mobile, nontender lymph nodes were palpable in the right swelling submandibular area, with the largest measuring about 5 cm × 7 cm.

**Laboratory examinations**

Results of biochemical, serologic, and pathologic examinations were all within normal limits. Bone marrow test showed normal erythrocyt/myeloid ratio and percentages of myeloid and lymphoid cells.
Imaging examinations
Ultrasound (7-12 MHz linear array transducer, ARIETTA 70, Hitachi Healthcare, Japan) of the right neck and submandibular area demonstrated that the volume of the right tonsil increased significantly. It appeared as a hypoechoic round mass with well-defined margins, homogeneous echo, and rich blood flow signals (Figure 1). In the level IA area of the right neck, multiple enlarged lymph nodes were seen with a clearly defined boundary and hypoechoic internal echoes. They partly integrated without visible echogenic hilar structures and remarkable blood flows could be observed on color Doppler imaging.

FINAL DIAGNOSIS
Non-germinal center type diffuse large B cell lymphoma (DLBCL) (Figure 2).

TREATMENT
The patient underwent chemotherapy followed by radiotherapy. The chemotherapy regimen included six courses of cyclophosphamide, doxorubicin, vincristine, and prednisone.

OUTCOME AND FOLLOW-UP
At the 6-mo follow-up, there were no signs of any recurrence of the tumor. No further follow-up was available to be reported.

DISCUSSION
Primary lymphomas are aggressive tumors of lymphoid tissues that are comprised of lymphocytic or reticulocytic derivatives of varying degrees of differentiation[4]. Lymphomas are the second most common malignancy of the head and neck after squamous cell carcinoma[5]. Approximately 2.5% of malignant lymphomas arise in the oral and paraoral region, mainly from Waldeyer’s ring, including the nasopharynx, palatine tonsils, adenoids, lingual tonsils, and the base of the tongue[6,7]. Within the Waldeyer’s ring, more than 50% of lymphomas arise in the palatine tonsil[8,9]. Most lymphomas involving the tonsil are non-Hodgkin’s lymphomas (NHLs), and the most prevalent lymphoma subtype is DLBCL[10,11], which comprises approximately 30% of all NHLs[12]. Tonsillar lymphomas are aggressive tumors of intermediate or high grade, mainly occurring in men with a male/female ratio of 1.3:1.1[1]. However, the disease can affect patients with a wide age range including children[13,14]. The tumors may present in early stage and have a favorable outcome despite a high incidence of aggressive histology. Common symptoms include mass in the throat, dysphagia, odynophagia, and sore throat, some of which are similar to those of tonsillitis. Only 25% of patients have systemic symptoms in head and neck lymphomas[2]. Due to the similar clinical presentations, differentiation of primary tonsil lymphoma from tonsillitis or peritonsillitis is difficult. The disease is easily misdiagnosed if patients have no lymphadenopathy symptoms[15]. As in the present case, the patient was misdiagnosed with tonsillitis and received unnecessary treatment of antibiotics. The misdiagnosis resulted in increased mental anguish as well as medical burdens to the patient. Unilateral tonsillar enlargement with regional swollen lymph nodes should raise suspicion for malignancy of the tonsils. Clinicians should be aware of such infrequent primary lymphoma in the tonsils so as to avoid the misdiagnosis. As for the treatment, combined chemotherapy and involved-field radiation therapy is currently the preferred treatment for the majority of patients with localized primary tonsillar lymphoma.

Currently, ultrasound is not routinely used for the diagnosis of oropharyngeal diseases. Coquia et al[16] obtained clear images of tonsils on B mode and color Doppler ultrasound. Normal tonsils are presented on ultrasound as homogeneously ovoid echogenic soft tissue with stripes and internal linear echogenicity. Posterior to the palatine tonsil is the pharyngeal constrictor, which is hypoechoic on the ultrasound. Color Doppler ultrasound can show the multiple vessels of the external carotid artery.
Figure 1 Ultrasound showed a hypoechoic round mass in the right tonsil with well-defined margins, homogeneous echogenicity, and rich irregular blood flow.

Figure 2 Photomicrograph of a diffuse large B cell lymphoma demonstrating that regional tumor cells (orange arrows) are mononuclear or multinucleated, resembling histiocytes and Reed-Sternberg cells (400 ×, hematoxylin-eosin staining).

supplying the palatine tonsil.

According to our observations, the characteristics of primary tonsil lymphomas are as follows: Spherical tonsils with significantly increased volume; hypoechoic structures with the loss of normal striated pattern; and vascular proliferation and the internal irregular color signal (Figure 3).

Contrast-enhanced computed tomography (CT) and positron emission tomography/CT are frequently used to confirm the diagnosis of oropharyngeal tumors. However, they are limited by the high cost, radiation dose, motion, and dental amalgam artifact. Currently, tissue-based histopathological examination remains the only reliable diagnostic method, but it is invasive. Ultrasound could be used for diagnosing oropharyngeal diseases as it is portable, readily available, nonionizing, and with better resolution. The present case suggests that ultrasound is useful for the differential diagnosis of oropharyngeal inflammation and tumor. However, more case studies are needed to establish the best effective diagnostic strategy for lymphoma of the tonsils.

CONCLUSION

Primary lymphoma involving the tonsils is a rare malignancy and it is difficult for clinicians to make a correct diagnosis timely based on the physical examination alone. Currently, multiple imaging modalities have been used in the differential diagnosis of oropharyngeal diseases. Ultrasound can clearly show the features of primary lym-
Jiang R et al. Ultrasound features of NHL of the tonsil

Figure 3 Comparison of bilateral tonsils. The normal tonsil (indicated by the arrows) presents as homogeneously echogenic soft tissue with stripes and linear echo inside, while the right tonsil as a hypoechoic round mass with the loss of normal striated pattern.

phoma of the tonsils and could be a useful imaging modality in diagnosing oropharyngeal diseases. However, a definitive diagnosis can be established only by histopathology.

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Percutaneous drainage in the treatment of intrahepatic pancreatic pseudocyst with Budd-Chiari syndrome: A case report

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Author contributions: Li B and Yang XL proposed the idea and supervised, reviewed and edited the writing; Zhu G collected the data, analyzed the literature, and wrote the manuscript; Peng YS collected and analyzed the literature; Fang C assisted with literature analysis, manuscript preparation and image analysis; All authors read and approved the manuscript.

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Abstract

BACKGROUND
Intrahepatic pancreatic pseudocyst (IHPP) is an extremely rare complication of acute pancreatitis, with only a few cases previously described in the literature. To the best of our knowledge, IHPP with Budd-Chiari syndrome (BCS) has not yet been described.

CASE SUMMARY
A 35-year-old male presented with abdominal pain, vomiting and anorexia, followed by severe swelling of the lower body after 4 d. The morphological assessment (using computed tomography revealed the presence of a huge cyst of 18.28 cm × 10.34 cm under the liver capsule accompanied by a large amount of ascites. Percutaneous puncture allowed us to detect a high level of amylase in the collection, confirming the diagnosis of IHPP. The cyst was treated by percutaneous drainage, producing complete resolution of the cyst.

CONCLUSION
IHPP can be treated with percutaneous drainage, endoscopic drainage, surgery or even conservative treatment, depending on the specific condition. We recommend percutaneous drainage as the first choice of treatment when IHPP with secondary BCS.

Key Words: Intrahepatic pancreatic pseudocyst; Pancreatic pseudocyst; Pancreatitis; Budd-Chiari syndrome; Percutaneous drainage; Case report

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Core Tip: Intrahepatic pancreatic pseudocyst (IHPP) is a rare complication secondary to pancreatitis. We present herein, a rare case of IHPP with Budd-Chiari syndrome (BCS), developed in a male patient who had undergone left kidney surgery for kidney rupture due to pancreatitis. Cyst drainage analysis showed high levels of amylase. This case highlights that for BCS secondary to IHPP, emergency percutaneous drainage is a safe and effective treatment strategy.

INTRODUCTION

Pancreatic pseudocysts are common complications that occur at least 4 wk after the manifestation of acute or chronic pancreatitis. They are a collection of tissue and fluid formed by a fibrotic non-epithelial wrap. Pancreatic pseudocysts can form anywhere in the abdominal cavity, but due to the presence of hydrolytic enzymes in pancreatic juice they most commonly form around the pancreas, and about 22.4% of patients may have ectopic pancreatic pseudocysts, such as mediastinum, spleen, stomach and even scrotum[1-3]. However, intrahepatic pancreatic pseudocysts (IHPPs) are very uncommon. We report an extremely rare case of a patient with secondary Budd-Chiari syndrome (BCS) caused by a huge IHPP compressing the hepatic vein, and the patient was cured by treatment with percutaneous drainage.

CASE PRESENTATION

Chief complaints

A 35-year-old male patient came to the emergency room of our hospital with complaints of abdominal pain and severe swelling of the lower body.

History of present illness

The patient’s symptoms started 2 wk prior and were accompanied by abdominal pain, vomiting, and anorexia, which had worsened during the last 48 h.

History of past illness

The patient had undergone partial left nephrectomy in an outside hospital 4 mo earlier due to rupture of his kidney caused by severe pancreatitis.

Personal and family history

His personal and family history was unremarkable.

Physical examination

Physical examination revealed obvious swelling of the body below the chest, tenderness in the abdomen, and palpable swollen liver under the costal margin, but no obvious jaundice was found (Figure 1A and B).

Laboratory examinations

Laboratory analyses revealed a white blood cell count of 7510/mm³ and hemoglobin level of 92 g/L. They also found slightly elevated levels of serum alanine aminotransferase (101 U/L), serum aspartate aminotransferase (81.1 U/L), and total bilirubin (24 µmol/L). Additionally, the levels of serum amylase, lipase and alkaline phosphatase were found to be elevated at 247, 297 and 336 U/L, respectively.

Imaging examinations

An admission abdominal computed tomography (CT) scan revealed the presence of
two low-density cystic lesions in the liver (the largest being 18.28 cm × 10.34 cm), multiple pancreatic pseudocysts, massive ascites, portal hypertension with open collateral circulation and high-density imaging of the left kidney area. An enhanced CT scan showed that the lesion caused significant compression of the inferior vena cava (Figure 2).

**FINAL DIAGNOSIS**

The final diagnosis of the presented case was IHPP with secondary BCS.

**TREATMENT**

Despite the lack of a definitive diagnosis based on the liver lesions, we decided to perform radiation-guided percutaneous drainage for intrahepatic lesions in order to relieve the compression of the inferior vena cava as soon as possible (Figure 3A). The cystic fluid was gray-yellow; analysis showed that it had high levels of amylase (16480 U/L) and fluid cultures were negative, consistent with pancreatic pseudocyst.

**OUTCOME AND FOLLOW-UP**

Approximately 1000 mL of fluid slowly flowed out of the cyst over a week and the patient was discharged 9 d after drainage without any complications, and all the original signs disappeared (Figure 1C and D). Due to the fear of recurrence of IHPP, the drainage tube was removed at the time of discharge. Eventually, 24 d after the drainage, the patient was free of disease and a CT scan showed the disappearance of
Figure 2 Computed tomography image before percutaneous drainage. A: Multiple cystic space in the liver (the size of the largest cyst was 18.28 cm x 10.34 cm), and fluid around the spleen; B: Multiple pseudocysts in the pancreatic body and tail; C: Enhanced computed tomography scan showing compressed inferior vena cava; D: High-density shadow after left kidney surgery.

Figure 3 Imaging during and after percutaneous drainage. A: Radiation-guided percutaneous drainage and diffusion of contrast agent in the cyst; B: Computed tomography scan shows disappearance of intrahepatic cysts and the drainage tube (orange arrow).

intrahepatic cysts (Figure 3B), so the drainage tube was then removed. During the 24 d of treatment, the patient performed well, without any complaints.

DISCUSSION
IHPPs are extremely rare and were first reported by Cécile et al[4] in 1974. CT is generally considered as the modality of choice for the diagnosis of IHPP, which can show low-density cystic lesions in the liver and the shape of the pancreas[5]. However
clinical diagnosis of IHPP is quite difficult, due to the rarity of the diagnosis of IHPP, and some patients with normal pancreatic shape only show elevated serum amylase and lipase[6]. Therefore, it is necessary to differentiate from a variety of intrahepatic cystic lesions, such as liver abscesses, peribiliary cysts, echinococcal cyst, intrahepatic bile duct dilatation, etc.

The formation of IHPP can be explained by two pathophysiological mechanisms. The first is that the pancreatic juice around the pancreas penetrates through the posterior layer of the parietal peritoneum to reach the lesser sac, and along the omentum or gastrohepatic ligament to the left hepatic lobe; this fluid will corrode the liver capsule and commonly causes a subcapsular cyst in the left hepatic lobe[7]. The other mechanism is that pancreatic juice can diffuse from the head of the pancreas to the porta hepatitis (transverse fissure) along the hepatoduodenal ligament, which results in the formation of intraparenchymal collections[8]. In our case, CT scans showed that the pancreas body and tail were abnormal, and the cysts were located under the liver capsule, which is more in line with the first mechanism. In addition, there is another mechanism, in which the patient’s retroperitoneum is incomplete due to kidney surgery, and the fluid around the pancreas could easily reach the liver, thus corroding the liver capsule and forming an IHPP.

Percutaneous, endoscopic, and surgical drainage are the main treatments for symptomatic pancreatic pseudocysts[9,10]. However, there is no clear guideline for pseudocysts in the liver. Analysis of the previous literature revealed that most patients can be treated by percutaneous or endoscopic drainage, although surgical resection is another option in the case of intrahepatic cyst rupture or drainage failure[11]. In addition, some patients can be cured by conservative treatment[12]. In the case described here, the patient also had secondary BCS, which, while rare, is accompanied by high mortality. If untreated, 70% of patients die within 1 year, and the most common cause of death is liver failure[13].

We treated the patient with emergency percutaneous drainage for the following four reasons. (1) Percutaneous drainage is safe and effective in treating subcapsular cysts of the liver. At the same time, the slow drainage of the cyst fluid can prevent the circulatory system disturbance caused by the sudden decrease of intra-abdominal hypertension. (2) The patient had multiple pancreatic pseudocysts, and the drainage tube connected to the outside can effectively prevent the recurrence of IHPP. (3) The patient also presented with acute secondary BCS. So, in order to prevent fulminant and progressive liver failure and hepatic encephalopathy, the treatment with emergency percutaneous drainage was safe and effective. And (4) Gastric or duodenal varices caused by portal hypertension due to BCS are contraindications of endoscopic drainage[14,15], and high complications of surgical drainage will also increase the risk of death for this patient. Therefore, percutaneous drainage is recommended for patients with huge intra-abdominal pressure caused by IHPP, especially for patients with BCS.

CONCLUSION

IHPP is a rare disease and CT is the primary diagnostic method. However, it is often necessary to distinguish IHPP from a variety of complex intrahepatic cystic lesions. The diagnosis can be confirmed if the analysis of cystic puncture fluid indicates high amylase levels. Treatment options for IHPP include percutaneous/endoscopic drainage, surgical resection, or conservative treatment. However, the appropriate treatment method should be selected according to the location, size, number and complications of IHPP in the liver.

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Postmenopausal women with hyperandrogenemia: Three case reports

Xiao-Dan Zhu, Lin-Yu Zhou, Jian Jiang, Tian-An Jiang

CASE REPORT

BACKGROUND
Diagnosing hyperandrogenemia in postmenopausal women is very difficult. It occasionally manifests as excessive hair growth or with no clinical manifestations, and is therefore often misdiagnosed or missed altogether. Ovarian steroid cell tumors that cause hyperandrogenemia in women account for approximately 0.1% of all ovarian tumors. Due to the low incidence, corresponding imaging reports are rare, so ovarian steroid cell tumors lacks typical imaging findings to differentiate it from other ovarian tumors. Therefore, we summarized its clinical and imaging characteristics through this case series, and elaborated on the differential diagnosis of steroid cell tumors.

CASE SUMMARY
We report three cases of postmenopausal women with hyperandrogenemia. Only 1 patient showed virilization symptoms, the other two patients were completely asymptomatic. All patients underwent total hysterectomy + bilateral adnexectomy. Histological results showed one case of Leydig cell tumor and two cases of benign, non-specific steroid cell tumor. After the operation, the androgen levels of all patients returned to normal, and there was no clinical recurrence since follow-up.

CONCLUSION
Although virilization caused by increased serum testosterone levels is an important clinical feature of ovarian steroid cell tumors, it is often asymptomatic. A solid, slightly hypoechoic, round or oval mass with uniform internal echo, richer blood flow in the solid part, and low resistance index are typical imaging features of ovarian steroid cell tumors. Diagnosis of ovarian steroid cell tumors after menopause is challenging, but surgery can be used for both diagnosis and clear treatment.
INTRODUCTION

Female androgenemia can cause virilization syndromes, such as progressive hirsutism, acne, vocal cord thickening, amenorrhea, breast atrophy, and male pattern baldness. However, the diagnosis of postmenopausal women with hyperandrogenemia is very difficult because the clinical manifestations are commonly absent or comprise mostly hair overgrowth, so the disease is often attributed to normal hormonal changes with ageing. Diseases that cause hyperandrogenemia in women include ovarian functional tumors, polycystic ovary syndrome, congenital adrenal hyperplasia, congenital follicular cell hyperplasia, acanthosis nigricans, and Cushing's syndrome, among others[1]. Ovarian steroid cell tumors (OSCTs) are a rare sex cord-stromal tumor and account for approximately 0.1% of all ovarian tumors[2]. In 2014, the WHO divided them into ovarian steroid cell tumor, not otherwise specified (OSCT-NOS), and ovarian Leydig cell tumors (OLCTs)[3]. OLCTs are very rare, mainly benign, and more common in menopausal women. These tumors usually occur in a unilateral ovary and are small and solid[4]. Most OSCT-NOS lesions consist of a solid, oval mass with a regular shape that occurs in a unilateral ovary, and is mainly benign. The average age of onset is 42 years. Occurrences in postmenopausal women or children are rare[5,6].

CASE PRESENTATION

Chief complaints

Case 1: A 60-year-old female, who had been menopausal for 7 years, presented with a progressive increase in body hair.

Case 2: A 55-year-old female, who had been menopausal for 5 years, presented with a mass in the left appendix on physical examination.

Case 3: A 52-year-old female, who had been menopausal for 1 year, presented with ovarian cysts found on physical examination.

History of present illness

Case 1: The patient with a progressive increase in body hair lasting for 6 mo.

Case 2: The patient’s mass had been present for 5 mo, and recently significantly increased in size.

Case 3: The patient’s mass had been present for 1 mo.

History of past illness

Case 1: The patient had a history of uterine fibroids and diabetes, and was currently...
taking metformin tablets, 0.5 g (Bid), and glimepiride tablets, 2 mg (Qd).

Case 2: The patient was in good health and had no history of special chronic diseases.

Case 3: The patient had a past history of hypertension, adenomyosis with multiple uterine fibroids, and bilateral kidney cysts.

**Personal and family history**

**Cases 1-3:** No abnormal personal or family histories.

**Physical examination**

**Case 1:** An increased amount of relatively long facial hair, pubic hair, and body hair in the groin area. No skin pigmentation, voice thickening, weight gain, facial fattening, abdominal circumference thickening, or other symptoms were observed.

**Cases 2 and 3:** There were no obvious abnormalities on physical examination.

**Laboratory examinations**

**Case 1:** The serum testosterone hormone level was significantly increased (504.5 ng/dL), but the levels of other sex hormones and tumor markers were normal. A mid-dose dexamethasone suppression test showed that testosterone was not suppressed (before inhibition: androstenedione, 3.7 ng/mL; testosterone, 504.5 ng/dL; and dehydroepiandrosterone sulphate, 65.5 µg/dL; after inhibition: androstenedione, 1.6 ng/mL; testosterone, 244.7 ng/dL; dehydrosulphate epiandrosterone, 41.2 µg/dL; and 17a hydroxyprogesterone, 0.1 nmol/L) (Table 1).

**Case 2:** The serum testosterone hormone level was significantly increased (258.09 ng/dL), and the levels of other sex hormones and tumor markers were normal (Table 1).

**Case 3:** The serum testosterone hormone level was significantly increased (326.03 ng/dL), but the levels of other sex hormones and tumor markers were normal (Table 1).

**Imaging examinations**

**Case 1:** Transvaginal ultrasonography (TVS) revealed atrophy of the uterus and bilateral ovaries. A slightly hyperechoic nodule with a diameter of approximately 1.23 cm was observed in the right ovary, with an unclear boundary (Figure 1A). Unfortunately, no blood flow images were available. Abdominal ultrasound showed normal liver, gallbladder, spleen and pancreas, and ascites was not detected. Enhanced magnetic resonance imaging (MRI) of the pelvis (Figure 2A) showed nodules in the right adnexal area, suggesting ovarian cysts. Contrast-enhanced computed tomography (CT) of the pelvis showed high-density shadows in the nodular tip of the right adnexal area, suggesting a sex cord-stromal tumor (Table 2).

**Case 2:** TVS revealed atrophy of the uterus. The left ovary showed a slightly hyperechoic mass of approximately 3.0 cm × 2.2 cm × 3.4 cm in size (Figure 1B), with clear borders (Table 2). Color Doppler flow imaging (CDFI) showed an abundant blood supply (Figure 3A), with a resistance index (RI) of 0.39. Abdominal ultrasound showed normal liver, gallbladder, spleen and pancreas, and ascites was not detected. Enhanced MRI of the pelvis revealed a space-occupying mass in the left adnexal area, suggesting a sex cord-stromal tumor (Figure 2C).

**Case 3:** TVS indicated a trend of uterine atrophy, with cystic and solid changes in the left ovary (Table 2). A solid, slightly hyperechoic mass of approximately 4.3 cm × 2.9 cm × 2.8 cm in size was observed in the left ovary (Figure 1C), with clear boundaries. CDFI showed an abundant blood supply in the mass (Figure 3B), with an RI of 0.55. Abdominal ultrasound showed normal liver, gallbladder, spleen and pancreas, and ascites was not detected. Enhanced CT of the pelvis showed a solid/cystic mass in the left adnexal area, suggesting a left uterine broad ligament fibroid with central degeneration (Figure 2D).
Table 1 Biochemical parameters determined before and after surgery

<table>
<thead>
<tr>
<th>Test (units/reference range)</th>
<th>Case 1 Before surgery</th>
<th>Case 1 After surgery</th>
<th>Case 2 Before surgery</th>
<th>Case 2 After surgery</th>
<th>Case 3 Before surgery</th>
<th>Case 3 After surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>LH (mUI/mL) (11.3-40.0)</td>
<td>9.91</td>
<td>18.58</td>
<td>16.98</td>
<td>38.61</td>
<td>6.72</td>
<td>ND</td>
</tr>
<tr>
<td>FSH (mUI/mL) (9.7-111.0)</td>
<td>22.9</td>
<td>48.7</td>
<td>20.75</td>
<td>107.99</td>
<td>14.88</td>
<td>ND</td>
</tr>
<tr>
<td>Total testosterone (ng/dL) (10.83-56.94)</td>
<td>504.5</td>
<td>35.7</td>
<td>258.09</td>
<td>17.5</td>
<td>326.03</td>
<td>21.25</td>
</tr>
<tr>
<td>Oestradiol (pg/mL) (&lt; 30)</td>
<td>51</td>
<td>11.8</td>
<td>73.21</td>
<td>10</td>
<td>71.38</td>
<td>ND</td>
</tr>
<tr>
<td>Progesterone (ng/mL)</td>
<td>0.49</td>
<td>0.3</td>
<td>0.43</td>
<td>0.1</td>
<td>0.24</td>
<td>ND</td>
</tr>
<tr>
<td>Androstenedione (ng/mL) (0.3-3.3)</td>
<td>1.6</td>
<td>ND</td>
<td>2</td>
<td>ND</td>
<td>1.7</td>
<td>ND</td>
</tr>
<tr>
<td>DHEA-S (mg/dL)</td>
<td>42.1</td>
<td>ND</td>
<td>50.5</td>
<td>ND</td>
<td>44.3</td>
<td>ND</td>
</tr>
<tr>
<td>17 OHP (ng/mL) (0.2-1.7)</td>
<td>1.7</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>17 OHP (ng/mL) 600 after ACTH stimulation test</td>
<td>0.1</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

17 OHP: 17-hydroxyprogesterone; ACTH: Adrenocorticotropic hormone; DHEA-S: Dehydroepiandrosterone-sulfate; FSH: Follicle-stimulating hormone; LH: Luteinizing hormone; ND: Not done.

Table 2 Radiological features

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelvic ultrasound</td>
<td>Hyperechoic nodule of Ro (12.3 mm)</td>
<td>Hyperechoic mass of Lo (34 mm x 22 mm)</td>
</tr>
<tr>
<td>Pelvic CT</td>
<td>Nodular slightly dense-shadow of Ro with visible enhancement after enhancement</td>
<td>ND</td>
</tr>
<tr>
<td>Pelvic MRI</td>
<td>Round-shaped abnormal signal range of Ro, T2W1 and DW1 are high signal, higher signal area can be seen in the center</td>
<td>A circular signal shadow of Lo, equal to T1 long and T2 signal, DW1 high signal, and obviously enhanced after enhancement</td>
</tr>
</tbody>
</table>

CT: Computed tomography; Lo: Left ovary; MRI: Magnetic resonance imaging; ND: Not done; Ro: Right ovary.

**FINAL DIAGNOSIS**

**Case 1**
Pathology indicated an LCT (Figure 4A): calretinin (CR) (+), chromogranin A (CgA) (-), cytokeratin (CK) (pan) (focus +), inhibin A (+), Ki-67 (6%), S-100 (-), CD99 (-), and smooth muscle actin (SMA) (-).

**Case 2**
Pathology showed an SCT-NOS lesion (Figure 4B): CK7 (-), CK (pan) (-), paired-box gene 8 (PAX-8) (-), inhibin A (+), CR (+), placental alkaline phosphatase (PLAP) (-), Wilms’ tumor gene (WT1) (-), Oct-4 (-), glypican 3 (GPC-3) (-), beta human chorionic gonadotropin (β-HCG) (-), Ki-67 (+, 3%), CD99 (+), S-100 (-), CD117 (-), CD30 (weak +), net dye (+), and E-cadherin (-).

**Case 3**
Pathology indicated an SCT-NOS lesion: CK (pan) (part +), estrogen receptor (ER) (-), progesterone receptor (PR) (-), inhibin A (+), CR (+), WT1 (-), human melanoma black 45 (HMB-45) (-), MelanA (+), CgA (-), synaptophysin (Syn) (-), Desmin (-), Ki-67 (+, 20%), CD34 (-), and epithelial membrane antigen (EMA) (-).
Figure 1 Transvaginal ultrasonography. A: A slightly hyperechoic nodule with an unclear boundary in the right ovary (case 1); B: The left ovary showed a slightly hyperechoic mass with clear boundary (case 2); C: A solid, slightly hyperechoic mass with clear boundary in the left ovary (case 3).

**TREATMENT**

**Case 1**
The patient underwent total hysterectomy + bilateral adnexectomy. A grey-white nodule with a diameter of approximately 1.7 cm was observed on the cut surface of the pathological specimen after the operation.

**Case 2**
The patient underwent total hysterectomy + bilateral adnexectomy. A clear, greyish-yellow, round nodule was observed on pathology after surgery, with a diameter of 2.3 × 3.0 cm.

**Case 3**
The patient underwent total hysterectomy + bilateral appendectomy. Intraoperative dissection showed that the left ovarian fluid was yellow and turbid, the cyst wall was thickened, and the inner section consisted of tough, yellowish tissue.

**OUTCOME AND FOLLOW-UP**

**Case 1**
The testosterone level of the patient was 57.1 ng/dL on the first postoperative day; the virilization symptoms gradually subsided. Follow-up after surgery continued for about 37 mo with no signs of clinical recurrence.

**Case 2**
The testosterone level of the patient was 17.5 ng/dL after the operation. Follow-up after surgery continued for about 21 mo with no signs of clinical recurrence.

**Case 3**
The testosterone level of the patient was 21.25 ng/dL after the operation. Follow-up after surgery continued for about 19 mo with no signs of clinical recurrence.
DISCUSSION

Sex cord-stromal tumors are classified into three main groups according to the WHO, and include pure stromal tumors, pure sex cord tumors, and mixed sex cord stromal tumors[7]. OSCTs belongs to a subtype of pure stromal tumors and is an ovarian tumor composed entirely or mostly of cells that secrete steroid hormones. OSCTs can secrete one or more steroid hormones, such as androgens, estrogen, cortisol, aldosterone, and progesterone, resulting in corresponding symptoms and signs, such as hyperandrogenemia, hyperestrogenia, Cushing syndrome, and refractory hypertension, with androgenemia as the most common[8]. In female hyperandro-
genism, adrenal and/or ovarian sources need to be distinguished. The cause of hyperandrogenemia caused by adrenal tumors is the secretion of excessive dehydroepiandrosterone sulphate[9], and the androgens secreted by most ovarian tumors are not regulated by gonadotropins or adrenocorticotropic hormone (ACTH). Therefore, adrenal CT and medium-dose dexamethasone suppression tests can be used to exclude adrenal sources. In case 1, the dose of dexamethasone experiment showed that testosterone was not inhibited, which confirmed this view.

The clinical manifestations of OSCTs are determined by the steroid hormones produced, and OSCTs can be divided into high-androgen types and high-estrogen types. Most OSCTs (80%) are of the high-androgen type, and approximately 20% of OSCTs are of the high-estrogen type[10,11]. High-androgen-type tumors mainly cause symptoms such as hirsutism, acne, a low and thick voice, an enlarged clitoris, laryngeal knots, breast atrophy, hair loss, and a low posterior hairline. High-estrogen-type tumors mainly cause symptoms such as irregular vaginal bleeding and endometrial hyperplasia. All patients in this case series exhibited high-androgen-type OSCTs. In case 1, the patient showed progressive hirsutism, and the patients in cases 2 and 3 showed no obvious clinical symptoms. We reviewed and summarized 87 cases of OSCTs reported in the English literature from 2000 to 2019, and found that only one case was reported as having no clinical symptoms[12]. All other OSCT patients will have corresponding clinical symptoms caused by endocrine abnormalities. In addition, clinical symptoms, such as abdominal pain and masses in the lower abdomen, can also occur. However, this asymptomatic patient has a long-term history of taking contraceptives, and OSCT was found during the diagnosis and treatment of infertility; the patient became pregnant naturally after tumor resection. Therefore, whether infertility is caused by OSCT is still inconclusive. In our case series, there are 2 cases without any clinical manifestations, so we believe that being clinically asymptomatic is one of the clinical features of OSCT that should be acknowledged.

Due to the low incidence of OSCTs, corresponding imaging reports are rare, and most of them are case reports, so the typical imaging features are not fully understood. Additionally, due to lack of clinical symptoms, particularly in postmenopausal patients, the patient is more likely to have a missed diagnosis or be misdiagnosed. On histology, OSCTs are generally well-defined and spherical, while LCTs are significantly smaller than SCT-NOS lesions. OSCTs are dominated by solid components; because most of them contain fat components, they were once called lipocytomas. On microscopy, the tumor cells are rich in lipids, and there are abundant capillary networks and vascular sinusoid structures in the tumor[13]. Ultrasound is the first choice for the detection and diagnosis of ovarian tumors due to its convenience, speed and non-invasiveness. OSCTs tend to occur in one ovary, and grey-scale ultrasound usually shows solid, round or oval nodules with clear boundaries. The internal echo is mainly slightly hyperechoic. The echo intensity may be related to the internal fat content. Because testosterone has the effect of increasing vasodilatory substances, most OSCTs exhibit rich blood flow signals dominated by low-resistance blood flow[14]. Since LCTs are very small and lack typical imaging features, this may cause poor visibility on ultrasound and CT examinations[15,16]. At the same time, in menopausal women, due to the reduced estrogen level and insufficient perfusion by
the ovarian artery blood, the appearance of the ovaries is reduced, and the echo of the ovaries is increased. CDFI usually indicates no blood flow signals in the ovaries[17]. Therefore, it is difficult to distinguish between OLCT tissue and normal atrophic ovarian tissue by ultrasound. At present, it is believed that SCT-NOS lesions are more easily recognized on imaging than LCTs.

Mature teratomas contain liquid fat and appear as a clear hyperechoic mass on grey-scale ultrasound. Thus, teratomas need to be differentiated from OSCTs. Especially when a small, hyperechoic mass appears on one ovary in menopausal women, the possibility of an OLCT cannot be ignored. However, most teratomas are mixed tumors with cystic and solid component. Lipid stratification can occur in the cystic part, and some of the lesions can contain bone tissue or teeth, appearing as hyperechoic nodules with rear acoustic shadows. CDFI usually shows no obvious blood flow signal these masses. Because teratomas contain very few non-secretory tissues that produce testosterone, they very rarely cause hyperandrogenism[18].

Thecoma that secrete estrogen are composed of lipid-rich ovarian membrane cells. Histologically, these tumors are mainly solid, with a hard texture and intact capsule, which can be combined with various forms of degeneration, such as calcification. On grey-scale ultrasound, thecoma appear as a round lobulated, hypoechoic mass with a smooth surface and are often accompanied by varying degrees of posterior sound attenuation, with clear or unclear boundaries; the internal echoes may be uniform or uneven. CDFI shows no obvious blood flow signals in thecoma, and estrogen secretion is the main distinguishing feature of OSCTs[19]. McGonagall syndrome can occur when the tumor is large.

Follicular membrane fibroids are derived from spindle-shaped collagen fibroblasts. They are sex cord-stromal tumors that occur in perimenopausal or postmenopausal women with inactive hormone secretion, and rarely become malignant. It accounts for 4% of all ovarian tumors, and often occurs in unilateral ovary. It is reported that the membrane fibroma may be related to Gorlin syndrome[20]. Follicular membrane fibromas and thecomas have similar features on grey-scale ultrasound. CDFI shows that these mass have no blood supply or secretory function, which are key to distinguishing follicular membrane fibromas from OSCTs.

When broad ligament leiomyomas become large and show degenerative changes, it is difficult to distinguish them from ovarian tumors. Therefore, accurate positioning of the ovary is the key to distinguishing between the two. Whirlpool or woven hypoechoic masses and pseudocapsules are characteristic ultrasound manifestations of leiomyomas. CDFI shows low blood flow signals inside and around these tumors. Similarly, the lack of endocrine function is also key to distinguishing leiomyomas from OSCTs.

Malignant sex cord stromal tumors arise from the primitive sex cord and/or stromal cells of the gonads, including granulosa, theca, Sertoli, or Leydig cells, as well as fibroblasts[21]. One of the most common subtypes is granulosa cell tumor (GCT), the adult and juvenile granulosa cell histological subtypes comprise the majority (> 70%) of malignant sex cord stromal tumors. GCTs are rare, low-grade ovarian stromal tumors with a granular cell morphology, and most secrete estrogen, which can induce endometrial hyperplasia. Endometrial hyperplasia and endometrial cancer, which is associated with GCTs, can manifest as abnormal uterine bleeding[21]. GCT is usually between 5 and 15 cm, and > 95% occurs unilaterally. Because GCT tissue is fragile and easily becomes detached, causing hemorrhagic necrosis and cystic transformation, the cut surfaces are typically solid and cystic with fluid or blood-filled cysts separated by solid, yellow to white, soft to firm tissue. So solid/cystic masses are typical imaging features of ovarian GCTs, and they are mostly arranged in intervals in a radial pattern. CDFI shows minimal to moderate blood flow signals in these tumors[22], with mostly low-resistance blood flow due to the vasodilator effect of estrogen. It is not difficult to distinguish ovarian GCTs from OSCTs using both clinical and imaging features.

Ovarian Sertoli-Leydig cell tumors (OSLCTs) with androgen secreting function is a subtype of malignant sex cord stromal tumor, second only to OGCT. Unlike OSCT patients, approximately 75% of patients with SLCTs are 30-years-old or younger, and only 10% > 50-years-old. They are composed of Sertoli cells and/or mesenchymal cells of different levels. Histologically, OSLCTs mainly manifest as a hard, lobulated mass, yellow to brown solid cross section with a complete capsule[23]. The tumor is usually cystic when it contains heterologous or retiform components. Tumors with a large, heterologous mucinous components may resemble a mucinous cystic tumor. The cysts in the retiform tumors may contain papillary or polyoid excrescences, potentially resembling a serous tumor[24]. On grey-scale ultrasound, OSLCTs are mainly solid/cystic masses with clear boundaries. Because the tumor cells contain more fibrous interstitium, the solid part of the tumor is less echogenic. Most of these tumors...
are rich in blood vessels, so they can show an abundant blood supply on imaging.

SCT-NOS lesions are the most prone to malignant transformation among OSCTs, with a malignant transformation rate of approximately 25%-43%[14]. When OSCTs undergo malignant transformation, necrosis, hemorrhage and cystic transformation may occur, and these OSCTs need to be differentiated from ovarian cystadenocarcinomas. Cystadenocarcinomas are malignant ovarian epithelial tumors, with an age at onset later than that of OSCTs. The grey-scale ultrasound features of serous cystic carcinomas include a single sac or cystic mass with compartments, usually accompanied by papillary protrusions. Mucinous cystadenocarcinomas are very large and are usually multilocular cystic masses with solid wall nodules, turbid cyst fluid and poor sound transmission. Since ovarian malignant tumor cells can produce vascular endothelial growth factor, etc., they can induce the formation of new blood vessels lacking smooth muscle tissue, which will lead to a low blood flow RI[25]. On CDFI, the solid component of ovarian cystadenocarcinomas shows abundant low-resistance blood flow signals. At the same time, the presence of endocrine function can also help further distinguish the type of tumor. It should be noted that Ki-67 is used as a tumor stem cell marker, and the research scope is mainly ovarian epithelioid tumors. Some studies believe that the Ki-67 index can help evaluate the malignancy and prognosis of ovarian tumors. When the positive cells are less than 10%, there is basically no recurrence. However, some studies have found that the distribution of positive cells in different parts of the same tumor is quite different. Therefore, there is some controversy in the evaluation of ovarian tumors. In Case 3, although Ki-67 (+, 20%), the pathological results still suggest benign SCT-NOS, and there are no signs of recurrence after about 14 mo of follow-up. Therefore, the evaluation and classification of SCT-NOS and outcome prediction still need to be integrated consider.

CONCLUSION

In summary, the diagnosis of postmenopausal OSCTs is mainly based on typical symptoms and signs, sex hormone determination, imaging features and pathological findings. The corresponding symptoms caused by endocrine abnormalities are the most intuitive clinical manifestations of the disease, especially virilization caused by hyperandrogenemia, which is more common, but there are still some patients who are completely asymptomatic. A solid, slightly hypoechoic, round or oval mass with a uniform internal echo and an abundant blood supply with low resistance are more typical imaging features of OSCTs. Diagnosing OSCTs is challenging, and surgery can be used for both diagnosis and clear treatment. Of course, histological examination is the gold standard for the final diagnosis of OSCTs.

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Extremely high titer of hepatitis B surface antigen antibodies in a primary hepatocellular carcinoma patient: A case report

Jing-Jing Han, Yu Chen, Yu-Chen Nan, Yong-Lin Yang

BACKGROUND
Hepatocellular carcinoma (HCC) may be caused by hepatitis B virus (HBV) infection. Post-infection recovery-associated changes of HBV indicators include decreased hepatitis B surface antigen (HBsAg) level and increased anti-HBsAg antibody titer. Testing to detect HBV DNA is conducted rarely but could detect latent HBV infection persisting after acute infection and prompt administration of treatments to clear HBV and prevent subsequent HBV-induced HCC development. Here, we present an HCC case with an extremely high anti-HBsAg antibody titer and latent HBV infection.

CASE SUMMARY
A 57-year-old male patient with abdominal pain who was diagnosed with primary HCC presented with an extremely high level (over 2000 ng/mL) of serum alpha-fetoprotein. Abdominal B-ultrasonography and computed tomography scan results indicated focal liver lesion and mild splenomegaly. Assessments of serological markers revealed a high titer of antibodies against hepatitis B core antigen (anti-HBcAg antibodies), an extremely high titer (1000 mIU/mL) of hepatitis B surface antibodies (anti-HBsAg antibodies, anti-HBs) and absence of detectible HBsAg. Medical records indicated that the patient had reported no history of HBV vaccination, infection or hepatitis. Therefore, to rule out latent HBV infection in this patient, a serum sample was collected then tested to detect
HBV DNA, yielding a positive result. Based on the aforementioned information, the final diagnosis was HCC associated with hepatitis B in a compensated stage of liver dysfunction and the patient was hospitalized for surgical treatment.

CONCLUSION
A rare HCC case with high serum anti-HBsAg antibody titer and detectable HBV DNA resulted from untreated latent HBV infection.

Key Words: Hepatocellular carcinoma; Hepatitis B virus DNA; Hepatitis B surface antibody; Hepatitis B core antibody; Occult hepatitis B virus infection; Case report

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Core Tip: Generally, hepatitis B surface antigen turning negative and the occurrence of hepatitis B surface antibody have been regarded as indicators of virus clearance and clinical recovery in hepatitis B patients. Here, we present a case of hepatitis B virus (HBV) infection-associated hepatocellular carcinoma with extreme high titer of hepatitis B surface antibodies, up to 30396 mIU/mL, and failure to eliminate HBV. This case provides details of a diagnostic process for HBV infection-associated hepatocellular carcinoma that should be considered in patients with highly elevated titer of anti-HBs.

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DOI: https://dx.doi.org/10.12998/wjcc.v9.i28.8492

INTRODUCTION
Hepatocellular carcinoma (HCC) is one of the most common gastrointestinal malignancies in China, with a mortality rate that ranks second highest of all rates of tumor-related mortality[1]. Generally, development of HCC is associated with genetic predisposition, environmental factors (metabolic syndrome, alcohol, aflatoxin B1, Aristotelian acid), and/or infections with hepatitis B virus (HBV) or hepatitis C virus (HCV)[2]. Among these risk factors, the most frequent contributing cause of HCC in China is chronic HBV infection, as supported by the fact that nearly 85% of HCC patients have tested positive for HBV serological markers[3].

Although several anti-HBV drugs that inhibit HBV replication in the host have been approved globally for clinical use, not all patients with HBV have access to these drugs[4]. Even patients who have developed full immune responses against HBV still carry low virus numbers, with residual virus acting as a persistent source of HBV that may later engage in replication and reactivation that can eventually initiate development of HBV-associated HCC[5,6]. This article reports an HCC case with an extremely high anti-hepatitis B surface antigen (HBsAg) antibody titer and latent HBV infection. The purpose of this work is to improve early HCC detection and help make a correct diagnosis to prevent development of HCC.

CASE PRESENTATION

Chief complaints
A 57-year-old male experiencing abdominal pain for 1 mo was admitted to our hospital in September 2020.

History of present illness
The patient developed epigastric pain 1 mo prior, which had worsened over the previous week.
**History of past illness**
The patient had a free previous medical history.

**Personal and family history**
Review of the patient’s medical records indicated the patient had denied any history of HBV vaccination, HBV infection or hepatitis, as well as any history of blood transfusion, tattooing, intravenous drug abuse or family history of HBV infection.

**Physical examination**
Initial physical examination of the patient demonstrated mental clarity and good spirits. The patient had a dull complexion with no yellow staining on sclera or skin surfaces. Cardiopulmonary auscultation showed no abnormality. No tenderness or rebound tenderness were found across the entire abdomen, except for percussive pain in the liver area. Bowel sounds were normal, no edema was detected in the lower extremities and the patient tested negative for hepatic encephalopathy asterixis.

**Laboratory examinations**
Results of laboratory testing assessments of serum marker levels were as follows: Serum alpha-fetoprotein (AFP) level greater than 2000.00 ng/mL (normal range: 0.89-8.78 ng/mL); negativity for both HBsAg and hepatitis B virus e antigen (HBeAg); and anti-HBsAg antibody level greater than 1000.00 mIU/mL (normal range: < 10 mIU/mL), anti-HBeAg level of 0.04 S/Co (normal range: > 1.0 S/Co) and anti-HBcAg level of 9.06 S/Co (normal range: > 1.0 S/Co). Analysis of serum marker levels related to liver function indicated abnormal liver function, with alanine aminotransferase of 29 U/L (normal range: 9-50 U/L), aspartate transaminase of 65 U/L (normal range: 15-40 U/L), lactate dehydrogenase of 274 U/L (normal range: 120-250 U/L), gamma glutamyl transpeptidase of 213 U/L (normal range: 10 to 60 U/L), alkaline phosphatase of 145U/L (normal range: 45-125 U/L) and alpha hydroxy butyric acid deaminase of 224 U/L (normal range: 72-190 U/L).

**Imaging examinations**
B-ultrasound scanning of the posterior abdomen revealed a hypoechoic solid mass in the right lobe of the liver with uneven density and irregular edges, a characteristic presentation of HCC. Moreover, mild splenomegaly was observed, which warranted further examination. Therefore, enhanced computed tomography (CT) scanning was conducted. CT scan results revealed an area of low-density soft tissue in a scanned plane within the upper abdomen, with mild density enhancement observed in the arterial phase and non-homogeneous density enhancement observed in the portal phase that together were suggestive of HCC accompanied by splenomegaly (Figure 1).

**Further diagnostic work-up**
The anti-HBs concentration of the patient's serum was quantified by chemiluminescent microparticle immunoassay after dilution, which was finally confirmed to be 30,936 mIU/mL. Next, we selected a sample from this patient and ordinary anti-HBs-positive (200 mIU/mL) samples to conduct in vitro serological neutralization experiments along with HBsAg samples. The results showed that the effective neutralization rate of patients' serum was 88.8%, which was much higher than the 21.9% of ordinary anti-HBs-positive serum. It is concluded that the surface antibody of hepatitis B still has a strong protective effect in patients, and the patients may still be in the active period of virus replication.

Results of all serum marker-based assessments of HBV disease status in this patient revealed very high titers of anti-HBsAg and anti-HBc antibodies. Meanwhile, Novartis screening test results of patient blood indicated a positive HBV DNA result (detection sensitivity: 3 IU/mL), supporting categorization of the patient’s disease status as an Occult Hepatitis B virus infection (OBI); OBI status refers to an HBV patient’s serological state as characterized by a negative HBsAg detection result accompanied by detectable HBV DNA in serum and/or liver tissues and a positive anti-HBcAg antibody detection result with or without detected anti-HBsAg antibody[7].

**FINAL DIAGNOSIS**
Based on the aforementioned serological test results, this patient could be clearly classified as a seronegative OBI case. To sum up, the patient was diagnosed with
Figure 1 Representative computed tomography image used for hepatocellular carcinoma diagnosis. A low-density soft tissue area was observed in the scanning plane of the upper abdomen. Mild density enhancement in the arterial phase and non-homogeneous density enhancement in the portal phase were observed. The tumor was about 10 cm × 12 cm in cross-section.

primary HCC associated with hepatitis B in a compensated stage of liver cirrhosis.

TREATMENT

After admission, the patient was given antivirus, liver protection, stomach protection, anti-infection and other treatment measures, and then transferred to other hospitals for surgical treatment.

OUTCOME AND FOLLOW-UP

The patient's abdominal pain was relieved prior to surgical treatment and HBV DNA was negative on review.

DISCUSSION

HCC, one of the most common gastrointestinal malignancies worldwide, occurs with an annual global incidence of greater than 626,000 cases per year. In China, the HCC mortality rate ranks second highest of all tumor-related mortality rates[8]. Clinical diagnosis of liver cancer is mainly based on ultrasound image-based examinations combined with assessments of serum AFP levels, with limitations of both assessments known to clinicians. Although AFP is the most widely used serum marker for HCC, its specificity as a marker for early diagnosis of HCC is 87%-93%, and its sensitivity is only 45.3%-62%[9]; its results need to be interpreted by experts, combined with analysis of imaging results. Meanwhile, ultrasound-based diagnosis is affected by operator skills, equipment sensitivity and patient characteristics that together decrease sensitivity to about 60%-80%[10]. Due to these limitations, CT scanning is considered a necessary step to confirm HCC diagnosis or to guide HCC clinical staging and treatment[11]. During CT plane-based scanning, HCC can be detected as regular or irregular low-density shadows, with occasional observations of isometric and high-density shadows (ruptured nodules). By contrast, enhanced CT scanning reveals typical "wash in and wash out" signs characterized by significantly enhanced signals in the enhanced arterial phase of tumor nodule scans and low signals in portal and delayed phase scans[12]. In this study, serum AFP level, ultrasound and CT results were all used together to confirm a diagnosis of HCC in this patient.

About 80% of primary liver cancers worldwide are associated with chronic hepatitis B virus infection[13], in line with the scenario in China, whereby 85% of HCC patients test positive for HBV serological markers[3]. At least three different mechanisms have
been proposed to contribute to development of HBV-related HCC. In the first proposed mechanism, HBV is not completely eliminated from infected patients, allowing low-level persistence in patient tissues of covalently closed circular DNA (cccDNA). Subsequently, cccDNA can integrate into the host genome and activate host genes controlling cell proliferation, while also triggering genomic instability that leads to inactivation of tumor suppressor genes and increased expression of cancer genes\[14, 15\]. As another mechanism, chronic inflammation caused by HBV infection has been posited to lead to hepatocyte destruction and regeneration during the chronic phase of HBV infection, resulting in accumulation of genetic mutations conferring a cell growth advantage\[16\]. In yet another mechanism, the HBV-X open reading frame encodes a nonstructural protein, HBVx, with multiple functions in viral replication and oncogenic transformation, which may promote tumorigenesis as well\[17\].

As compared to indicators used for HBV diagnosis, hepatitis B serological markers are generally used to guide disease prognosis. Based on the fact that HBsAg is translated from HBV cccDNA transcripts, HBsAg levels are thought to reflect the level of cccDNA in HBV-infected hepatocytes as evidence of active HBV infection. Indeed, detection tests based on HBV cccDNA have already been used effectively to detect HBV DNA in both acute and chronic hepatitis B patients as well as in asymptomatic carriers\[18\]. In fact, for the majority of acute hepatitis B patients, HBsAg levels become undetectable after clinical recovery from HBV, while persistence of detectable HBsAg levels for 6 mo or longer is a sign of disease progression to a chronic hepatitis B infection phase. Meanwhile, anti-HBsAg antibodies are capable of neutralizing HBV and thus play a protective role against HBV infection. Therefore, a change in HBsAg detection status to undetectable along with detection of serum anti-HBsAg antibodies are viewed together as indicators of virus clearance and clinical recovery after hepatitis B infection. However, in the unique case presented here, HBV DNA was still detectable at a high level in the patient in spite of indicators of clinical recovery (both an undetectable HBsAg level and high-level anti-HBsAg antibody titer). Thus, taken together all findings here pointed to active HBV replication in this patient that may have led to development of HCC, as consistent with the proposed diagnosis of OBI\[19\].

The prevalence of OBI varies greatly across the world and across patient populations, with higher rates reported in Asia. The prevalence of OBI is higher in patients with chronic liver disease and may be as high as 40% to 75% in those with HBsAg-negative HCC. It is almost equivalent to a persistent HBsAg-positive HCC patient\[20\]. Although causative factors of OBI remain unclear, in OBI cases a strong anti-HBsAg antibody response in vivo may result in binding of antibodies to HBsAg to form immune complexes that are rapidly removed from circulation, resulting in low serum HBsAg levels. Concurrently, partial or full HBV genomes may integrate into genomic DNA of hepatocytes to support constant HBV replication and release of HBV DNA into the circulation in spite of an abundance of anti-HBsAg antibodies. Such persistent low-level viral replication may then act as a source of escape mutants that are not neutralized by host anti-HBsAg antibodies that are also undetectable using current HBsAg assays\[21\]. Based on this scenario, it is possible that the patient here is currently infected with a rare HBV subtype with one or more unique mutations that cannot be detected using current HBsAg detection reagents. We are currently sequencing the full genome of HBV DNA from this patient to confirm this speculation. Meanwhile, in a recent report, a meta-analysis of 44,553 patients suggested that in HBsAg-negative patients with chronic liver disease, anti-HBc positivity is strongly associated with the presence of HCC, which suggested that more factors may be involved in development of HCC in this group of patients\[22\].

**CONCLUSION**

Here, a case of HBV infection-associated primary HCC is described with an extremely high serum titer of hepatitis B surface antibodies and detectable HBV DNA. Based on literature review and case findings presented here, HBV infection-associated HCC can occur in “clinically recovered” HBV patients with high serum levels of anti-HBsAg and undetectable HBsAg levels. To prevent later HCC development in such patients, routine screening for HBV DNA is required and testing should be expanded to include additional hepatitis B serum markers, in order to improve early HCC detection and prevent development of HCC.
REFERENCES


Surgical treatment of liver metastasis with uveal melanoma: A case report

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Abstract

BACKGROUND
Uveal melanoma is the most common primary intraocular malignant tumor affecting the eyes in adults. Nearly half of all primary uveal melanoma tumors metastasize; yet, there are currently no effective treatments for metastatic uveal melanoma. At the time of diagnosis, less than 4% of patients with uveal melanoma have detectable metastatic disease. Uveal melanoma disseminates hematogenously, with the most common site of metastasis being liver (93%), followed by lung (24%) and bone (16%).

CASE SUMMARY
A 57-year-old woman was diagnosed with a dysplastic nevus on her eyelid, which was histologically confirmed as malignant melanoma after resection. The patient had no evidence of metastasis to other organs and received both radiation therapy and chemotherapy. After systemic treatment, a metastatic left neck lymph node was found and another round of chemotherapy was performed after resection. Positron emission tomography-Computed Tomography tracking after completion of chemotherapy revealed two metastatic liver nodules. The patient underwent partial liver resection and showed no signs of recurrence at 1 year after surgery.

CONCLUSION
Surgery is an effective treatment for metastatic uveal melanoma. In patients with liver metastatic lesions, hepatectomy improves outcome.

Key Words: Uveal melanoma; Metastatic melanoma; Liver metastasis; Hepatectomy; Prognosis; Case report
Uveal melanoma is the most common primary intraocular malignant tumor affecting the eyes in adults[1]. While this type of melanoma can affect any part of the uveal tract, the choroid is predominant (86.3%), whereas iris and ciliary body are far less frequently involved[2]. Most patients with uveal melanoma are between 50 and 80 years of age, with the peak occurrence in the 70s[1] and a mean age of 58 years at the time of diagnosis[3]. Exposure to solar ultraviolet radiation is a well-known risk factor for the development of cutaneous melanoma, but evidence of its role in the development of uveal melanoma is inconclusive[4]. Other possible etiological factors include fair skin and oculodermal melanocytosis[5,6].

Because of the lack of lymphatics in the eye itself, uveal melanoma disseminates hematogenously, showing a high propensity for the liver, which accounts for 93% of cases of metastases, followed by the lungs (24%) and bones (16%). It can also metastasize to the brain, skin, and other sites. Indeed, most patients with metastatic disease have metastases at multiple sites[7]. Recent efforts to reduce mortality caused by metastatic uveal melanoma have not been successful. Survival in the presence of metastatic disease is 2–7 mo, depending on the treatment method, and the 1-year overall survival is low, ranging from 13%-29%. The most common contributors to negative prognosis are an age of more than 60 years, male sex, a short interval between primary diagnosis and manifestation of first metastases, and multiple liver metastases[8,9].

Metastatic uveal melanoma requires complex therapy. Treatment most often includes systemic chemotherapy (e.g., dacarbazine or fotemustine) and immunotherapy[9]. However, treatment is complicated by the presence of isolated liver metastases, which necessitate surgery and chemoembolization[8,10].

INTRODUCTION

CASE PRESENTATION

Chief complaints
A 57-year-old woman was admitted for treatment of liver nodules. Three years prior, she had been diagnosed with histologically-confirmed uveal melanoma in the left eye and had been treated with chemotherapy after undergoing resection of the affected eye and upper and lower eyelids. At her 3-year follow-up, metastatic lesions were found on the liver via positron emission tomography (PET) and computed tomography (CT).

History of present illness
Originally, the patient had visited the outpatient ophthalmology clinic with complaint of left eyeball discomfort. In May 2011, the patient had been diagnosed with dysplastic nevus. Accordingly, a mass was removed from the left eye and confirmed by histology as malignant melanoma (Figure 1A); the patient underwent subsequent treatment by radiotherapy (total 6400 cGY, 32 wk) and chemotherapy (single-agent dacabazine 150 mg/m² daily for 5 d every 4 wk, four rounds). In December 2012, she underwent total exenteration of the left eye for local invasion of the melanoma (Figure 2), and a follow-
up PET-CT revealed metastases in the left jugular lymph nodes. In March 2013, a left radical neck lymph node dissection was performed, after which the patient underwent chemotherapy with high-dose interferon (IFN)-alpha administered on a 2-d interval schedule for 48 wk. Neither abdominal nor thoracic CT showed metastatic lesions in the solid organs or ascites. In June 2014, the patient completed IFN-alpha chemotherapy, but follow-up PET-CT in July 2014 revealed two metastatic nodules in the right lobe of the liver, being 2.5 cm (segment #7) and 2.3 cm (segment #5) in size (Figure 3).

**History of past illness**
The patient did not have any underlying disease.

**Personal and family history**
The patient had no notable family or personal history.

**Physical examination**
The patient had no unusual abdominal symptoms.

**Laboratory examinations**
The whole blood count, serum electrolyte levels, liver function test results, urea nitrogen level, creatinine level, and C-reactive protein level were normal.

**Imaging examinations**
Serial PET-CT found hypermetabolic sites. In December 2011, a PET-CT had revealed the metastatic lesion in the left eyelid, and metastases had been detected in the left
jugular lymph nodes in December 2012. In June 2014, the follow-up PET-CT revealed two metastatic nodules in the right lobe of the liver (2.5 cm in segment #7 and 2.3 cm in segment #5) (Figure 3).

**FINAL DIAGNOSIS**

The clinical features and radiological findings supported a diagnosis of liver metastasis from uveal melanoma.

**TREATMENT**

The patient underwent partial hepatectomy with the removal of segments #5 and #7 of the liver in July 2014 (Figure 4). Histological findings confirmed metastatic malignant melanoma, with clear resection margins and no lymphovascular invasion (Figure 1B).

**OUTCOME AND FOLLOW-UP**

The patient was discharged without postoperative complications. She had no signs of recurrence in the liver 3 mo later on abdominal CT and at 12 mo postoperative on PET-CT. She was lost to follow-up at 18 mo because she did not want any further follow-up care.

**DISCUSSION**

We report a case of surgical treatment for uveal melanoma with liver metastasis. The patient was first diagnosed with uveal melanoma in December 2012 and received systemic dacabazine chemotherapy. One year later, she underwent cervical lymph node removal and received IFN-alpha chemotherapy. In July 2014, we detected liver metastasis, and performed a partial hepatectomy. After surgery, she received dacabazine chemotherapy. Although the follow-up had been cut off after 18 mo of chemotherapy, the outcome to that point was good.

The patient had a positive prognosis because she was younger than 60 years of age, female, and had a low-severity liver metastatic burden (Eastern Cooperative Oncology Group performance status 0, normal ranges on liver function tests). Negative prognosis factors for her, however, were the short interval between uveal melanoma diagnosis and the diagnosis of multiple liver metastases. We performed a hepatectomy based on the patient’s performance status and absence of signs of distant metastasis. The results were satisfactory in that the metastatic lesion was removed with clear resection margins and no lymphovascular invasion was detected.
In a large study that enrolled 602 patients with primary uveal melanoma, Kodjikian et al.\cite{9} reported that complete surgical removal of metastases with postoperative intra-arterial chemotherapy was more effective for prolonging survival than partial removal of metastases along with postoperative intra-arterial chemotherapy or best supportive care. Other studies have demonstrated that radical resection of up to four to five liver metastases without signs of micrometastases may improve the prognosis of metastatic disease\cite{11}. A French study of 3873 patients with uveal melanoma, including 798 who developed liver metastases, found that time to diagnosis of liver metastasis (< 24 mo after primary diagnosis), nonradical resection of liver metastases (R1–2), more than four liver metastases, and confirmed miliary metastases were all negatively associated with overall survival\cite{12}. Close follow-up of all patients with uveal melanoma is recommended to detect possible metastases at the earliest possible time. Prompt detection of metastasis allows for surgical resection and systemic treatment aimed at complete regression.

As liver metastases are usually hypervascular, chemoembolization or intra-arterial chemotherapy are effective treatments. The reported response rate to chemoembolization is 36%, but survival benefits similar to those of systemic chemotherapy have not been reported\cite{13}. Dacarbazine, cisplatin, fotemustine, or their combinations are frequently used in chemoembolization and intra-arterial chemotherapy\cite{9,13,14}. In our case, the patient was given four courses of systemic single-agent dacarbazine chemotherapy and a 52-wk course of IFN-alpha.

Although we removed the metastatic lesions from the liver and there were no signs of recurrence in our patient, regular follow-up and evaluation should be performed in cases of malignancies to obtain the best possible survival outcomes.

CONCLUSION

This article reports on the successful surgical treatment of liver metastasis from uveal melanoma. Uveal melanoma itself has a poor prognosis, especially if metastasis is involved. For metastatic melanoma, liver resection may be a good option if liver metastases develop despite systemic treatment. Careful selection and implementation of an optimal treatment plan, within a timely manner, are required to achieve the best outcome for patients with uveal melanoma liver metastasis.

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Intermittent appearance of right coronary fistula and collateral circulation: A case report

Wen-Jie Long, Xi Huang, Yuan-Hong Lu, Hao-Ming Huang, Guo-Wei Li, Xia Wang, Zhi-Ling He

Abstract

BACKGROUND
Congenital coronary artery fistula can lead to symptoms of chest tightness, chest pain, or exertional dyspnea, which is a congenital vascular malformation that should not be ignored. Patients who have such malformations are frequently observed with different concurrent abnormal anatomic structures. Collateral circulation may have a positive effect on improving the patients' symptoms.

CASE SUMMARY
A 53-year-old female experienced episodic chest discomfort for the past month with symptoms manifesting when she was agitated or overexerted. After a positive treadmill test, the patient underwent coronary angiography. “Ghostlike” intermittent appearance of coronary ventricular fistula and collateral branching were observed. The patient was diagnosed with a right coronary ventricular fistula and collateral circulation.

CONCLUSION
This case shows the likelihood of collateral circulation in patients with coronary
artery fistula. This may provide medical staff with novel solutions to treat insufficiency of myocardial blood supply induced by cardiovascular malformations.

Key Words: Coronary fistula; Collateral circulation; Congenital coronary artery; Case report

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Core Tip: Congenital coronary artery fistula is a congenital vascular malformation that should not be overlooked. It can lead to symptoms of myocardial ischemia. In the report, we describe a patient who had episodic chest discomfort. Coronary angiography demonstrated a “ghostlike” intermittent appearance of coronary ventricular fistula and collateral branching. The patient was diagnosed with a right coronary ventricular fistula and collateral circulation. This case shows the likelihood of collateral circulation in patients with coronary artery fistula and may provide us with novel strategies for solving insufficiency of myocardial blood supply induced by cardiovascular malformations.

INTRODUCTION

Congenital coronary artery fistula has an incidence of about 0.002% in the general population and is a rare coronary anomaly. Due to the coronary steal phenomenon, this disease often leads to myocardial ischemia, causing patients to experience chest tightness, chest pain, or exertional dyspnea. The severity of symptoms is closely associated with the size of the fistula. In severe cases, intervention or surgery is required[1-4].

The establishment of collateral circulation may have a positive influence on symptoms in these patients[5]. However, collateral circulation is more frequent in patients with severe coronary stenosis and severe myocardial ischemia but is rarely observed in patients with coronary artery fistula[5,6].

We present herewith an adult female who presented with episodic chest discomfort. In addition to the presence of a right coronary artery fistula, collateral circulation was also observed. The patient was treated with Chinese medicine and her symptoms resolved with no recurrence.

CASE PRESENTATION

Chief complaints

A 53-year-old woman presented to the Cardiology Department of our hospital complaining of episodic chest discomfort.

History of present illness

She had experienced episodic chest discomfort for the past month with symptoms arising when she was agitated or when she overexerted herself.

History of past illness

The patient had a medical history of asthma.

Physical examination

There was no obvious abnormality in the patient’s physical examination.
**Laboratory examinations**
Routine blood tests, routine urine tests, routine fecal tests, blood biochemistry, immune indexes, and infection indexes were normal. Chest radiography and echocardiography were unremarkable. However, the electrocardiogram showed occasional premature ventricular beats, and the treadmill test was positive.

**Imaging examinations**
Coronary angiography showed that no stenosis was observed in the left or right coronary artery (Figure 1A-C, see Video 1). However, “ghostlike” intermittent appearance of coronary ventricular fistula and collateral branching was observed. The right coronary ventricular fistula and collateral circulation appeared abruptly (Figure 1D and E, Video 2), and then was undetectable (Figure 1F, Video 3). Nevertheless, the patient refused the computed tomography angiography because of her medical insurance.

**FINAL DIAGNOSIS**
A final diagnosis of coronary heart disease with right coronary artery fistula and the presence of collateral circulation was made.

**TREATMENT**
The patient was initiated with 23.75-mg metoprolol controlled release, zero order kinetics once a day.

**OUTCOME AND FOLLOW-UP**
After treatment, the patient reported no symptoms during the follow-up period. It is not necessary for this patient to undergo coronary angiography again.

**DISCUSSION**
Congenital coronary artery fistula has several types and includes right coronary artery-right ventricle fistula, right coronary artery-left ventricle fistula, left coronary artery-right ventricle fistula, left circumflex artery-right atrium fistula, bilateral coronary artery-cardiac chamber fistula, and cardiopulmonary bypass [7].

Congenital coronary artery fistula is frequently observed concurrently with artery aneurysm or congenital atresia of the main coronary artery. These abnormal anatomic structures significantly increase the risk of thrombosis, myocardial ischemia, ruptured aneurysms, or other life-threatening complications in these patients [8, 9]. In this report, our patient had symptoms of myocardial ischemia due to the presence of a right coronary artery fistula.

Coronary angiography performed on this patient showed intermittent signs of collateral circulation of the coronary artery. This may have had a positive effect on relieving chest tightness in the patient. Due to the adverse effect of coronary artery fistula on the normal myocardial blood supply, new collateral circulation may manifest to supply blood to the ischemic regions when chronic myocardial ischemia occurs. This explains why the patient only had symptoms of episodic chest discomfort [10].

Ilhan et al [11] presented a case of coronary superior vena cava fistula and variant angina in a patient. This demonstrates the ability of coronary fistulas to develop collateral vessels, such as coronary arteries.

In this case, the patient had collateral circulation from left to right when the left and right blood vessels were unobstructed, i.e. blood flow from the arterial fistula side to the normal blood vessel, which has rarely been observed. Because of fluid shear stress, collateral circulation often flows from the normal blood vessels to the occluded blood vessels to relieve insufficient blood supply at the occluded blood vessel [10]. This suggests that collateral circulation of the coronary arteries may be mended, but how this happens is to be deciphered.
Figure 1 Coronary angiography. A-C: No stenosis was observed in the left or right coronary artery; D and E: The right coronary ventricular fistula and collateral circulation appeared abruptly; F: Then was undetectable. Orange arrows in panel D-E depict the coronary fistula and collateral vessels. LAD: Left anterior descending artery; LCX: Left circumflex; RCA: Right coronary artery.

Heil and Schaper[12] suggested that the generation of collateral circulation arteries requires two stages, i.e. the activation of vascular endothelium and the release of growth factors by white blood cells to stimulate the proliferation of vascular cells.

Previous studies have suggested that granulocyte colony-stimulating factor therapy, physical exercise, and external counterpulsation may stimulate the formation of collateral circulation[10].

Concerning small-sized fistulae without the presence of clinical symptoms, regular monitoring can be embraced. For symptomatic and large-sized or giant fistulae, percutaneous coronary intervention or coronary artery bypass graft is recommended [13-15].

CONCLUSION

Only a few reports on congenital coronary artery fistula with concurrent collateral circulation have been reported in patients. Since coronary artery fistulas have been associated with several complications, early detection and treatment are critical.

After performing coronary angiography in this patient who had mild symptoms, we were pleasantly surprised to observe collateral circulation in this patient who was diagnosed with coronary artery fistula. Is the appearance of this structure a congenital coincidence or a compensation mechanism induced by insufficient blood supply? Additional clinical observations and studies are necessary to determine this. Furthermore, the intermittent collateral circulation that was observed in our patient induced a dynamic shunt of the coronary blood flow and hence reveals the complexity of coronary microcirculation.

REFERENCES


Synchronous concomitant pancreatic acinar cell carcinoma and gastric adenocarcinoma: A case report and review of literature

Tian Fang, Ting-Ting Liang, Yi-Zhuo Wang, Hai-Tao Wu, Shu-Han Liu, Chang Wang

Abstract

BACKGROUND
Multiple primary malignant tumors are two or more malignancies in an individual without any relationship between the neoplasms. In recent years, an increasing number of cases have been reported. However, concomitant primary gastric and pancreatic cancer reported a relatively small incidence, involving no pancreatic acinar cell carcinoma reports. Here, we present the first case of concomitant pancreatic acinar cell carcinoma and gastric adenocarcinoma.

CASE SUMMARY
A 69-year-old male presented to our department with a history of vomiting, epigastric pain, and weight loss. Imaging revealed space-occupying lesions in the stomach and the tail of the pancreas, respectively. The patient underwent laparoscopic radical gastrectomy and pancreatectomy simultaneously. The pathologies of surgical specimens were completely different: The resected gastric specimen was moderate to poorly differentiated adenocarcinoma, whereas the pancreatic tumor was consistent with acinar cell carcinoma. The patient was treated with six cycles of oxaliplatin and S-1 chemotherapy. As of March 2021, the patient was healthy without any recurrence or metastasis. After thoroughly reviewing the literature on simultaneous pancreatic and gastric cancers at home and abroad, we discussed the clinical characteristics of these rare synchronous double cancers. Most of the cases had undergone surgery and adjuvant chemotherapy, and all of the cases were pathologically confirmed by the postoperative specimen.

CONCLUSION
Synchronous pancreatic acinar cells and gastric adenocarcinoma can occur and should be considered when tumors are found in these organs.

Key Words: Synchronous concomitant cancers; Pancreatic neoplasms; Stomach neoplasms; Pancreatic acinar cell carcinoma; Surgical procedures; Case report
Acinar cell carcinoma of the pancreas is a rare form of pancreatic cancer, and the incidence of synchronous concomitant pancreatic and gastric cancer is relatively low. We report a patient with simultaneous acinar cell carcinoma of the pancreas with gastric cancer, and he underwent radical surgery for both the pancreas and the stomach. This is the first case of concomitant cancers related to pancreatic acinar cell carcinoma and gastric cancer. We also reviewed the literature on simultaneous pancreatic and gastric cancers.

INTRODUCTION
Pancreatic and gastric carcinoma are the second and fifth most common digestive system tumors, respectively[1]. Pancreatic cancer is one of the deadliest malignancies and is usually diagnosed at an advanced stage, leading to poor overall survival, particularly the relatively low pancreatic acinar cell adenocarcinoma (PACC) incidence, accounting for approximately 1%-2% of exocrine pancreatic neoplasms[2]. This report describes the first case of concomitant cancers related to PACC and gastric adenocarcinoma. Furthermore, we review the literature of synchronous gastric and pancreatic tumors in the PubMed, Web of Science, CNKI, and Embase databases and discuss the principles of treatment and prognosis of concomitant gastric and pancreatic cancer.

CASE PRESENTATION

Chief complaints
A 69-year-old male came to our department with a history of vomiting, epigastric pain for 3 mo, and weight loss of approximately 5 kg.

History of present illness
The patient developed vomiting, epigastric pain for 3 mo.

History of past illness
The patient had no past illness.

Personal and family history
Two younger brothers of patient had lung cancer and laryngocarcinoma, respectively.

Physical examination
The patient was afebrile at 36.3 °C, the heart rate was 65 beats per min, respiration was 17 breaths per min, and blood pressure of 131/86 mmHg. Clinical abdominal examination showed tenderness in the upper abdomen without mass upon palpation, soft and relaxed, and no rebound pain.

Laboratory examinations
Laboratory test results were normal, including blood, urine, and stool were within the normal ranges. However, the carcinoembryonic antigen in tumor markers was slightly elevated at 4.06 ng/mL (normal values: < 3.4 ng/mL).

Imaging examinations
Gastroscopy revealed a large ulcer of approximately 5.5 cm × 6.6 cm × 0.5 cm originating from the gastric fundus, and pathological biopsy revealed gastric
adenocarcinoma. In addition, abdominal contrast-enhanced computed tomography (CT) indicated uneven thickening in the antrum of the stomach with irregular mucosa and heterogeneous contrast enhancement on the antrum of the gastric wall and a space-occupying lesion of approximately 34 mm × 16 mm in the tail of the pancreas (Figure 1). However, there were no definite contraindications; therefore, the patient underwent laparoscopic exploration, which revealed the stomach and pancreatic masses. After evaluating the resectability of the gastric and pancreatic tumors, he underwent laparoscopic radical gastrectomy, gastric vagotomy, pancreatectomy, and splenectomy (Figure 2).

**FINAL DIAGNOSIS**

The resected stomach lesion was 5 cm × 5 cm × 1.5 cm, and the Lauren classification was the intestinal type. The pathology of the resected specimen from the stomach confirmed a moderately to poorly differentiated adenocarcinoma [pStage IIIIB, T4aN2M0 per the American Joint Committee on Cancer (AJCC) eighth edition criteria] (Figure 3A). The tumor had invaded the serous membrane but did not involve the adjacent structures. Perineural and vascular infiltration were observed. Regional nodes were positive (4/32), and the resection margins were free of tumor cells. The cancer cells did not infiltrate the omentum, and there was no metastasis in the omentum lymph nodes.

Immunohistochemistry indicated positivity for pan-cytokeratin and villin and partial positivity for CK7 (Figure 3B). The tumor was negative for HER-2 (4B5) and CK20. The Ki-67 positivity was approximately 50% in a high-power field.

The volume of the resected pancreatic specimen was 4.1 cm × 2.2 cm × 1.5 cm. The pathology was consistent with PACC (pStage III, T3N1M0 per the AJCC eighth edition criteria) (Figure 4A and B). Perineural infiltration was observed, but there was no vascular infiltration. Regional nodes were negative, and the resection margins were free of tumor cells. Immunohistochemistry indicated positivity for CAM5.2, CK19, CK7, and membranous expression of beta-catenin and scattered positivity for carcinoembryonic antigen. The Ki-67 positivity was 30% in one high-power field (Figure 4C-F). The tumor was negative for vimentin, chromogranin A, synaptophysin, CD10, and CD56.

**TREATMENT**

One month after the operation, chemotherapy consisting of oxaliplatin and S-1 (SOX) was initiated and the patient was then treated with six chemotherapy cycles.

**OUTCOME AND FOLLOW-UP**

As of March 2021, the patient was healthy without any recurrence or metastasis.

**DISCUSSION**

Gastric cancer is characterized by a synchronous second primary cancer in 1.0%–5.0% of cases[3-5]. This is the fourth most common cancer associated with pancreatic carcinoma, comprising approximately 5% of all cases of gastric carcinoma associated with carcinoma of other organs[3]. Gastric cancer is the most common synchronous tumor associated with pancreatic cancer[6]. Patients with pancreatic and stomach cancers demonstrated significantly better OS (33.9 mo) than patients with only pancreatic cancer (17.0 mo)[6]. This may be because pancreatic cancer is generally early-stage when synchronous concomitant cancers are diagnosed.

A review of the literature on simultaneous pancreatic and gastric cancers at home and abroad revealed that synchronous concomitant tumors involving the two organs are rare, and PACC is more uncommon. Details of reported cases are shown in Table 1 [7-20], including our case. The average age at diagnosis is 67 years (42–77 years), and men are twice as likely to be diagnosed with synchronous pancreatic and gastric cancer than women. Pancreatic ductal adenocarcinoma (PDAC) is the most common
### Table 1 Reported cases of synchronous gastric and pancreatic tumors

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Age</th>
<th>Gender</th>
<th>Gastric tumor location</th>
<th>Gastric histology</th>
<th>Pancreatic histology</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erioguchi et al[7], 2000</td>
<td>76</td>
<td>Male</td>
<td>Upper gastric angle</td>
<td>Moderately differentiated tubular adenocarcinoma</td>
<td>Not mentioned</td>
<td>Well to moderately differentiated tubular adenocarcinoma</td>
</tr>
<tr>
<td>Kubota et al[8], 2009</td>
<td>67</td>
<td>Male</td>
<td>Not mentioned</td>
<td>Moderately differentiated adenocarcinoma</td>
<td>Not mentioned</td>
<td>Absence of pancreatic histology</td>
</tr>
<tr>
<td>Meng et al[9], 2011</td>
<td>42</td>
<td>Male</td>
<td>Gastric antrum</td>
<td>Gastric GIST</td>
<td>Pancreatic head</td>
<td>Pancreatic GIST</td>
</tr>
<tr>
<td>Shen et al[10], 2010</td>
<td>72</td>
<td>Female</td>
<td>Major gastric curvature</td>
<td>Gastric GIST</td>
<td>The head of the pancreas</td>
<td>Poorly differentiated PDAC; malignant fibrous histiocytoma</td>
</tr>
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<td>Munro et al[11], 2010</td>
<td>73</td>
<td>None</td>
<td>Gastric antrum and pyloric portion</td>
<td>Moderately differentiated adenocarcinoma</td>
<td>Uncinate portion of the pancreas</td>
<td>Poorly differentiated PDAC</td>
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<td>Dasanu et al[12], 2011</td>
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<td>Male</td>
<td>Not mentioned</td>
<td>GIST</td>
<td>The head of the pancreas</td>
<td>Moderately to poorly differentiated carcinoma</td>
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<tr>
<td>Kourie et al[13], 2013. case 1</td>
<td>56</td>
<td>Male</td>
<td>Anterior part of the antrum</td>
<td>Poorly differentiated adenocarcinoma with independent mucus-secreting cells</td>
<td>The head of the pancreas</td>
<td>Necrotic ductal adenocarcinoma</td>
</tr>
<tr>
<td>Kourie et al[13], 2013. case 2</td>
<td>62</td>
<td>Male</td>
<td>Gastric wall of the greater curvature</td>
<td>Gastric adenocarcinoma with mucinous component</td>
<td>Tail of the pancreas</td>
<td>Tubular adenocarcinoma (ck7+; ck20; ck19+)</td>
</tr>
<tr>
<td>Obisubo et al[14], 2013</td>
<td>77</td>
<td>Male</td>
<td>In the middle of stomach</td>
<td>Adenocarcinoma stage IB, T2N0M0</td>
<td>Pancreatic head</td>
<td>Adenocarcinoma stage IIA, T3N0M0</td>
</tr>
<tr>
<td>Baha et al[15], 2015</td>
<td>70</td>
<td>Male</td>
<td>The fundal region and greater curvature of the stomach</td>
<td>Low grade gastric calcified stromal tumor (GIST)</td>
<td>The head of the pancreas</td>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>Ghothim et al[16], 2015. case 1</td>
<td>73</td>
<td>Male</td>
<td>The antrum of the stomach</td>
<td>Adenocarcinoma (pT1N1M0 stage IB, G2)</td>
<td>The head of the pancreas</td>
<td>Ductal pancreatic cancer. (pT2N1M0, stage IB, G3)</td>
</tr>
<tr>
<td>Ghothim et al[16], 2015. case 3</td>
<td>74</td>
<td>Male</td>
<td>The antrum of the stomach</td>
<td>Gastric adenocarcinoma diffuse type (pT2bN2M0, G3)</td>
<td>Pancreatic head</td>
<td>Papillary mucinous carcinoma (pT2N1M0, stage IB, G1)</td>
</tr>
<tr>
<td>Fiore et al[17], 2015. case 1</td>
<td>63</td>
<td>Male</td>
<td>Not mentioned</td>
<td>Gastric GIST (T2N0)</td>
<td>Pancreatic head</td>
<td>Adenocarcinoma (T2N0)</td>
</tr>
<tr>
<td>Santos-Fernández et al[18], 2015</td>
<td>64</td>
<td>Female</td>
<td>Prepyloric antral ulcer</td>
<td>Well differentiated gastric adenocarcinoma</td>
<td>Pancreatic tail</td>
<td>Pancreatic adenocarcinoma</td>
</tr>
<tr>
<td>Arabadzhieva et al[19], 2016</td>
<td>60</td>
<td>Female</td>
<td>In the pyloric area</td>
<td>Gastric GIST</td>
<td>Pancreatic body</td>
<td>Pancreatic neuroendocrine tumor</td>
</tr>
<tr>
<td>Yonenaga et al[20], 2016</td>
<td>63</td>
<td>Male</td>
<td>Antrum of the stomach</td>
<td>Poorly differentiated adenocarcinoma</td>
<td>The body of the pancreas</td>
<td>PACC</td>
</tr>
<tr>
<td>Our case, 2021</td>
<td>69</td>
<td>Male</td>
<td>Antrum of the stomach</td>
<td>Gastric adenocarcinoma</td>
<td>The tail of the pancreas</td>
<td>PACC</td>
</tr>
</tbody>
</table>

GIST: Gastrointestinal stromal tumors; PDAC: Pancreatic ductal adenocarcinoma; PACC: Pancreatic acinar cell carcinoma.

Pancreatic tumor in these cases. Among the 17 synchronous concomitant cancer cases, PDAC accounted for 70.6% (12/17) and PACC accounted for 11.1% (2/17). The pathological type was not mentioned in the remaining three cases. The most common tumor location was the head of the pancreas, accounting for 66.7% of cases (10/15). Two cases of tumors in the body of the pancreas and three cases of tumors located in the tail of the pancreas have been described. In two cases, the tumor location was not reported. Eleven patients (64.7%) underwent surgery for pancreatic and gastric tumors. All were diagnosed pathologically after surgery—which is consistent with our
Fang T et al. Synchronous concomitant pancreatic and gastric cancer

Figure 1 Imaging examinations performed before surgery. On contrast-enhanced computed tomography of stomach, arrow on the left showed uneven thickened with irregular mucosa and heterogeneous contrast enhancement on the antrum of gastric wall; arrow on the right indicated a space-occupying lesion about 34 mm × 16 mm in the tail of the pancreas.

Figure 2 Resection specimen. A: Resection specimen of gastric tumor; B: Resection specimen of pancreatic tumor.

case—and none were diagnosed before surgery. These patients underwent curative resection; this may indicate that these patients were diagnosed at earlier stages and are likely to have better prognoses than patients with only pancreatic cancer. Nevertheless, concomitant cancers exist, and a second tumor should not necessarily be considered as a metastasis from another organ, leading to misdiagnosis and the abandonment of surgical resection.

The clinical manifestations of PACC are related to the location and size of the tumor. Unlike patients with PDAC, patients with PACC present with nonspecific symptoms, including abdominal discomfort, weight loss, weakness, nausea, vomiting, melena, and diarrhea\cite{21}. However, the clinical symptoms of PDAC, such as painless obstructive jaundice, are uncommon in PACC\cite{22}.

Endoscopic ultrasonography (EUS) and imaging findings such as CT and magnetic resonance imaging (MRI) help achieve a correct preoperative diagnosis for concomitant cancers\cite{23}. CT is a valuable tool for the accurate preoperative evaluation of the local extent of gastric cancer; EUS can be used for histopathological confirmation\cite{24}. PACC tumors tend to be solid when small and contain cystic or necrotic areas when large. These tumors generally lack dilatation of the biliary or pancreatic ducts on CT\cite{25}. However, PACC can be difficult to diagnose based on radiological findings alone. EUS-guided fine-needle aspiration (EUS-FNA) has a very high sensitivity (> 85%) and specificity (> 95%) for diagnosis of malignancy in a solid pancreatic mass compared to cross-sectional imaging (CT/MRI)\cite{26}. Whereas the position of the pancreas is relatively deep and EUS-FNA is difficult. An experienced radiologist can give a preliminary imaging diagnosis of PDAC, which tends to be hypovascular, appearing hypoechogenic on imaging\cite{27}. However, it is difficult to distinguish whether
or not the primary tumor has metastasized to other organs in imaging, because tumors can also metastasize through the hematogenous or the lymphatic pathway in addition to direct invasion. If necessary, preoperative pathology must be performed to opt for the correct surgical approach. The present case of abdominal CT revealed a 41-mm heterogenous mass with a clear boundary in the tail of the pancreas, which is suggestive of a primary tumor.

The prevalence of pancreatic metastasis of gastric cancer is extremely rare with, only 12 cases of isolated pancreatic metastasis in gastric cancer have been reported in the literature[28]. Correspondingly, metastatic gastric tumor secondary to pancreatic carcinoma is clinically unusual, with only seven cases of gastric metastasis of pancreatic cancer have been reported in the literature[29-35]. In all these cases, the histopathology and immunohistochemical of primary cancer and metastatic cancer are consistent. However, this is completely different from our case. The histopathology of the two resected specimens was different, showing adenocarcinoma in the stomach and acinar cell carcinoma in the pancreas. Moreover, immunohistochemical studies showed differences in staining at the two sites. Finally, we concluded that both of
them were primary tumors and not metastatic tumors.

PACC is associated with a better prognosis than PDAC but a worse prognosis than pancreatic neuroendocrine tumors[36]. Metastatic PACCs are generally not curable and are treated with systemic chemotherapy[37]. The treatment regimens have not yet been standardized. Takahashi et al.[38] reported that platinum-containing regimens exhibited some potential efficacy in patients with advanced PACC. The response to platinum-containing regimens was 40%, and the overall survival tended to be better in patients who had received a platinum-containing regimen[38]. Simultaneous removal of concomitant primary carcinomas should be attempted; radiotherapy and chemotherapy should also be considered for patients who need adjuvant treatment decided by both disease stages[39]. If adjuvant treatment is required, the physician should select an antineoplastic therapy that considers both cancers. In our case—whether gastric adenocarcinoma or PACC—the optimal chemotherapy regimen was SOX.

CONCLUSION

The presence of synchronous multiple primary malignancies does not necessarily signify an unfavorable prognosis as long as adequate diagnosis and effective treatment are performed. In the future, well-powered clinical trials will be needed to augment our understanding of these processes.

REFERENCES


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Spontaneous resolution of gallbladder hematoma in blunt traumatic injury: A case report

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Abstract

BACKGROUND

We report a case of intragallbladder hematoma and biliary tract obstruction caused by blunt gallbladder injury. We report that the patient was safely treated by conservative treatment after the obstruction was resolved by endoscopic retrograde cholangiopancreatography (ERCP).

CASE SUMMARY

A 67-year-old man was admitted via the emergency department due to complaints of right-sided abdominal pain that started 2 d prior. Four days prior to presentation, the patient had slipped, fallen and struck his abdomen on a motorcycle handle. His initial vital signs were stable. On physical examination, he showed right upper quadrant pain and Murphy’s sign, with decreased bowel sounds. Additionally, he had a poor appetite for 4 d. He had been on aspirin for 2 years due to underlying hypertension. Initial simple radiography revealed a slight ileus. The laboratory findings were as follows: white blood cell count, 15.5 × 10^3/µL (normal range 4.8 × 10^3–10.8 × 10^3); hemoglobin, 9.4 g/dL; aspartate aminotransferase/alanine transferase, 423/348 U/L; total bilirubin/direct bilirubin, 4.45/3.26 mg/dL; -GTP, 639 U/L (normal range 5–61 U/L); and C-reactive protein, 12.32 mg/dL (0–0.3). Abdominal computed tomography showed a distended gallbladder with edematous wall change and a 55 mm × 40 mm hematoma. Dilatation was observed in both the intrahepatic and common bile duct areas. Antibiotic treatment was initiated, and ERCP was performed, with hemobilia found during treatment. After cannulation, the patient’s symptoms were relieved, and after conservative management, the patient was discharged with no further complications. After 1-month follow-up, the gallbladder hematoma was completely resolved.
CONCLUSION
In the case of traumatic injury to the gallbladder, conservative treatment is feasible even in the presence of hematoma.

Key Words: Gallbladder; Trauma; Abdominal injuries, Blunt injuries; Cholecystitis; Gallstone; Case report

Core tip: Intragallbladder hematoma is a rare event in trauma. Most of the hematomas in the gallbladder and blunt traumatic injury of the gallbladder itself can lead to complications such as delayed perforation, gallstone formation due to clot retention, and hemorrhagic cholecystitis. In most cases, these gallbladder hematomas require cholecystectomy or external drainage. However, such as in our case, after endoscopic retrograde cholangiopancreatography was performed and retention of the tract was resolved, conservative treatment should be considered as a treatment option if the laboratory test results show improvement, and the patient shows a favorable clinical course.

INTRODUCTION
Intragallbladder hematoma is a rare event in trauma. Most hematomas of the gallbladder, as well as blunt traumatic injury of the gallbladder itself, can lead to complications such as delayed perforation, gallstone formation due to clot retention, and hemorrhagic cholecystitis. Therefore, in most cases, these gallbladder hematomas require cholecystectomy or external drainage. Here, we report a case of intragallbladder hematoma and biliary tract obstruction caused by blunt gallbladder injury. Despite the large hematoma causing formation of gallbladder stones and prominent symptoms, the obstruction was removed, and there was spontaneous resolution of the hematoma. We show that, in the case of traumatic injury to the gallbladder, conservative treatment is feasible even in the presence of hematoma.

CASE PRESENTATION
Chief complaints
A 67-year-old man was admitted via the emergency department due to right-sided abdominal pain that started 2 d prior.

History of present illness
Four days prior to presentation, the patient had slipped and fallen, striking his abdomen on a motorcycle handle. The initial vital signs were stable.

History of past illness
He had been taking aspirin for 2 years due to underlying hypertension.

Personal and family history
He had been experiencing a poor appetite for 4 d.

Physical examination
Additionally, on physical examination, the patient showed right upper quadrant pain
and Murphy’s sign, with decreased bowel sounds.

**Laboratory examinations**

The laboratory findings were as follows: white blood cell count, $15.5 \times 10^3/\mu L$ (normal range $4.8 \times 10^3-10.8 \times 10^3$); hemoglobin, 9.4 g/dL; aspartate aminotransferase/alanine transferase, 423/348 U/L; total bilirubin/direct bilirubin, 4.45/3.26 mg/dL; -GTP 639 U/L (normal range 5–61 U/L); and C-reactive protein, 12.32 mg/dL (normal range 0–0.3 mg/dL).

**Imaging examinations**

An initial simple radiography revealed a slight ileus (Figure 1). Abdominal computed tomography (CT) showed a distended gallbladder with edematous wall change and a 55 mm × 40 mm hematoma.

**FINAL DIAGNOSIS**

The patient had biliary colic pain, and laboratory findings showed elevations in bilirubin and liver function enzymes and a markedly increased γ-glutamyl transferase level. Furthermore, the intrahepatic bile duct dilatation finding on CT suggested a common bile duct obstruction. Based on these findings, gallbladder hematoma (55 mm × 40 mm) with common bile duct obstruction due to traumatic injury was diagnosed.

**TREATMENT**

Following antibiotic treatment, we performed endoscopic retrograde cholangiopancreatography (ERCP). There was a suspicion of amorphous filling defects in the common bile duct. Hemobilia was observed on cannulation during endoscopy (Figure 2). We deployed a 5 Fr, 4-cm, single-pigtail plastic stent. After stent deployment, the patient’s symptoms were slightly relieved, and the laboratory findings showed improvement. After antibiotic treatment with 2 g cefotaxime and 500 mg metronidazole every 8 h for 5 d, the patient was discharged.

**OUTCOME AND FOLLOW-UP**

After a 1-week interval, the patient revisited the hospital due to slight abdominal discomfort and constipation, after which he was admitted to the inpatient ward for close observation. On admission, a stool softener was administered, as stool impaction was observed on abdominal X-rays, and the patient had constipation. The abdominal pain was relieved, and no other specific symptoms or fever developed. The laboratory findings were within the normal ranges without antibiotic treatment. In the follow-up CT performed after 10 d, hematoma and distension showed improvement, but mild edematous wall thickening of the gallbladder remained. The stent had been spontaneously removed. The patient’s course was uneventful, and he was discharged 1 wk after CT follow-up. When the patient visited our clinic for the 1-month follow-up, abdominal CT showed an improved hematoma and a distended gallbladder with mild edematous wall thickening (Figure 3).

**DISCUSSION**

Intragallbladder hematoma injury accounts for < 2% of blunt intra-abdominal injuries [1,2]. Intra-abdominal hematoma frequently occurs in patients with underlying conditions such as anticoagulation therapy, cirrhosis, renal failure, or even angiosarcoma[3]. Therefore, in traumatic events, checking a patient’s medication history or underlying disease state is crucial[4,5].

Cholecystitis symptoms such as right upper quadrant tenderness, fever, and leukocytosis might occur in blunt injury with intragallbladder hematoma. In addition, symptoms such as hematemesis, melena, and hemobilia may also occur. Most hematomas in the gallbladder lead to blood clots and obstruction of the common bile duct. This can result in cholangitis, which should be closely monitored, as a delay in
Jang H et al. Spontaneous resolution of gallbladder hematoma

Figure 1 A 55 mm × 40 mm hematoma was seen in the initial computed tomographic scan. A: The Hounsfield unit values of the gallbladder stone-like lesions ranged from 60 to 67, and no gallbladder wall defect lesion was found (arrow); B: Dilatations of the intrahepatic and common bile ducts are seen (arrow), and there was a suspicion of distal common bile duct obstruction.

Figure 2 Endoscopic retrograde cholangiopancreatography was performed. A: There was a suspicion of amorphous filling defects in the common bile duct; B: Hemobilia was seen on cannulation during endoscopy. A 5 Fr, 4-cm, single pigtailed plastic stent was deployed.

diagnosing the obstruction can worsen the prognosis[6,7].

Furthermore, blunt traumatic injury of the gallbladder itself can lead to other complications, such as delayed perforation, gallstone formation due to clot retention, and hemorrhagic cholecystitis. In such cases, if there is no improvement, cholecystitis requires surgery. In patients who are unstable, cholecystostomy can be an option[5,8]. Due to concerns of delayed complications such as gallbladder necrosis or ischemia, physicians are reluctant to provide conservative treatment[2,9].

However, as in our case, after retention of the bile tract is resolved, conservative treatment should be considered as an option if the laboratory test results show improvement and the patient shows a favorable clinical course.

Our decision on conservative treatment was challenging. As a surgeon, treatment by a surgical approach is a tempting method and is easily performed. However, considering the patient’s symptoms and laboratory findings, we decided to consider other treatment options. In this patient’s case, after ERCP and cannulation were performed, the patient’s abdominal tenderness improved daily. Furthermore, the patient’s gallstones were spontaneously formed by hematoma, his fever was relieved, and his laboratory findings decreased to within the normal ranges. With symptom improvement and no other complications, stopping antibiotics was the final consideration for treatment that was completed with a conservative approach.

However, before considering conservative treatment, it is necessary to confirm whether there are other accompanying intra-abdominal injuries in the patient and whether the required treatment of such injuries is likely to prolong the hospital stay. Furthermore, in cases where gallbladder stones are present or the clinical
manifestation is cholecystitis, surgery or cholecystostomy should be considered as treatment options. This patient’s gallbladder hematoma size gradually decreased and completely resolved after long-term follow-up. Therefore, no other interventions were needed.

The clinical picture of cholelithiasis and cholecystitis usually occurs in acute or chronic forms. Acute cholecystitis usually requires treatment with antibiotics or cholecystectomy. In the case of acute cholecystitis, gallbladder resection is a common treatment of choice after diagnosis. If urgent cholecystectomy is not possible, surgery can be postponed until the acute course of symptoms is resolved. If symptoms resolve and the processes are controlled, surgery can then be selectively performed.

We searched PubMed for a review of treatment options for similar cases of traumatic gallbladder hematoma. In a case reported by Nishiwaki et al\[10\], the patient was managed conservatively over 30 d and eventually underwent cholecystectomy. In this case, the patient had liver cirrhosis and consistent anemia detected during the admission period. For further evaluation, the authors performed ultrasonography-guided aspiration. In these circumstances, continuing conservative treatment may have resulted in a fatal situation.

When the diagnosis is unclear in isolated gallbladder injury, CT scan and cholecystectomy are considered the treatment of choice, as reported by Birn et al\[11\]. This was supported by the postoperative diagnostic results in Birn et al\[11\] case of a partially avulsed gallbladder specimen that was not identified on CT.

In a blunt trauma case reported by Tudyka et al\[12\], a hydroptic gallbladder with intraluminal hematoma and dilatation of the common bile duct was found in the patient’s CT scan. Without other options, the patient underwent explorative laparotomy, and cholecystectomy was performed. There was no perforation of the resected gallbladder, and a large intraluminal hematoma was seen in the specimen. In a similar case of isolated blunt gallbladder trauma with intraluminal hemorrhage reported by Como et al\[13\], the patient underwent laparoscopic cholecystectomy due to suspected hemorrhagic findings in the gallbladder on CT scan. Even though the patient had tenderness in the right upper quadrant of the abdomen, combined right second to fourth rib fractures and pneumothorax may have also explained their pain. As seen in our case, conservative treatment options may have been carefully considered in these two cases.

ERCP treatment might also cause iatrogenic complications. In a case report by Staszak et al\[14\], ERCP with stent placement was performed to treat hemobilia of cholangitis, and after the procedure, laparoscopic cholecystectomy was performed the following day for the treatment of combined cholecystitis. However, after these interventions, pseudoaneurysms of the posterior margins of the liver just above the gallbladder border developed. Even if this case was not caused by traumatic events, the risks of hemobilia and ERCP treatment should not be underestimated.

Our case showed spontaneous resolution even with the presence of a large (4 × 5 cm) gallbladder hematoma. Therefore, when symptoms occur, it is important to determine the cause of biliary colic pain before proceeding with cholecystitis treatment. In fact, in our patient, a stepladder pattern was seen on simple radiography, and physical examination showed increased bowel sounds at the time of the visit. This
can be seen as a visceral pain pattern caused by blockage of the cystic duct, and the contractions were caused by the impacted stone. In most cases, the presence of blunt injury cannot rule out that of coexisting bowel injury; therefore, it is important to monitor for this type of pain. If pain persists and worsens, treatment should be determined based on the development of additional cholecystitis, cholangitis, or accompanying pancreatitis.

In this patient, the stone-like hematoma of the gallbladder spontaneously resolved; however, if it remained in the form of a gallstone after treatment, the course of the disease was monitored periodically. If there is recurrent pain in the form of biliary colic pain that leads to later inflammation, surgical treatment would have been needed.

**CONCLUSION**

Despite the relatively large hematoma in the form of gallbladder stones and prominent symptoms, conservative treatment may be an effective treatment option if obstruction of the bile duct is resolved.

**REFERENCES**

Rupture of ovarian endometriotic cyst complicated with endometriosis: A case report

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Abstract

BACKGROUND
Endometriosis (EMs), an estrogen-dependent disease, refers to the appearance of mucosa-covered endometrial tissues (glandular and interstitial) growing in the uterine cavity outside the uterine myometrium. It is commonly seen in women aged 25 to 45, with an incidence of approximately 10%-15%.

CASE SUMMARY
A 35-year-old unmarried female who denied a history of sex with an intact hymen had multiple dysmenorrhea and pain in the left lower abdomen that recurred during menstruation. Ultrasound examination revealed a dark cystic area measuring 4.9 cm × 4.6 cm on the left side with poor light transmittance, which suggested a left endometriotic cyst. The patient was treated with pain medications (four capsules t.i.d., p.o.). After one month, computed tomography of the abdomen and pelvis revealed a low-density focus measuring approximately 38 mm in diameter, a blurred mesentery fat plane in the pelvic cavity, and pelvic effusion. Ultrasound showed a complex echo density measuring 5.2 cm × 3.0 cm × 4.2 cm in the left ovarian area and a fluid sonolucent area with a depth of 2.0 cm in the pelvic cavity. Left ovarian cystectomy, electrocautery for endometriotic lesions, myomectomy, and pelvic adhesion lysis were performed under laparoscopy. The postoperative diagnosis was left ovarian chocolate cyst rupture and EMs (stage III, ovarian type, peritoneal type).

CONCLUSION
Laparoscopic surgery can safely control the symptoms of EMs and effectively eradicate the disease.

Key Words: Ovary; Rupture of endometriotic cyst; Endometriosis; Laparoscopic surgery; Case report

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Core Tip: With the advancement of laparoscopic technology, minimally invasive laparoscopic surgery has successfully become the treatment option for ruptured chocolate cysts. We would like to share our experience of laparoscopic treatment of ruptured ovarian endometriotic cysts.

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INTRODUCTION
Endometriosis (EMs) is a benign disease caused by the presence of endometrium outside the uterine cavity. It is commonly seen in women aged 25 to 45, with an incidence of 10%-15%, and frequent symptoms, including lower abdominal pain, infertility, and dysmenorrhea, adversely affect both health and quality of life[1,2]. There are three types of EMs: Ovarian EMs, peritoneal EMs, and deep invasive EMs, among which ovarian endometriotic cysts (commonly known as chocolate cysts) are a common type, accounting for approximately 80% of EMs, with an incidence of approximately 20%-45% in females with infertility[3,4]. Studies have revealed a relationship between EMs and heredity, immunity, inflammation, and so on[5]. The incidence of both chocolate cyst rupture and EMs are increasing; however, EMs is often misdiagnosed as diseases such as trans pelvic inflammatory disease, ectopic pregnancy, and appendicitis[6].

With the development of laparoscopic technology, laparoscopic surgery has become the primary method for treating chocolate cyst rupture given its accurate diagnosis, symptom alleviation and success in adhesion separation and lesion elimination. This article analyzed the effect of laparoscopic surgery on a patient with ruptured ovarian cysts with the following report.

CASE PRESENTATION

Chief complaints
The patient was a 35-year-old unmarried female who denied a sexual history and presented with an intact hymen. Menophania occurred at 14 years of age, with a menstrual cycle of 30 d and a 7-10 d duration for each cycle. Breast swelling occurred prior to each period with no significant changes in leukorrhea. Positive results for polymenorrhea and dysmenorrhea were obtained, but the symptoms worsened over the prior four months, mostly at the beginning of each period. The previous menstrual period was on May 4, 2020, and the last menstrual period was on June 11, 2020, with the dysmenorrhea slightly improved over that of the previous month.

History of present illness
Beginning in February 2020, the patient started to experience recurrent left lower abdominal pain 2 d prior to and during the first 3 d of the period, which was associated with persistent anal distension but no nausea or vomiting or radiating pain. She did not seek medical advice, as the pain was tolerable for her at the beginning. This lasted until May 9, 2020, when the patient presented to our clinic with recurrent perimenstrual left lower quadrant pain that worsened over a day.

Physical examination
At 1 pm on June 16, the patient started to experience intermittent upper abdominal pain without inducement, associated with anal distension and fever of 38.3°C. There was no constipation, diarrhea, cold sweat, dizziness, or syncope.

Laboratory examinations
Coronavirus disease 2019 was ruled out at the fever clinic.
Imaging examinations
Ultrasound examination revealed a dark cystic area measuring 4.9 cm × 4.6 cm on the left side with poor light transmittance, which suggested a left endometriotic cyst. Accordingly, the patient was given pain medications (four capsules t.i.d., p.o.). She returned to our clinic on June 10, 2020, and her period started the next day with significant relief of dysmenorrhea. The ultrasound results on June 15 again showed a cystic lesion, now measuring 5.66 cm × 6.58 cm × 5.79 cm, without an obvious fluid sonolucent area in the pelvic cavity. The patient refused the recommendation for surgical treatment. At 1 pm on June 16, she presented to our emergency clinic at approximately 11 pm, and abdominopelvic computed tomography (CT) confirmed a low-density focus measuring approximately 38 mm in diameter, a blurred mesentery fat plane in the pelvic cavity, and pelvic effusion. Ultrasound showed a complex echo density measuring 5.2 cm × 3.0 cm × 4.2 cm in the left ovarian area and a fluid sonolucent area with a depth of 2.0 cm in the pelvic cavity.

FINAL DIAGNOSIS
Left ovarian chocolate cyst rupture; EMs (stage III, ovarian type, peritoneal type).

TREATMENT
With no pain relief and after diagnosis of left ruptured ovarian cyst, the patient was admitted to the hospital on June 17, and left ovarian cystectomy, electrocautery for the endometriotic lesions, myomectomy, and pelvic adhesion lysis were performed laparoscopically.

The patient was placed in a supine position, and the lower abdomen was routinely disinfected after successful anesthesia induction. A 1.0 cm transverse incision was made at the umbilicus, where a 10 mm trocar was placed after placement of a Veress needle followed by pneumoperitoneum with CO₂. Under the direct inspection of a laparoscope, two 5 mm trocars were placed at McBurney’s point and its reflection on the left side, and a 10 mm trocar was placed approximately 3 cm from the left side of the umbilicus. The laparoscopic view revealed a normal-sized uterus, while there was a 1 cm myoma-looking lesion at the front wall. The left ovarian cyst had enlarged to approximately 5 cm × 6 cm × 5 cm, had ruptured with some active bleeding, and was closely attached to the posterior portion of the broad ligament, the posterior wall of the uterus and the intestines. Douglas’ pouch was partially obstructed, the right ovary was slightly swollen, and there were multiple follicular cysts and blue-purple nodules on its surface. Extensive adhesion of some of the intestines to the posterior portion of the right broad ligament as well as the isthmus of the uterus was observed. The posterior wall of the uterus was covered with flocculent secretions, blue-purple nodules, and flame-shaped lesions. The American Society for Reproductive Medicine score was 36, and there was approximately 200 mL of free chocolate-colored fluid in the pelvic cavity. The bilateral fallopian tubes were soft with free and mildly swollen fimbriated extremities.

The surgical steps were as follows: (1) Pelvic blood was irrigated and evacuated with negative suction; (2) Blunt and sharp dissection were combined during adhesion lysis to rebuild the normal anatomy; an incision was made along ruptured end of the left ovarian cyst to fully remove the cyst wall, and it was closed with interrupted 3-0 absorbable sutures. The uterine fibroma at the front wall was resected, followed by electrocautery to the endometriosis focus. After complete excision of the specimen, it was found to consist of grayish, swirl-like fibroid tissue surrounded by a smooth cyst wall. The specimen was sent for surgical pathology after review with the patient’s family; (3) Thorough irrigation, suction of the abdominopelvic cavity, and satisfactory hemostasis were performed, and 3 pieces of soluble hemostatic gauze and 2 pieces of gel foam were left at the surgical field; and (4) The trocars were removed after desufflation, and the incisions were closed.

The surgery was uneventful, and the patient remained stable during the whole procedure. The total blood loss was approximately 5 mL; the urine output was 300 mL and clear. The patient was sent back to the ward safely after surgery.

Zoladex was provided as supplemental medical therapy after surgery, with one dose every 28 d (one cycle) via subcutaneous injection in the abdomen for 6 cycles.
OUTCOME AND FOLLOW-UP

Blood-related indexes
A chemiluminescence immunoassay (DIX800 Chemiluminescence Immunoassay Analyzer from Beckman Coulter, United States) was used to determine serum anti-Müllerian hormone (AMH, reference range 2-6.8 ng/mL), follicle-stimulating hormone (FSH, 5-40 mIU/L), and carbohydrate antigen 125 (CA-125, < 35 U/mL) levels. The white blood cell count (3.5-9.5 × 10⁹/L) and neutrophil count (40%-75%) of the patient were measured with a routine blood analyzer (Japan Bier Company, model Sysmex XN-3000). Hypersensitive c-reactive protein was determined by a double-antibody sandwich enzyme-linked immunosorbent assay (Johnson & Johnson, model VITROS 5.1FS), with a reference range of ≤ 5 mg/L. D-dimer was detected by an automatic blood coagulation analyzer (Japan Bier Company, model Sysmex CS-5100), with a reference range of ≤ 5 mg/L. The specific detection time and results are shown in Table 1.

Ultrasound
June 15, 2020: The uterus was antepositioned, with normal size and shape, uniform echo in the myometrium, and a thickness of 0.97 cm. The right ovary presented with a normal size and shape and no abnormal echo. The left ovary was not clearly demonstrated, with a 5.66 cm × 6.58 cm × 5.79 cm cystic lesion with clear margins, poor transmittance, and layering. An area of hyper echogenicity measuring 1.3 cm × 0.5 cm was also observed. Color Doppler flow imaging (CDFI) did not exhibit obvious flow, and no evident free fluid was seen in the pelvis (Figure 1).

June 16, 2020: The uterus was retropositioned, with normal size, uniform echo in the myometrium, and a thickness of 0.64 cm. A cystic lesion measuring 2.1 cm × 0.9 cm × 1.9 cm was observed in the right ovary. A mixed echoic area measuring 5.2 cm × 3.0 cm × 4.2 cm was identified on the left, with clear margins but an irregular shape. Dark fluid shadows were observed within, measuring approximately 4.2 cm × 3.0 cm × 3.8 cm, with poor transmittance. CDFI indicated blood flow in and around the mixed echoic area, and free fluid in the pelvis had a depth of approximately 2.0 cm, poor transmittance, and dense light spots. A 0.7-cm hyperechogenic spot was also observed in the gallbladder.

Whole abdominal CT
The uterus was considered in a normal state in terms of shape, size, and density. A low-density focus at the left ovarian area was observed, with a diameter of approximately 38 mm, clear margins, blurred mesentery fat plane, and spots with fluid density.

DISCUSSION
The mechanism behind the formation of chocolate cysts remains unclear but is currently thought to be secondary to the following process[7,8]. Pieces of endometrium travel back to the pelvic cavity with menses via the fallopian tubes and are seeded onto the ovarian surface; during each cycle and under the effect of estrogen, the pieces of endometrium seeded onto the ovary bleed and gradually form into a cyst when drainage is unsatisfactory. Before and during every menstrual period, the cyst grows and undergoes high amounts of tension, thus leading to its rupture. The thick contents of chocolate cysts are sufficiently irritating to cause extreme abdominal pain, which in all probability contributed to the recurrent perimenstrual left lower abdominal pain in our patient. When such cases are not treated in time, the contents of the cyst can spread throughout the abdominal cavity, resulting in more severe conditions, aka generalized peritonitis. Given the easy ruptures around periods giving rise to sudden pain, misdiagnoses of appendicitis are frequently made. Research has shown that approximately 1/3 of patients with chocolate cysts complain of lower abdominal pain (unilateral or bilateral)[9]. The recurrent perimenstrual pain in our patient that started in February 2020 and began clinically declining in May 2020 might have been associated with adhesions in the pelvis from the cyst.

The gold standard diagnostic tool for this condition is laparoscopy, which allows visualization of the chocolate fluid in the cyst under direct observation and resection of the cyst for final pathological diagnosis[10]. In our case, the postoperative diagnosis of EMs and ruptured chocolate cyst agreed with the pathology. Ultrasound allows
Table 1 Blood-related indexes at different time points

<table>
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<tbody>
<tr>
<td>CA-125</td>
<td>41.65 U/mL</td>
<td>31.09 U/mL</td>
<td></td>
<td></td>
<td>723.29 U/mL</td>
<td>125 448.32 U/mL</td>
</tr>
<tr>
<td>WBC</td>
<td>13.88 × 10^9/L</td>
<td>9.98 × 10^9/L</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>hs-CRP</td>
<td>8.6 mg/L</td>
<td>3380 μg/L</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>NEU</td>
<td>88.7%</td>
<td>79.0%</td>
<td></td>
<td></td>
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<tr>
<td>D-D</td>
<td>3380 μg/L</td>
<td>2220 μg/L</td>
<td></td>
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</tr>
<tr>
<td>AMH</td>
<td>3.09 ng/mL</td>
<td>8.50 IU/L</td>
<td></td>
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<tr>
<td>FSH</td>
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CA-125: Carbohydrate antigen 125; WBC: White blood cell; hs-CRP: Hypersensitive c-reactive protein; NEU: Neutrophil count; D-D: D-dimer; AMH: Anti-Müllerian hormone; FSH: Follicle-stimulating hormone.

Figure 1 Ultrasound on Jun 15, 2020.

only a rough evaluation of chocolate cysts, which may consequently result in the misdiagnosis of physiologic cysts that disappear when the period concludes as chocolate cysts. Moreover, small cysts likely shrink after taking birth control pills due to their inhibitory effects on the endometrium[11]. When our patient was found to have a 4.9 cm × 4.6 cm dark cystic area around the left ovary on ultrasound that suggested a potential left endometriotic cyst on May 9, 2020, she was treated with pain medication, which contributed to inhibiting endometrial growth and shrinking the cyst. However, a repeat ultrasound on June 15, 2020, revealed that the dark region had grown to a size measuring 5.66 cm × 6.58 cm × 5.79 cm; the patient refused the recommendation of surgical treatment and returned to the hospital with abdominal pain the next day. Abdominal CT suggested free fluid collection in the pelvis, and ultrasound was remarkable, revealing a 5.2 cm × 3.0 cm × 4.2 cm complex echo density around the left ovarian area as well as a 2.0-cm deep fluid pocket. The patient was admitted on the 17th day of June with a ruptured ovarian cyst, and surgical resection was completed with laparoscopy[12,13]. Once the disease is diagnosed, surgery should be performed promptly. The outflow of the contents of chocolate-like cysts after rupture results in secondary chemical peritonitis by irritation of the peritoneum, which may be fatal for the patient. Differentiation of rupture of ovarian ectopic cysts from other acute abdominal diseases, such as acute appendicitis, is imperative. The incidence of endometriosis comorbid with infertility is as high as 50%. The cyst content flows into the abdominal cavity after rupture, which may result in secondary adhesions and endometrial implantation without timely treatment, leading to further fertility damage. Therefore, timely and accurate diagnosis is paramount. If the cyst
content outflow is insufficient to cause acute abdomen due to a small rupture, the patient might be asymptomatic. However, the inflammatory response could lead to the formation of adhesions in the surrounding region, and the cyst could undergo repetitive processes of shrinkage, regrowth, rupture, bleeding, and healing, imposing more complexity on the potential surgical treatment. Since ovarian endometrial cysts are often accompanied by symptoms such as abdominal pain and anal swelling during or near the menstrual period, a detailed medical history and gynecological examination before surgery present great potential in providing a more accurate diagnosis in the treatment of the acute abdomen, thereby alleviating the pain and economic burden of the patient.

Chocolate cysts not only manifest with severe abdominal pain but also worsen pelvic adhesions and potential new EMs, eventually triggering infertility. For patients of childbearing age, conservative surgery to preserve reproductive and endocrine function is the treatment of choice. Surgical treatment, its promising therapeutic effect notwithstanding, is undermined by a high recurrence rate, especially conservative surgery and semi radical surgery. It has been reported that the recurrence rate of endometriotic cysts subjected to surgery is higher than that for unruptured patients, which emphasizes the importance of thorough irrigation of the abdominal cavity during surgery to prevent iatrogenic secondary seeding by the extensive contamination of the contents of the cyst in the pelvic cavity. In our case, consolidate treatment with Zoladex for 6 mo after surgery was applied to prevent recurrence. Laparoscopic surgery has now become the first treatment of choice with more advantages than open surgery; it is minimally invasive and offers a high chance of maintaining sexual function while avoiding harm to other organs in the abdomen[14]. In this case, left ovarian cystectomy, electrocautery for the endometriotic lesions, myomectomy, and pelvic adhesion lysis were performed. Under laparoscopic view, the adhesions were thoroughly irrigated and lysed to achieve the maximal therapeutic effect and preserve as much normal tissue as possible. Postoperatively, Zoladex is used to act on the hypothalamic-pituitary axis, suppressing FSH release and glandular growth of the target lesion, promoting apoptosis, and alleviating invasiveness[15]. AMH normally ranges from 2-6.8 ng/mL, and FSH normally ranges from 5-40 mIU/L[16,17]. The postoperative AMH level in our patient was 3.09 ng/mL, and the FSH level was 8.50 IU/L; as they were within the normal ranges, these levels indicated improvement after surgical therapy. Carbohydrate antigen, with its ability to trigger the immune response, is beneficial for monitoring disease and predicting prognosis in breast, lung, colon, and many other cancers.

The carbohydrate antigen level increases to a lesser degree in the presence of benign tumors and inflammatory disease than in malignant conditions. Studies have also demonstrated that CA-125 Levels are increased in the presence of benign ovarian tumors[18,19]. Koo et al[20] reported lower levels of CA-125 after treatment in chocolate cyst patients. D-dimer is a marker for fibrinolysis, and increased levels indicate hyperfibrinolysis, which causes a hypercoagulative state. In our patient, the postoperative levels of D-dimer and CA-125 decreased, which suggested that coagulation function can be improved in patients with chocolate cysts treated with laparoscopic surgery.

CONCLUSION

We reported a case of a ruptured chocolate cyst. Ultrasound, abdominopelvic CT, and serum D-dimer and CA-125 were useful diagnostic tools, and laparoscopic surgery was confirmed to be safe for symptom control and effective disease eradication.

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Rotarex mechanical thrombectomy in renal artery thrombosis: A case report

Wen-Rui Li, Ming-Yuan Liu, Xue-Ming Chen, Zhi-Wen Zhang

BACKGROUND
Acute renal artery thrombosis is a relatively rare disease. Early diagnosis and emergent treatment can prevent the loss of renal function and the development of hypertension.

CASE SUMMARY
We report a patient with acute renal artery thrombosis who presented to our hospital with acute-onset right flank pain and was treated by percutaneous interventional therapy using the Rotarex device. After 2 mo, right kidney function had recovered slightly.

CONCLUSION
Renal artery thrombosis may lead to loss of renal function and the development of hypertension. Rotarex mechanical thrombectomy may be a viable treatment option for rapid recanalization of the renal artery in patients with renal artery thrombosis.

Key Words: Renal artery; Thrombosis; Thrombectomy; Renal infarction; Endovascular; Case report

Core Tip: Acute renal artery thrombosis is a relatively rare disease, and will lead to acute renal infarction. Several options have been reported such as systemic anticoagulation, percutaneous interventional therapy and surgical operation. It is the first time that Rotarex mechanical thrombectomy catheter was used to treat renal artery thrombosis. Our case confirmed that the Rotarex system may be a safe way to rapidly recanalize the renal artery in renal artery thrombosis patient. It may be a treatment
INTRODUCTION

Acute renal artery thrombosis (RAT) is a relatively rare disease, and can lead to acute renal infarction. Most of the literature on this disease is published in case reports and retrospective studies[1,2]. Because of its low incidence and atypical symptoms, and as it usually manifests as abdominal pain similar to acute pyelonephritis or renal colic, acute RAT is easily misdiagnosed[3,4]. Early diagnosis and emergent treatment can prevent the loss of renal function and the development of hypertension. A contrast-enhanced computed tomography (CT) scan is considered necessary for the diagnosis [5]. There are no available guidelines for the treatment of this rare entity, and the therapeutic options for acute renal infarction include anticoagulation, thrombolytics, and surgical thrombectomy or catheter-based treatments[6]. Here we report a patient with acute RAT who presented to our hospital with acute-onset right flank pain and was treated with percutaneous mechanical thrombectomy (PMT) using the Rotarex device. To the best of our knowledge, this is the first case report of Rotarex mechanical thrombectomy for RAT.

CASE PRESENTATION

Chief complaints

A 41-year-old man presented to the Emergency Department with acute onset right-sided flank pain that started 20 d prior to admission. Twenty days previously, the patient had acute right flank pain at night, and a CT scan showed no obvious abnormalities. According to his symptoms, the patient was diagnosed with urinary calculi. A few hours later, the patient's symptoms resolved spontaneously. He had similar symptoms again 10 d later, and the findings of a CT scan were similar to those of the first scan. His symptoms resolved after pethidine administration. He presented to our hospital with right-sided flank pain and vomiting. The pain was continuous, non-radiating and without any aggravating or relieving factors.

History of present illness

The patient had no history of fever, jaundice, constipation, diarrhea, burning micturition, hematuria, trauma, drug intake, alcohol intake, or weight loss.

History of past illness

He had a history of arrhythmia and was treated with radiofrequency ablation, but the specific type of arrhythmia was not clear.

Personal and family history

No positive history of family members was reported.

Physical examination

Physical examination showed a body temperature of 36.2 °C, blood pressure of 169/119 mmHg, pulse rate of 88 bpm, and respiratory rate of 18 breaths/min, and oxygen saturation was 97%. Cardiac and respiratory examinations were unremarkable. The abdomen was soft and not distended, moving normally with respiration, with no tenderness, no guarding or rigidity, no organomegaly, no free fluid in the abdomen, and normal bowel sounds. The urine output was maintained.
**Laboratory examinations**

Blood tests revealed normal hemogram, blood sugar, serum lipase, and serum amylase levels, and liver function, urine examination, lipid profile, and electrocardiogram were also normal. The serum lactate dehydrogenase level was 338 IU (< 250 IU). Renal parameters at the time of admission showed blood urea of 4.97 mmol/L (3.1-8 mmol/L) and serum creatinine of 115.9 μmol/L (59-103 μmol/L).

**Imaging examinations**

Because the previous two CT scans did not find the cause of abdominal pain, the possibility of mesenteric ischemia was suggested, and a contrast-enhanced CT scan of the abdomen was performed, which showed an area of non-enhancement in the right kidney and reduced flow in the right renal artery (Figure 1). He was immediately transferred to our department, and renal artery color Doppler ultrasound was performed, which confirmed stenosis of the right renal artery. In order to evaluate the current sub-renal function, renal dynamic imaging was carried out, and the glomerular filtration rate (GFR) in the left kidney was 89.5 mL/min, and was 20.9 mL/min in the right kidney.

Other laboratory tests were performed to exclude coagulation disorders, including protein C, protein S, antithrombin III, erythrocyte sedimentation rate, C-reactive protein, anti-neutrophil cytoplasmic antibody, and antinuclear antibody, and the results were all negative except for increased protein S level, which was 148.9% (55%-130%).

**FINAL DIAGNOSIS**

The final diagnosis was acute renal artery thrombosis.

**TREATMENT**

In order to avoid further RAT and prevent the loss of renal function and the development of hypertension, it was decided to use a Rotarex PMT device to restore the blood supply to the right kidney. The patient underwent arteriography via right femoral artery access. The left-sided renal angiography was normal, and the right-sided renal angiography showed thrombotic occlusion of the renal artery (Figure 2A). A 0.018-in wire was passed through the occluded segment to the distal artery as far as possible with the purpose of sufficient support. The PMT device used was the Rotarex system (Straub Medical, Wangs, Switzerland), with a 6F sheath diameter device. The Rotarex device was inserted over the wire and then activated (Figure 2B). Small careful forward and backward passages were slowly performed twice. Repeated aspiration resulted in good flow without significant stenosis (Figure 2C). The patient tolerated the procedure well. Postoperatively, the patient was started on low molecular weight heparin. His pain was relieved, blood pressure had returned to normal, but there was worsening of renal parameters on the second day. His serum creatinine reached 118.9 μmol/L (59-103 μmol/L). Three days later, his renal function improved with an increase in urine output, and his serum creatinine was 112.8 μmol/L (59-103 μmol/L). Renal artery color Doppler ultrasound confirmed complete patency of the right renal artery. He was discharged on rivaroxaban and aspirin.

**OUTCOME AND FOLLOW-UP**

After 2 mo, the patient’s serum creatinine had dropped to 95.2 μmol/L (59-103 μmol/L). Renal dynamic imaging showed that his right kidney function had recovered slightly. The GFR in the left kidney was 70.5 mL/min, and 25.0 mL/min in the right kidney.

**DISCUSSION**

RAT is relatively rare, often manifest by renal infarction, and may be life-threatening. The results of an autopsy study showed that the incidence rate was
Li WR et al. Mechanical thrombectomy in renal artery thrombosis

14/1000 people. Renal infarction is a rare condition, with an estimated incidence in the Emergency Department of 0.004% [7]. RAT may be related to atrial fibrillation [4]. In addition, any renal artery damage caused by endovascular treatment or trauma may also lead to thrombosis, and RAT may also occur as a result of renal artery stenosis. There are also many patients with idiopathic renal artery thrombosis [8]. Our patient had a history of arrhythmia and elevated protein C levels, which may have caused RAT.

Clinical manifestations of RAT include acute onset of flank pain or lower back pain, and hematuria without signs of peritonitis [4]. The diagnosis of renal artery thrombosis is often delayed or missed due to both the rarity of the disease and its non-specific clinical presentation, and has become a diagnostic challenge in the Emergency Department. There are reports that serum LDH sensitivity can reach approximately 90%, but the specificity is poor. Therefore, a low LDH level can be used as a marker to rule out acute RAT [1,9]. An unenhanced CT scan can rule out urolithiasis, but renal artery thrombosis may be missed as in our patient. A contrast-enhanced CT scan allows a definite diagnosis of RAT and can evaluate the range of the thrombus [1,10].

Currently, there are no guidelines on the treatment of RAT. Several options have been reported such as systemic anticoagulation, percutaneous interventional therapy, and surgery [2,9]. The use of anticoagulant agents as the sole therapy has often been insufficient to alleviate symptoms and renal dysfunction resulting from renal infarcts. Endovascular treatment includes local intra-arterial thrombolysis, catheter aspiration, balloon dilatation, and stent placement [4,6,9]. The purpose of these treatments is to restore the blood supply to the ischemic kidney as soon as possible, thereby preventing the loss of renal function and the development of hypertension. In general, the period from the onset of symptoms to the onset of irreversible renal injury is 3 h [11]. However, because the diagnosis is difficult, and treatments such as anticoagulation and local intra-arterial thrombolysis take a long time, most patients cannot restore the blood supply to the kidneys during this period. However, case reports have described the recovery of kidney function after a long occlusion period of even weeks. In another case, renal artery stenting was performed 1 wk after acute renal artery occlusion, and recovery of renal function was also observed [6]. Our patient was treated 20 d after the onset of symptoms, and the creatinine level rose briefly after treatment. However, renal function of the affected side also recovered slightly after 2 mo, indicating that revascularization for subacute RAT may have the potential to reverse recalcitrant conditions. There are also reports which show unsuccessful outcome after renal artery revascularization following a prolonged period of ischemia [2,12]. In addition to the duration of ischemia, the prognosis may also depend on collaterals from the lumbar, suprarenal, and ureteral vessels, and the degree of obstruction, as subtotal obstruction results in hibernation of renal parenchyma [4,13].

PMT represents a minimally invasive option for rapid recanalization of the target artery. Manual suction thrombectomy has been used in the treatment of RAT, but the thrombus may not be removed completely and there is also the risk of damaging the
Figure 2 Angiography findings. A: Angiography revealed thrombotic occlusion in the main trunk of the right renal artery (orange arrow); B: Rotarex system (Straub Medical, Wangs, Switzerland) was activated in the right renal artery (orange arrow); C: Restoration of flow after mechanical thrombectomy in the renal artery on completion angiography.

The Rotarex system is one of the PMT devices, and has been widely used in thrombotic diseases of lower limb arteries and is sometimes used in superior mesenteric artery thrombosis[14,15]. This rotational thrombectomy is capable of precluding and replacing thrombolysis, and may be an effective and safe modality for restoring blood supply to the target kidney faster. Local catheter-based intra-arterial thrombolysis may require a longer treatment period. At the same time, because of the angle between the renal artery and aorta, it is difficult to maintain the catheter in the proper position during the entire process. Despite the good technical and clinical success rates in our report, long-term follow-up and more studies are needed to verify the effectiveness and safety of this treatment.
CONCLUSION

This is the first time that the Rotarex mechanical thrombectomy catheter has been used to treat RAT. Our case confirmed that the Rotarex system is a safe device for rapid recanalization of the renal artery in patients with RAT, and may be a treatment option for RAT in the future.

REFERENCES


CASE REPORT

Necrotizing fasciitis of cryptoglandular infection treated with multiple incisions and thread-dragging therapy: A case report

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Author contributions: Tao XC and Hu DC performed the operation; Yin LX and Wang C assisted in the follow-up treatment; Tao XC wrote the initial draft of the article; Wang C and Lu JG reviewed and edited the article. All authors actively reviewed and revised the manuscript and approved the finally submitted manuscript.

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Informed consent statement: The patient provided the consent form to give his consent for materials in the report to appear in academic journals and associated publications.

Conflict-of-interest statement: All the authors declare that we do not have any commercial or associative interest that represents a conflict of interest in connection with the

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Abstract

BACKGROUND
Necrotizing fasciitis is a fulminant necrotizing soft tissue disease with a high fatality rate. It always starts with impact on the deep fascia rapidly and might result in secondary necrosis of the subcutaneous tissue, fascia, and muscle. Thus, timely and multiple surgical operations are needed for the treatment. Meanwhile, the damage of skin and soft tissue caused by multiple surgical operations may require dermatoplasty and other treatments as a consequence.

CASE SUMMARY
Here, we report a case of 50-year-old male patient who was admitted to our hospital with symptoms of necrotizing fasciitis caused by cryptoglandular infection in the perianal and perineal region. The symptoms of necrotizing fasciitis, also known as the cardinal features, include hyperpyrexia, excruciatingly painful lesions, demonstration gas in the tissue, an obnoxious foul odor and uroschesis. The results of postoperative pathology met the diagnosis. Based on the premise of complete debridement, multiple incisions combined with thread-dragging therapy (a traditional Chinese medicine therapy) and intensive supportive therapies including comprising antibiotics, nutrition and fluids were given. The outcome of the treatment was satisfactory. The patient recovered quickly and achieved ideal anal function and morphology.

CONCLUSION
Timely and effective debridement and multiple incisions combined with thread-dragging therapy are an integrated treatment for necrotizing fasciitis.

Key Words: Necrotizing fasciitis; Cryptoglandular infection; Traditional Chinese medicine; Multiple incisions and thread-dragging therapy; Integrated treatment; Case report

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A 50-year-old male patient was admitted to our institute for perianal swelling and discomfort.

**History of present illness**

The patient had become aware of anal pain and discomfort with no obvious cause 6 d prior to admission. He did not report abdominal pain, and there was no bleeding during defecation. He had visited the local hospital 2 d earlier for pain, at which time the doctor diagnosed a perianal abscess and performed an incision and drainage. One day later, the perianal swelling had not subsided and had spread to the base of the scrotum; a local incision showed yellowish gray necrotic tissue with a fishy odor. At the same time, the patient developed a high fever. He was admitted to our hospital with a body temperature of 38.2 °C, respiratory rate of 21 breaths/min, heart rate of 81 beats/min, blood pressure of 105/69 mmHg, and dysuresia. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/License
History of past illness
On admission, the case was considered perianal necrotizing fasciitis extending to the perineal region. In contrast to conventional cases of necrotizing fasciitis, the patient denied any underlying diseases. In addition, his physical and laboratory examination confirmed no signs of type 2 diabetes, malignancy, or any of the other common diseases associated with necrotizing fasciitis.

Personal and family history
The patient stated that he has no relevant family history.

Physical examination
Physical examination showed that the entire anal margin was swollen and the skin was in red and black. It was also found after palpation that the previous incision on the posterior of the anal margin had yellow-white frothy secretions overflowed. The patient complained of severe pain. The skin on both sides and the base of the scrotum felt tender and warm to the touch, and there was crepitus when palpating the level of the left pubic symphysis (Figure 1).

Laboratory examinations
Laboratory and imaging examinations were promptly performed upon admission. Laboratory examination results during the patient’s hospital stay are shown in Table 1.

Imaging examinations
A lower abdominal and pelvic computed tomography (CT) scan suggested necrotizing fasciitis based on the demonstration of gas in the tissue on both sides of the buttocks, left perineal area, the subcutaneous soft tissues of the groin and the root of the thigh. The scan also showed urine retention and multiple lymph nodes in the inguinal area (Figure 2).

FINAL DIAGNOSIS
After a comprehensive assessment of symptoms, signs and the examination results, the patient was diagnosed with perianal and perineal necrotizing fasciitis, unfortunately aggravated by inadequate drainage in the early stage.

TREATMENT
Based on a clear diagnosis, the operation was performed under timely spinal anesthesia. To distinguish the structure and avoid urethra damage, urethra catheter surgery was performed before surgery. Under a lithotomy position, an obvious defect was found in the anal gland near the posterior dentate line, which was considered to be the primary opening, and the defect was connected to the previous wound. Therefore, it was inferred that the internal opening was the resource of this infection, which means the case was caused by cryptoglandular infection and aggravated by the poor drainage.

During the surgery, the main incision between the previous wound and the internal opening was completely excised and debrided. A probe and clamp were used to explore the infection area and scissors and diathotomy were used to remove the necrotic tissues. Multiple incisions were performed in the epidermis within a distance of 5 to 8 cm from the main incision. Later, other incisions were performed in the epidermis within a distance of 5 to 8 cm from the former ones until the outermost incision enveloped the entire area of infection. Rubber catheters were used as loose setons for adequate drainage between the incisions on two ends. Finally, the incision outside the level of the bilateral symphysis pubis reached outward of the skin on both sides of the ischium nodules and a total of 21 loose rubber setons were used for these incisions. It is important to keep the skin at the base of the scrotum intact to avoid extensive damage and postoperative sexual dysfunction.

The patient was transferred to the intensive care unit after surgery. Fourth-generation cephalosporin and metronidazole were given to control the infection, and human blood albumin, vitamins, lipids, and other essential nutrition were administered as supportive treatments. Daily laboratory examination was performed to observe the dynamic changes and to adjust treatment (Table 1). The wound was
Table 1 Laboratory data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Reference (range)</th>
<th>On arrival</th>
<th>2 h postop</th>
<th>The postop day</th>
<th>3 d postop</th>
<th>7 d postop</th>
<th>Before discharge</th>
</tr>
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<tbody>
<tr>
<td>White cell count (× 10^9/L)</td>
<td>3.50-9.50</td>
<td>14.29</td>
<td>15.26</td>
<td>11.64</td>
<td>8.82</td>
<td>6.68</td>
<td>6.44</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>40.00-75.00</td>
<td>85.10</td>
<td>79.90</td>
<td>72.10</td>
<td>75.00</td>
<td>74.00</td>
<td>71.30</td>
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<tr>
<td>Lymphocytes</td>
<td>20.00-50.00</td>
<td>6.70</td>
<td>8.30</td>
<td>14.30</td>
<td>11.00</td>
<td>20.00</td>
<td>21.70</td>
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<tr>
<td>Monocytes</td>
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<td>8.00</td>
<td>11.60</td>
<td>11.30</td>
<td>6.00</td>
<td>5.00</td>
<td>5.90</td>
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<td>Eosinophils</td>
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<td>0.10</td>
<td>2.10</td>
<td>4.00</td>
<td>1.00</td>
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<td>Hemoglobin (g/L)</td>
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<td>123.00</td>
<td>102.00</td>
<td>93.00</td>
<td>95.00</td>
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<td>Hematocrit (%)</td>
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<td>C-reactive protein (mg/L)</td>
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<td>126.40</td>
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<td>Sodium (mmol/L)</td>
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<td>146.80</td>
<td>142.70</td>
<td>142.60</td>
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<td>Potassium (mmol/L)</td>
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<td>3.50</td>
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<td>3.30</td>
<td>3.90</td>
<td>3.80</td>
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<td>Creatinine (μmol/L)</td>
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<td>42.80</td>
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<td>Glucose (mmol/L)</td>
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<td>Alanine aminotransferase (U/L)</td>
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<td>24.00</td>
<td>31.00</td>
<td>40.00</td>
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<td>Aspartate aminotransferase (U/L)</td>
<td>15.00-46.00</td>
<td>35.00</td>
<td>24.00</td>
<td>26.00</td>
<td>36.00</td>
<td>31.00</td>
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<tr>
<td>Albumin (g/L)</td>
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<td>33.70</td>
<td>28.50</td>
<td>32.20</td>
<td>35.90</td>
<td>34.40</td>
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<td>D-dimer (mg/L)</td>
<td>&lt; 0.55</td>
<td>7.30</td>
<td>2.75</td>
<td>6.47</td>
<td>4.29</td>
<td>2.03</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1 The condition at the time of admission.

The surgical area was rinsed with 1:1 hydrogen peroxide and oxygenate and the necrotic tissue was trimmed. The rubber setons were removed after pus was no longer observed.

Three days after surgery, the necrotic perineal skin was completely removed. Another CT scan of lower abdomen and pelvis showed the loose setons around the anus, buttocks, perineum, and scrotum, with a small amount of gas shadow and catheter drainage (Figure 3). A final drainage incision was made at the junction of the patient's right groin and pubic symphysis under local anesthesia (Figure 4).

Perianal magnetic resonance imaging and laboratory examinations (Table 1) were performed 1 wk after the surgery, and all results showed the patient was stable. He was transferred to the general ward in the anorectal department. The antibiotic treatment was stopped but nutrition support continued. Daily dressing changes were cleaned and changed daily.
Figure 2  A lower abdominal and pelvic computed tomography scan on admission.

Figure 3  A lower abdominal and pelvic computed tomography scan on day 3 postoperation.

performed as described above (Figure 4).

OUTCOME AND FOLLOW-UP

Two weeks after admission, the patient clinically improved and was discharged with the stable laboratory examination results (Figure 5 and Table 1). He continued to visit the outpatient department for examination once a week. Most parts of wound had healed at 3 wk after discharge (Figure 6). At the 6 mo follow-up, the perianal morphology was retained (Figure 6), and anorectal manometry results indicated the function had recovered. The patient was cured and satisfied with the treatment.

DISCUSSION

Necrotizing fasciitis is a fulminant soft tissue disease with a high fatality rate. The affected patients often have comorbid diabetes, tumors, hypohepatia, chronic renal failure, immune system disorders and other chronic conditions[4]. In this case, the patient denied any underlying disease, but he presented with varying signs and symptoms including fever greater than 38 °C, scrotal swelling, purulence or wound discharge and flatulence All symptoms and signs led to a tentative diagnosis[5]. A strong “repulsive, fetid odor” is also one overwhelming feature of the presentation that is associated with the condition. Thus, combined with the examination results, the diagnosis can be clearly defined as perianal and perineal necrotizing fasciitis. The peculiarity of this case is the cause, and the intraoperative examination gave the answer. An obvious defect on the anal gland confirmed the cryptoglandular infection was the resource of the subsequent necrotizing fasciitis. More confirmation of this point was the pus culture. It showed the presence of Proteus mirabilis, which is usually be found in the intestinal and urinary tracts[6], not a common pathogen of necrotizing fasciitis. A review of the present illness history bears out that necrotizing fasciitis onset is largely related to poor drainage of perianal abscesses and failed treatment of the infected internal opening in the early stage. It emphasizes the importance of complete debridement and drainage for perianal abscesses[7]. Early identification and treatment of the infection source are critical when addressing severe perianal infections[8]. In this case, the patient's condition was under control after the internal opening was completely excised and debrided.
What’s more, the key to cure necrotizing fasciitis is timely and thoroughly debriding the affected area[9]. The reason why we performed surgery immediately after the patient’s admission was based on the symptoms and examination findings, which surely confirmed the diagnosis. Since necrotizing fasciitis is always caused by anaerobic bacteria, complete debridement is one of the treatment principles. Drainage of the wounds makes the oxygen in the air to react with anaerobic bacteria. The physiological effects have the ability to enhance leukocyte to kill aerobic bacteria, stimulate the formation of collagen and increase the levels of superoxide dismutase, resulting in better tissue survival[10]. Hydrogen peroxide is also used to achieve this effect in dressing change. Sometimes, patients will even be placed in an environment of increased ambient pressure for breathing 100% oxygen to take hyperbaric oxygen therapy. Adequate oxygenation has the benefits of optimal neutrophil phagocytic function, inhibition of anaerobic growth, increased fibroblast proliferation and angiogenesis, reduction of edema by vasoconstriction, and increased intracellular antibiotics transportation[11]. More and more studies demonstrated that hyperbaric
oxygenation is an important therapeutic adjunct in the treatment of necrotizing fasciitis[12], including improving the effectiveness of several antibiotics such as vancomycin and ciprofloxacin.

When it comes to antibiotics, empiric broad-spectrum antibiotic therapy should be instituted as soon as possible according to the guidelines. Since the pathogens of necrotizing fasciitis also include staphylococcal and streptococcal bacteria, gram-negative, coliforms, pseudomonas, bacteroides, and clostridium, third or fourth generation cefalosporins, aminoglycosides, metronidazole and penicillin are all recommended, which is called a classically triple therapy[2]. Fourth-generation cephalosporin and metronidazole were given in this case. And some clinical guidelines recommend the use of carbapenems or piperazline-tazobactam to replace the classically triple therapy for the advantages of larger distribution and lesser renal toxicity[13].

In our experience, although debridement is conducive to adequate oxygen, extensive skin damage caused by surgery may generate other side effects, such as increasing the risks of postoperative hypoproteinemia, wound bleeding, slow healing and dermatoxplasty. Mallikarjuna suggested debridement should be stopped when separation of the skin and the subcutaneous is not performed easily, because the cutaneous necrosis is not a good marker[14]. Keeping as much normal skin tissue as possible may avoid large scale scar. In particular, a large scar at the base of the scrotum may cause erection difficulties due to scar contracture, which need further scrotal skin flap or dermatoxplasty[15]. Even skin grafting was used, the penis and scrotum may still lose normal shape and form artificial deformity. It means the patient may loss the normal erection function, or get barely erection with no normal intercourse[16]. Therefore, we insist that attention should be paid to the protection of scrotal skin at the first time.

In this case, we performed multiple incisions and implanted loose rubber setons to minimize skin and muscle tissue damage on the basement of complete drainage and oxygenation. This approach was combined with standard anti-infective treatment and nutrition support therapy. The patient was discharged 2 wk post-operation and fully recovered 5 wk post-operation. Thorough debridement in this case did not require the removal of all the skin and tissue involved; rather, we ensured that the drainage orifice reached the edge of the lesion, and the central area was addressed with incisions to ensure complete drainage. The use of multiple incisions reduced damage and maintained morphology; it also decreased fluid leakage, reduced energy consumption, thus less nutrition support was required. Satisfactory treatment results were obtained by removing necrotic tissue during daily dressing changes, which means “Staged Therapy,” also called “Canshi Therapy” in TCM, a special method that is just like silkworm eating the mulberry leaf.

**CONCLUSION**

We describe a case with necrotizing fasciitis of cryptoglandular infection in the perianal and perineal region that was successfully treated in our hospital. We hypothesize that the timely diagnosis and thorough treatment are the main reasons for the positive outcome. Meanwhile, multiple incisions combined with thread-dragging therapy expressed a curative effect with more effective tissue protection and accelerated recovery comparing to the traditional complete debridement.
REFERENCES


Endoscopic joint capsule and articular process excision to treat lumbar facet joint syndrome: A case report

Hong-Jie Yuan, Chun-Yan Wang, Yu-Feng Wang

Abstract

BACKGROUND
Lumbar facet joint syndrome (LFJS) is a pain condition arising from lumbar facet joint diseases. Treatments of LFJS includes patient education, oral medication, bed rest, physical therapy, and procedural interventions. For some refractory cases that fail conservative therapies, dorsal ramus medial branch radiofrequency ablation is warranted. However, as nerve fibers can regenerate, their efficacy is impermanent, and the recurrence rate is relatively high. Considering synovial impingement is a paramount pathogenesis of LFJS, in this case, we removed the culprit hyperplastic articular capsule and the articular process partially through a spinal endoscope. As the culprit hyperplastic joint capsule was excised, it is supposed to generate more prolonged efficacy and a lower recurrence rate than radiofrequency treatment.

CASE SUMMARY
A 40-year-old female patient was diagnosed with LFJS. She complained of low back pain and right buttock pain for half a year. The patient was placed in the prone position. After disinfection and draping, a 25-cm 18-gauge needle was inserted into the dorsal surface of the right L5 articular process. Subsequently, a guidewire, dilating tubes, and a working cannula was inserted successively. The spinal endoscope was positioned in the working cannula. Under the endoscope, the microvascular tissue, muscle tissue attached on the L5 inferior articular process and S1 superior articular process, as well as the capsule and minor portion of the inferior articular process were removed. After the joint space was clear and no bleeding points existed, the endoscope and working cannula were shifted, and the incision was sutured. After treatment, the symptoms were
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**Manuscript source:** Unsolicited manuscript

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**Country/Territory of origin:** China

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CONCLUSION
The endoscopic partial joint capsule and articular process excision is an effective procedure for LFJS, especially for cases caused by synovial impingement.

**Key Words:** Endoscopic; Facet joint pain syndrome; Joint capsule; Radiofrequency; Articular process; Excision; Case report

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**Core Tip:** For intractable lumbar facet joint syndrome (LFJS), medial branch radiofrequency ablation is a commonly used therapy. However, the recurrence rate of radiofrequency treatment is relatively high. In this case, we removed the lumbar facet joint capsule and articular process partially through the guidance of endoscope. The patient's symptoms were relieved for the next 6 mo. We assert that this treatment can generate long-lasting efficacy as this innovative treatment directly removes the hyperplastic joint capsule. It is supposed to be an effective treatment for LFJS caused by synovial impingement.

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**DOI:** https://dx.doi.org/10.12998/wjcc.v9.i28.8545

**INTRODUCTION**
Lumbar facet joint syndrome (LFJS) is a pain condition arising from lumbar facet joint disease. As a common disease, LFJS accounts for about 15%-40% of low back pain patients[1,2]. The treatments of LFJS include patient education, oral medication, bed rest, physical therapy, and procedural interventions[3]. For patients refractory to preservative treatments, dorsal ramus medial branch radiofrequency ablation is widely applied. However, as nerve fibers can regenerate, their efficacy is impermanent, and the recurrence rate of radiofrequency ablation treatment is relatively high [4,5]. The chronicity and tendency of relapsing of this disease remain a severe challenge for clinical physicians. Considering synovial impingement is one of the paramount pathogenesis of LFJS[6], in this case, we directly removed the culprit hyperplastic articular capsule and the articular process partially through a spinal endoscope. The symptoms of this patient were relieved entirely for 6 mo. It was the first report to apply endoscopic partial joint capsule and articular process excision to treat LFJS.

**CASE PRESENTATION**

**Chief complaints**
A 40-year-old female patient complained of low back pain for half a year. The pain was located mainly at the right side of the lumbar back, and radiated to the right buttock. The pain was aggravated during lumbar dorsal extension and left lateral flexion. The patient felt obvious pain, especially during the cause of unbending the waist from the sitting position. The pain could be alleviated during lumbar anterior bending. She could walk and stand normally. A long time of standing and sitting did not aggravate pain. The VAS score was 4.

**History of present illness**
The patient was diagnosed with LFJS in other clinics and underwent oral medication,
bed rest, facet joint steroid injection, etc. However, the symptoms could only be relieved slightly and temporarily.

**History of past illness**

No history of high blood pressure, diabetes mellitus, and no history of trauma existed.

**Personal and family history**

No family history of chronic low back pain was reported.

**Physical examination**

Physical examination manifested tenderness on the paravertebral region on the L5-S1 level. The lower leg muscle force and sensory function were normal. The straight leg raising test was negative.

**Laboratory examinations**

Complete blood count, erythrocyte sedimentation rate, and automated blood chemistry testing were within the normal range.

**Imaging examinations**

The lumbar spine magnetic resonance imaging (MRI) indicated degenerative changes in the L5-S1 disc and with no sign of spinal nerve compression (Figure 1). Plain radiography was standard. Lateral flexion and extension views showed no sign of lumbar instability.

**FINAL DIAGNOSIS**

The diagnosis was confirmed as LFJS, and the culprit’s joint was defined as right L5-S1.

**TREATMENT**

As the conservative treatments failed, endoscopic partial joint capsule and articular process excision were warranted. After the medical consent form was signed, the patient was placed in the prone position with a pillow under the abdomen to flex the lumbar spine. The right L5-S1 facet joint was positioned by a C arm X-ray and was marked. After disinfection, draping, and local anesthesia, a 25-cm 18-gauge needle was punctured into the dorsal surface of the right L5 articular process. Subsequent anteroposterior confirmed the location. A guidewire was inserted through the stylet, the dilating tubes, and the working canal was inserted successively through a 0.7-cm skin incision centered on the guidewire. Anteroposterior view and lateral view confirmed that the working cannula was located on the posterior surface of the L5-S1 facet joint (Figure 2). The spinal endoscope was positioned through the working cannula. The microvascular tissue, muscle tissue attached to the L5 inferior articular process and S1 superior articular process was removed endoscopically by a grasper. The bipolar radiofrequency probe was used for hemostasis. L5 inferior articular process, S1 superior articular process, the joint capsule was exposed (Figure 3). After the removal of the capsule, the joint space was revealed. A minor portion of the articular process was removed with a chisel. The tissue compressed in the joint space was also wiped out. After the joint space was clear and no bleeding points were existed (Figure 4), the endoscope and the working cannula were removed, and the incision was sutured.

**OUTCOME AND FOLLOW-UP**

After the treatment, the symptoms were utterly relieved. The patient was pain-free during the follow-up period of 6 mo. No complication was observed.
DISCUSSION

Low back pain was generally acknowledged as a highly complicated and hard-to-diagnose disease in clinical practice. Lumbar disc, facet joint, lumbar muscular fascia, and the sacroiliac joint were all possible pain generators [3]. LFJS is defined as a pain condition emanating from facet joint lesions. The pathologic changes of LFJS include facet joint arthritis, synovial impingement, meniscoid entrapment, pseudogout and intrafacetal cysts, etc. [6]. LFJS account for about 15%-40% of low back pain patients [1, 2].

As the pathogenesis of LFJS varied, the diagnosis of LFJS is relatively complicated. The diagnosis should be supported by a combination of clinical history, physical examination, radiography, and diagnostic block, the latter of which is the most reliable method for diagnosis [3, 7]. In this case, based on typical symptoms, physical examination as well as positive diagnostic block, the diagnosis of LFJS was verified.

Treatment for LFJS should be multimodal, consisting of conservative and interventional treatments. It was generally accepted that interventional therapy was necessitated after conservative treatments failed. Medial branch radiofrequency was the most commonly applied therapy, and reported to be an effective therapy for LFJS with high-level evidence [8-11]. As the mechanism of radiofrequency therapy is to ablate the nociceptive nerve conduction, the duration of treatment was reported to be 6 mo to 1 year, as the nerve fibers may regenerate [8, 9, 12, 13]. Apart from medial branch
radiofrequency, Song reported endoscopic medial branch neurotomy to treat LFJS[14]. This innovative treatment was reported to generate a longer pain relief duration compared to conventional radiofrequency treatment. However, the mechanism of the two treatments was the same. Therefore, after nerve regeneration, symptoms relapse may also occur. Facet joint osteoarthritis is reportedly the primary pathological mechanism for facet joint syndrome[15]. However, in this case, the lumbar spinal MRI indicated no significant lesion of the facet joint. Instead, the patient’s pain could be aggravated during lumbar dorsal extension and left lateral flexion, especially during the cause of unbending the waist from sitting position and relieved during lumbar anterior bending. From her symptoms, we speculated that synovial impingement or meniscoid entrapment might exist and be located at the dorsal part of the facet joint in this case (the exact reason will be discussed below). Therefore, we implemented endoscopic partial facet joint capsule and articular process excision instead of medial branch radiofrequency, which applied conventionally.

The superiority of endoscopic partial joint capsule and articular process excision over radiofrequency treatment was supposed to be longer and even permanent pain relief as the culprit hyperplastic joint capsule was removed. However, the theory mentioned above is based on presumption and necessitates further clinical research.
Haufe and Mork[5] reported a novel treatment named endoscopic facet debridement to treat facet arthritic pain. However, in this paper, the facet joint capsule was removed but not the articular process, and multiple facet joint capsules were removed. The reported therapeutic theory was to clear out the end-plate receptors located on the joint capsule, and aimed the procedure was to treat facet arthritic pain.

In our case, apart from resecting the joint capsule, a minor part of the lower articular process was removed to expose the joint space and clear out the hyperplastic capsule compressed in the joint space. And our procedure was for the treatment of LFJS due to synovial impingement.

A point to note is which segment of facet joint should be treated. In our pain clinic, we chose the segment where the tenderness was located and the segment corresponding to the affected lumbar disc. As reported by Song et al[16], facet joint lesions tend to occur at the same level of narrowed lumbar disc. For example, if the patient’s MRI indicated L4-5 lumbar disc degeneration, especially the decreased height of the disc, the L4-5 facet joint was the most likely culprit joint.

Another point that merits consideration is which part of the facet and joint capsule should be removed. No report was available regarding the right point the articular capsule was entrapped. For this case, the pain was aggravated during lumbar dorsal extension and left lateral flexion, especially during the cause of unbending the waist from sitting position. The most likely point the capsule compressed is the dorsal part of the facet joint, as the dorsal joint gap widens during lumbar flexion and narrows during lumbar extension. As the widening of the joint gap, the compressed capsule is also relaxed, and the symptoms will be relieved accordingly. By contrast, as the joint gap narrowed, the capsule compression of the joint gap will be more severe. After that, the symptom will be aggravated.

The impact on the lumbar stability was the last but not the slightest concern for endoscopic partial joint capsule and articular process excision. However, the axial load is mainly supported by the lumbar disc. The facet joint only plays a minor role in load bearing[17]. Furthermore, only a tiny part of the joint was removed. Therefore, we argue that the procedure has little impact on lumbar stability.

This study had some limitations. First, the follow-up period of this case was relatively short. Second, the superiority of endoscopic partial joint capsule and articular process excision over medial brunch radiofrequency treatment was grounded by presumption. Therefore, further clinic trial with more participants and a more extended follow-up period was warranted.

CONCLUSION

Endoscopic partial joint capsule and articular process excision is an effective procedure for LFJS, especially for cases caused by synovial impingement. As the culprit hyperplastic joint capsule was removed, it is supposed to more prolonged and even permanent efficacy and a lower recurrence rate.

REFERENCES

Yuan HJ et al. Endoscopic treatment for LFJS


Spinocerebellar ataxia type 3 with dopamine-responsive dystonia: A case report

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**CASE REPORT**

Spinocerebellar ataxia type 3 (SCA3) is a rare neurodegenerative disease with high genetic heterogeneity. SCA3 mainly manifests as progressive cerebellar ataxia accompanied by paralysis of extraocular muscles, dysphagia, lingual fibrillation, pyramidal tract sign, and extrapyramidal system sign. However, it rarely has clinical manifestations similar to Parkinson-like symptoms, and is even rarer in patients sensitive to dopamine. We report a patient initially diagnosed with dopamine-responsive dystonia who was ultimately diagnosed with SCA3 by genetic testing, which was completely different from the initial diagnosis.

**CASE SUMMARY**

A 40-year-old Chinese woman was admitted to hospital due to severe inflexibility. At the beginning of the disease, she presented with anxiety and sleep disorder. At the later stage, she presented with gait disorder, which was similar to Parkinson's disease. Her medical history was unremarkable, but her mother, grandmother, and uncle all had similar illnesses and died due to inability to take care of themselves and related complications. Laboratory and imaging examinations showed no abnormalities, but electromyography and electroencephalography revealed delayed somatosensory evoked potentials and slow background rhythm, respectively. Her symptoms fluctuated during the daytime, and we initially diagnosed her with dopamine-responsive dystonia. After treatment with low-dose levodopa, the patient's symptoms were significantly improved, but the final genetic diagnosis was SCA3.

**CONCLUSION**
A 40-year-old Chinese woman was admitted to hospital due to a 3-year history of limb inflexibility, which had become aggravated in the previous year.

**History of present illness**

Three years before presenting to our clinic, the patient developed a feeling of heaviness and inflexibility in the right lower extremity, which was aggravated after fatigue. It could be relieved after getting up in the morning or resting and was accompanied by emotional irritability and insomnia. She went to a local hospital. The doctor diagnosed her with anxiety and depression and administered paroxetine orally. After 3 mo, her symptoms were not alleviated; thus, she discontinued the drug herself. Two years ago, the patient began to gradually experience difficulties with limb movement. One year ago, the patient’s gait disorder progressively aggravated. It manifested as laborious lifting of the feet off the ground, stiffness of the lower limbs, increase in gait time, and difficulty maintaining balance. The patient could not take care of herself, so she visited our hospital for treatment.

The patient had a 3-year history of moves with difficulty, reduced arm swing, and other symptoms similar to Parkinson’s disease. She had a leaning forward and a forward gait, inability to stop immediately, difficulty turning around, reduced arm swing, and other symptoms similar to Parkinson’s disease. She had a history of anxiety and depression, and the disease was diagnosed 3 years ago.

**INTRODUCTION**

Spinocerebellar ataxia type 3 (SCA3), also known as Machado Joseph disease, is an autosomal dominant genetic disease first described by Nakano et al[1] among Portuguese immigrants in the United States in 1972. It is characterized by progressive cerebellar ataxia accompanied by paralysis of extraocular muscles, dysphagia, lingual fibrillation, pyramidal tract signs, extrapyramidal system signs, and other clinical manifestations. However, it rarely presents with symptoms of Parkinson’s disease and peripheral nerve lesions and is even less common in patients sensitive to levodopa[2-5]. This phenotype has been described in cases in Singapore, but further evidence on this phenotype is needed[6]. The clinical manifestation of the patient described in this report was typical of dopamine-responsive dystonia, with symptoms fluctuating during the daytime. The effect of low-dose levodopa treatment was significant, but unexpectedly, a final diagnosis of SCA3 was confirmed by genetic testing.
History of past illness
The patient’s medical history was unremarkable.

Personal and family history
The patient’s mother, grandmother, and uncle all had similar illnesses, and they eventually died because of related complications.

Physical examination
The patient’s vital signs were stable, and no abnormalities were found in cardiopulmonary or abdominal examinations. The patient exhibited bradykinesia, and slight horizontal nystagmus could be seen when staring left and right. There was mild lead tube-like increase in the muscle tone of extremities, a positive Romberg sign, hyperreflexia of tendons at extremities, and positive bilateral Chaddock sign and Gordon sign.

Laboratory examinations
Routine laboratory tests showed no abnormalities, and thyroid function, blood ammonia, and ceruloplasmin were all within the normal range.

Imaging examinations
There were no obvious abnormalities in brain or spinal cord imaging.

Neuroelectrophysiological examination and genetic test
In an electromyogram, the differentiation of the P15 and N20 somatosensory evoked potentials in both lower extremities was acceptable, with roughly normal incubation periods and reduced amplitudes. The incubation period of the P40 somatosensory evoked potential in both lower extremities was slightly prolonged, the waveform differentiation was poor, and the repeatability was also poor. The patient’s background rhythm in an electroencephalogram was slightly slower than normal.

Genetic test showed 18 and 65 CAG repeat units of the ATXN3 gene (Figure 1).

FINAL DIAGNOSIS
The final diagnosis was SCA3.

TREATMENT
According to the clinical symptoms, the patient was administered a small oral dose (one quarter of a pill) of madopar once a day (each pill contains 200 mg levodopa and 50 mg benserazide). After 14 d of treatment, the patient’s limb mobility improved significantly, and she was able to take care of herself and work normally. The final diagnosis was SCA3 by genetic testing in this patient who was sensitive to dopamine, which is extremely rare[7].

OUTCOME AND FOLLOW-UP
After discharge, the patient continued to take the same daily dose of oral madopar. She was able to work and perform daily activities normally.

DISCUSSION
The present patient had a long clinical course of the disease. The initial manifestation was one-sided limb inflexibility with perceived heaviness, which did not affect the patient’s daily life. She went to a local hospital for medical treatment and was diagnosed with somatization caused by anxiety. Although the symptoms were gradually aggravated in the later stage, she did not comply with the treatment. SCA is characterized by progressive cerebellar ataxia and pyramidal signs[8] and is sometimes accompanied by extrapyramidal symptoms and muscle atrophy caused by peripheral nerve damage. In addition, gaze, dystonia, and facial and lingual atrophy...
are characteristics of SCA3. It has been reported\cite{9} that gait ataxia is the first symptom in 92.4% of patients with SCA3. Our patient did not have these manifestations in the early stage of the disease. The initial presentation was mild anxiety symptoms and sleep disorder. In the later stage, it gradually progressed and manifested as dopamine-responsive dystonia, but Parkinson's disease could not be ruled out. Therefore, the differential diagnosis of this case was complex.

During the treatment period, the patient mainly presented with inflexibility and stiffness in the limbs, a toe-first and forward-leaning gait, small strides, difficulty turning around, reduced arm swing, and other symptoms similar to Parkinson's disease. Her symptoms fluctuated during the daytime and could be relieved after rest. Based on the family history and the lack of obvious signs of spinal cord or cerebellar atrophy on cranioencebral and spinal cord imaging, we diagnosed the patient with dopamine-responsive dystonia. After treatment with low-dose levodopa, her symptoms were significantly improved and controlled. However, the final genetic test confirmed a diagnosis of SCA3, which was quite different from the initial diagnosis. SCA3 has a wide range of clinical phenotypes, and many researchers believe that there are six clinical subtypes\cite{10-12}. Our patient presented with slow progressive Parkinsonism and was sensitive to low-dose levodopa. Her cerebellar function defect was mild, and gene testing showed short CAG repeats. These are rare in patients with SCA3, so this patient can be classified as SCA3 type IV. The patient had late onset and mild clinical symptoms. Genetic testing showed 18 and 65 CAG repeat units. This is consistent with the fewer CAG repeats reported in the literature in patients with late onset and mild symptoms. SCA3 can present with Parkinsonian symptoms and has characteristics of diurnal fluctuation, which are mainly related to disease progression in the dopaminergic system in the substantia nigra. Some scholars believe that the pathological mechanism of SCA3 is related to lesions of the substantia nigra and dentate nucleus in the cerebellum\cite{5}. This may be the main pathological mechanism of SCA3 in the Parkinsonian/ataxia phenotype. Therefore, dopamine is clinically effective in the treatment of this disease.

The onset of this disease was relatively late in the present patient, and there were no obvious signs of spinocerebellar injury. There was no apparent ataxia throughout the clinical course. The clinical manifestation of the patient was dopamine-responsive dystonia, which made the detection of spinocerebellar signs and diagnosis difficult. It is challenging to distinguish between dopamine-responsive dystonia, SCA3, and Parkinson’s disease. Clinicians should carefully enquire about the medical and family history of such patients and conduct a physical examination. Genetic testing is an important technique for the diagnosis of genetic diseases. Clinicians should carry out genetic testing earlier for suspected genetic diseases that are difficult to identify. The patient’s levodopa treatment was delayed for 3 years, and she remained sensitive to madopar. The treatment was well-tolerated, and she was followed up for 21 mo with good symptom control.

CONCLUSION

This case suggests that SCA3 has various clinical phenotypes which must be differentiated from Parkinson’s disease and dopamine-responsive dystonia. For patients with atypical SCA3 with anxiety symptoms, sleep disorders, and a relevant family history, clinicians should perform genetic testing as soon as possible. Therefore, sensitivity to levodopa may be a clinical feature of SCA3, and this report could add to the evidence
on the clinical phenotype of SCA3.

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Disseminated soft tissue diffuse large B-cell lymphoma involving multiple abdominal wall muscles: A case report

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BACKGROUND

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma, and patients with DLBCL typically present rapidly growing masses. Lymphoma involving muscle is rare and accounts for only 5%; furthermore, multiple muscles and soft tissue involvement of DLBCL is unusual. Due to unusual clinical manifestation, accurate diagnosis could be delayed.

CASE SUMMARY

A 61-year-old man complained of swelling, pain and erythematous changes in the lower abdomen. Initially, soft tissue infection was suspected, however, skin lesion did not respond to antibiotics. 18F-Fluoro-2-deoxy-D-glucose (18F-FDG) positron emission tomography-computed tomography demonstrated FDG uptake not only in the skin and subcutaneous tissue of the abdomen but also in the abdominal wall muscles, peritoneum, perineum, penis and testis. DLBCL was confirmed by biopsy of the abdominal wall muscle and subcutaneous tissue. After intensive treatment including chemotherapy with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone, central nervous system prophylaxis (intrathecal injection of methotrexate, cytarabine and hydrocortisone) and orchiectomy, he underwent peripheral blood stem cell mobilization for an autologous hematopoietic stem cell transplantation. Despite intensive treatment, the disease progressed rapidly and the patient showed poor outcome (overall survival, 9 mo; disease free survival, 3 mo).

CONCLUSION

The first clinical manifestation of soft tissue DLBCL involving multiple muscles was similar to the infection of the soft tissue.

Key Words: Primary extranodal diffuse large B-cell lymphoma; Soft tissue lymphoma; Disseminated muscles and soft tissue invasion; Atypical presentation of diffuse large B-cell lymphoma; Central nervous system relapse; Case report
Core tip: The majority of diffuse large B-cell lymphomas (DLBCLs) initially present in lymph nodes as rapidly growing masses. Herein, we report an unusual case of DLBCL involving multiple muscles and soft tissue and appearing as soft tissue inflammation. Soft tissue biopsy was performed because there was no response to antibiotics, and DLBCL was confirmed. Despite aggressive chemotherapy and central nervous system (CNS) prophylaxis, the disease recurred with CNS invasion and progressed rapidly. This case highlights that skin invasions of aggressive lymphoma should be considered if there is a soft tissue infection that is unresponsive to antibiotics or progresses rapidly.

INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most common histologic subtype of non-Hodgkin lymphoma and typically presents with rapidly growing lymph nodes in the neck or abdomen[1]. However, approximately 40% of DLBCL cases are initially present in extranodal sites, such as the gastrointestinal tract, central nervous system (CNS), breast, or testis. These are referred to as primary extranodal DLBCL[2,3]. Among them, lymphoma involving muscle accounts for only 5%; furthermore, multiple muscles and soft tissue involvement of DLBCL is unusual. Here, we report a case of soft tissue DLBCL disseminated to multiple abdominal wall muscles, skin, and subcutaneous tissue of the abdomen/perineum and scrotum. The first clinical manifestation was similar to that of soft tissue infection, and the disease progressed rapidly in a short period of time.

CASE PRESENTATION

Chief complaints

A 61-year-old man visited the emergency room complaining of lower abdominal wall swelling and pain.

History of present illness

The patient presented with a history of lower abdominal swelling and discomfort that started two weeks before admission and gradually worsened. He was examined at a primary medical center before visiting our hospital and was suspected of having soft tissue inflammation, such as Fournier gangrene or cellulitis.

History of past illness

The patient had no pertinent previous medical history.

Personal and family history

The patient did not have any relevant family history.

Physical examination

The lower abdomen, penis, and scrotum were edematous and the skin showed erythematous changes. He complained of mild pain on palpation.

Laboratory examinations

An initial laboratory test revealed that lactate dehydrogenase level of 1570 IU/L (normal range, 140-280 IU/L) and creatine kinase level of 1028 IU/L (normal range, 22-198 IU/L). The other blood test results were normal.
**Imaging examinations**

To evaluate the cause of the skin and genital lesions, a computed tomography (CT) scan was performed and soft tissue infiltration involving abdominal wall muscles, groin area, peritoneum, and retroperitoneal cavity was detected (Figure 1). Subsequently, $^{18}$Fluoro-2-deoxy-D-glucose positron emission tomography-CT ($^{18}$F-FDG PET-CT) was performed, and diffuse FDG uptake was detected throughout the abdominal wall muscles, skin, and subcutaneous tissue of the lower abdomen, peritoneum, periurethral, anus, penis, testis, and cardia of the stomach (Figure 2).

**FINAL DIAGNOSIS**

A soft tissue infection was suspected and antibiotics were administered; however, the skin lesions did not improve. Ultrasonography-guided percutaneous biopsy of the abdominal muscles and endoscopic biopsy of the stomach were performed. DLBCL, not otherwise specified, germinal center B-cell like immunophenotype was confirmed (positive for CD20, CD10, BCL6, BCL2, and MYC). Fluorescence in situ hybridization (FISH) analysis was conducted to determine whether it was a double-hit or triple-hit lymphoma, and MYC rearrangement was detected.

**TREATMENT**

The patient received six cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) plus CNS prophylaxis (intrathecal injection of methotrexate, cytarabine, and hydrocortisone) and subsequently, underwent orchectomy. Considering the aggressive nature of the disease, we planned an autologous hematopoietic stem cell transplantation (auto-HSCT), and peripheral blood stem cell mobilization with dexamethasone, cytarabine, and cisplatin was performed.

**OUTCOME AND FOLLOW-UP**

Despite aggressive treatment, the disease recurred with CNS invasion one month after peripheral blood stem cell harvest. In sequence to high-dose methotrexate therapy, three cycles of rituximab, ifosfamide, carboplatin, etoposide, and dexamethasone were administered as salvage therapy. Unfortunately, the patient died four weeks after salvage chemotherapy due to rapid disease progression. The overall survival and disease-free survival rates were 9 mo and 3 mo, respectively.

**DISCUSSION**

The patient initially presented with edema, pain, and erythematous changes in the lower abdomen and scrotum. Subsequently, soft tissue infection or inflammation was suspected and intravenous antibiotics were administered. However, the skin lesions did not show any improvement. CT revealed diffuse soft tissue infiltration in the lower abdomen and perineum; therefore, we assumed that an aggressive cancer, such as soft tissue sarcoma, arose from the abdominal wall. Subsequently, $^{18}$F-FDG PET/CT was performed, and diffuse FDG uptake in the abdominal wall muscles, including the rectus abdominis, external/internal oblique muscles, transverse abdominis, and iliacus muscles was detected. Additionally, $^{18}$F-FDG PET-CT revealed diffuse involvement of the skin and subcutaneous tissue in the lower abdomen, peritoneum, anus, penis, scrotum, testis, and stomach. Tissue samples were obtained from the abdominal wall muscle and stomach, and DLBCL was confirmed unexpectedly. Although some cases of muscle involvement of lymphoma, especially primary skeletal muscle DLBCL, have been reported to date[4-6], skeletal muscle involvement is rare and accounts for approximately 5% of extranodal lymphomas[7]. The most common sites of skeletal muscle lymphoma were the extremities and presented as painful and palpable masses. It is very rare and unusual that DLBCL initially presents as diffuse infiltration without mass formation in multiple skeletal muscles and soft tissues. This makes differentiating lymphoma from soft tissue infections challenging.
Ultrasonography is the most widely used medical imaging modality to evaluate abdominal pain or masses; however, ultrasonography features of lymphomas involving muscles are non-specific and heterogeneous. Ultrasonography shows an ill-defined hypoechoic solid mass with irregular or poorly defined margins, coarsening of fibro-adipose septa, and swelling of muscle bundles. On the other hand, magnetic resonance imaging (MRI) is considered as the most useful modality to assess muscular lymphoma. Tumors show equal to slightly increased signal intensity on T1-weighted images and intermediate signal intensity compared with fat tissue on T2-weighted images. Diffuse homogeneous enhancement is usually demonstrated; however, peripheral, thick, band-like or marginal septal enhancement as well as thick irregular enhancement of both deep and superficial fascia may be found. Therefore, further evaluation such as MRI is required if there is difficulty distinguishing soft tissue inflammation from lymphoma by ultrasound.

After six cycles of R-CHOP plus CNS prophylaxis, the case patient underwent orchiectomy, and peripheral blood stem cell mobilization was performed for auto-HSCT. However, despite aggressive and intensive therapy, the disease recurred with CNS invasion one month after stem cell mobilization. Although the patient received salvage therapy immediately; he died because of rapid disease progression. The overall survival and disease-free survival rates were 9 mo and 3 mo, respectively. DLBCL with testicular invasion is associated with poor outcomes and CNS relapse. After rituximab was introduced for the treatment of DLBCL, the eradication of systemic disease resulted in improvements, leading to a decrease in the risk of recurrence. However, the rate of CNS relapse is still high, and treatment is challenging. In the current patient, CNS relapse occurred despite receiving CNS...
prophylaxis. The underlying pathophysiology of DLBCL invading immune-privileged sites has been investigated to date. It has been observed that lymphoma cells invading immune-privileged sites can escape from host immunity owing to loss of human lymphocyte antigen expression on the tumor cell surface and high levels of somatic hypermutation in the immunoglobulin heavy chain genes[13]. Booman et al[14] reported that the tumor cells of primary DLBCL of immune-privileged sites share a mutation in the suppressor of p53 and apoptosis pathway. For these reasons, lymphoma involving immune-privileged sites is more aggressive than nodal disease. MYC rearrangement is an adverse prognostic factor and has been reported in 10% of DLBCL patients[15]. The 2 year overall survival of MYC rearrangement-positive patients was 35%, which was significantly lower than that of DLBCL patients without MYC rearrangement (67%)[15]. MYC rearrangement is also involved in double-hit or triple-hit lymphoma with BCL2 and BCL6 rearrangements. Since these high-grade lymphomas have a very poor prognosis, it is essential to evaluate the gene rearrangement of BCL2, BCL6, and MYC. This patient was also considered to have a double-hit or triple-hit lymphoma. However, we were not able to conduct BCL2 and BCL6, FISH, or next generation sequencing; a sufficient amount of tissue for mutation tests could not be obtained with core needle biopsy. Treatment had to be started immediately due to rapid progression; therefore, there was no time to complete additional biopsies.

CONCLUSION
In this report, we present an unusual case of DLBCL with diffuse muscle and soft tissue invasion which initially appeared to be soft tissue infection or inflammation. Due to unusual clinical manifestations, the first diagnosis was incorrect, and the disseminated extranodal invasion resulted in poor clinical outcomes. We suggest that skin invasions of aggressive lymphoma must be considered in differential diagnosis if there is a soft tissue infection that is unresponsive to antibiotics or progresses rapidly.

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CASE REPORT

Genetic characteristics of a patient with multiple primary cancers: A case report

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Author contributions: Lu B designed the research project; Li QY drafted the manuscript; Ouyang WW and Yang WG were responsible for the treatment of the patient; Ouyang WW collected the patient’ clinical data; Wu LJ and Yang Y performed the data analyses; Su SF assisted in the writing of the manuscript; all authors have read and approved the manuscript.

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Abstract

BACKGROUND

Two or multiple primary malignant neoplasms (MPMN) rarely occur in the same patient. It has been reported that MPMNs are easily misdiagnosed as the recurrence or metastasis of malignancies in clinical practice, affecting the choice of treatment for the patients, thereby resulting in the delay of optimal diagnosis. Next generation sequencing (NGS) can be used to distinguish between multiple primary lung cancers and intrapulmonary metastasis, and may distinguish the origin of tumours in different sites of the body.

CASE SUMMARY

We report the case of 66-year-old woman who suffered from different malignant neoplasms in the rectum and esophageal and gastrointestinal tract. The first neoplasm rectal adenocarcinoma was diagnosed and removed in 2016. The second and third lesions were diagnosed with esophageal squamous-cell carcinoma (ESCC) and gastrointestinal stromal tumour (GIST), respectively, in 2019. Next-generation whole exome sequencing was performed on the tissue specimens of rectal carcinoma, esophageal cancer, GIST, and white blood cells to investigate the relationship between malignancies at different timeframe and determine whether the ESCC and GIST evolved from the rectal adenocarcinoma. Mutations including v-Ki-ras2-Kirsten rat sarcoma viral oncogene homolog, adenomatosis polyposis coli, and lysine methyltransferase 2D were detected in rectal adenocarcinoma sample, mast/stem cell growth factor receptor was detected in GIST tissue, and mothers against decapentaplegic homolog 4 were detected in ESCC specimen. Overall, ESCC and GIST were not genetically evolved from rectal adenocarcinoma, and this patient did not have a trunk driven clone.
INTRODUCTION

Multiple primary malignant neoplasms (MPMNs), also known as multiple primary cancers, refer to the simultaneous occurrence of two or more primary malignancies in one or more organs and tissues of the same patient. To our knowledge, MPMNs are easily misdiagnosed as the recurrence or metastasis of malignant tumours in clinical settings, which affects the choice of treatment for the patients and further delays the optimal diagnosis. As diagnostic techniques and treatments develop, the life of patients with MPMNs is increasing.

Colorectal cancer is a malignant tumour with high morbidity and mortality in the world[1]. In recent decades, the incidence rate of colorectal cancer remains high in developing countries[2]. Esophageal cancer is the fourth most common cause of cancer-related death worldwide, ranking sixth in incidence[3]. There are two main subtypes of this disease, including esophageal squamous-cell cancer (ESCC) and esophageal adenocarcinoma. The incidence of these two types varies by geographic areas, with approximately over half of the esophageal cancer cases detected in China, especially ESCC[4]. MPMNs may occur simultaneously or successively in different sites in an individual with colorectal cancer, accounting for about 4.5%[3-8]. Dual primary tumours are most common in MPMNs, while triple primary tumours are rare[9]. The second most frequently reported cancers since 2011 are renal, uterine, cervical, and lung cancers[9]. Zhou et al[10] reported a case of coexistence of gastrointestinal stromal tumour (GIST) and esophageal and gastric cardia carcinomas in 2013. In the following year, Suzuki et al[11] described a 76-year-old man with a large GIST along with advanced adenocarcinoma in the rectum complicated with prostate carcinoma in 2014. Fan et al[12] also presented a rare case of synchronous occurrence of hereditary gastric adenocarcinoma, gastrointestinal stromal tumour, small cell esophageal carcinoma, and squamous carcinoma in situ in 2017. However, colorectal cancer, esophageal cancer, and GIST have rarely been reported in the same patient and there is no analysis of gene mutations in these rare cases.

In the present study, we report a patient who developed ESCC and GIST in 2019, with a history of surgery for rectal adenocarcinoma 3 years ago. Whole exome sequencing (WES) was used to investigate the patient’s genetic characteristics, as well as the relevance of different tumours in this patient.

CONCLUSION

NGS is an effective tool to study clonal evolution of tumours and distinguish between MPMNs and intrapulmonary metastasis.

Key Words: Multiple primary malignant neoplasms; Whole exome sequencing; Rectal carcinoma; Esophageal squamous-cell carcinoma; Gastrointestinal stromal tumour; Case report

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Core Tip: We report a case of multiple primary malignant neoplasms. In this case, next-generation whole exome sequencing confirmed that esophageal squamous-cell carcinoma and gastrointestinal stromal tumour were not genetically evolved from rectal adenocarcinoma that was removed 3 years ago but occurred independently. The results of next-generation whole exome sequencing of the tumour tissues confirmed the specimens’ evolution relationship.
CASE PRESENTATION

Chief complaints
In February 2019, a 66-year-old woman was admitted to Guizhou Cancer Hospital with swallowing and choking difficulties for more than 5 mo, and her symptoms worsened in the past 1 mo.

History of past illness
In March 2016, the patient was hospitalized at a local hospital due to anal distention and changes in bowel habits. On admission, the colonoscopy and biopsy examinations revealed a rectal carcinoma with high-grade epithelioid neoplasia. Meanwhile, digital rectal examination showed the presence of an ulcerous neoplasm that was palpable 4-5 cm from the lateral wall of the rectum and invasive for about half a week. Besides, the neoplasm was about 3 cm × 3 cm in size, hard in texture, and inactive. In the same month, the case received laparoscopic radical resection of rectal carcinoma and rectal sigmoid anastomosis, whereas preoperative neoadjuvant therapy was not performed at the patient’s request. Finally, the patient was diagnosed with stage IIIB (T3N1cM0) mucinous adenocarcinoma of the rectum with a tumour size of 4.5 cm × 3.5 cm. After discharge, the patient did not return for further treatments such as chemotherapy.

Personal and family history
The patient had no family history of similar lesions.

Physical examination
Karnofsky Performance Status Scale (KPS) has been widely adopted to quantify the functional status of cancer patients. In this study, the KPS of the case was 80.

Laboratory examinations
Postoperative pathology exhibited moderately to highly differentiated ESCC (4 cm × 2 cm) (Figure 1A), with tumour invasion of the whole esophageal wall, vascular invasion (+), and nerve invasion (+/-), without the two cutting edges of the samples. The results of hematoxylin-eosin stained tissue morphology and immunohistochemical markers revealed four spindle cell nodules in the lesser curvature and cardia, including one leiomyoma and three GISTs (Figure 1B) (nuclear fission: 0-1/5 mm², tumour size: 1 cm × 0.8 cm × 0.2 cm, and extreme low risk for invasion). Immunohistochemical staining showed CD117+, Calponin-, MSA-, Des-, SMA-, CK-, Vim+, Ki67+ (2%), CD34+ and Dog+ in GIST cells, and MSA+, Des+, SMA+ and Ki67+ (2%) in smooth muscle cells.

Imaging examinations
Enhanced computed tomography (CT) scans of the chest showed a thickened esophageal wall and enlarged peripheral lymph nodes, suggesting esophageal cancer with peripheral lymph node metastasis (Figure 2A). In addition, the increased density of the lower lobe of both lungs might be caused by inflammation. Subsequently, esophagoscopy examination showed esophageal neoplasia with stenosis, indicating progressive esophageal cancer. Pathological results revealed that ESCC was about 25 cm away from the incisors. The CT image of nodules of the lesser curvature of the stomach is shown in Figure 2B.

FINAL DIAGNOSIS
The patient was diagnosed as having postoperative stage III middle thoracic ESCC (pT4N0M0), and spindle cell nodules of the lesser curvature and cardia (1 leiomyoma and 3 GISTs) after rectal adenocarcinoma.

TREATMENT
The patient underwent thoracoscopic radical resection of esophageal cancer, reconstruction of the digestive tract, and systematic lymph node dissection. After surgery, she received both adjuvant chemotherapy and targeted therapy (5-fluorouracil, cisplatin, and docetaxel therapy and nimotuzumab). On day 1, the patient...
Figure 1 Postoperative histopathology of two lesions. A: Postoperative histopathology of esophageal squamous-cell carcinoma lesion (magnifications, × 400); B: Postoperative histopathology of gastrointestinal stromal tumour lesion (magnifications, × 400).

Figure 2 Preoperative computed tomography images. A: Computed tomography (CT) scans of the chest showed a tumour in the esophagus; B: CT image of nodules of the lesser curvature of the stomach. The orange circles indicate tumour lesions.

was administered intravenously with nimotuzumab (100 mg) for more than 60 min, followed by intravenous infusion of cisplatin (75 mg/m², 100 mg) on days 2 and 3. At the same time, she also received pump injection of fluorouracil (500 mg/m²/d, 3400 mg) on days 1 to 5. Besides, the patient was treated by antiemesis, acid suppression, gastric protection, hydration, dexamethasone allergy prevention and nutritional support for 21-18 d/cycle, followed by re-examination after two cycles of chemotherapy. During targeted drug therapy, vital signs were monitored for 7 d/cycle. There was no postoperative treatment for leiomyoma or gastric GISTs.

OUTCOME AND FOLLOW-UP

The observation indexes were non-target lesion and the occurrence of new lesion. The efficacy and the toxic and side effects were evaluated according to the RECIST standard and CTC4.0 standard, respectively. After the completion of chemotherapy and targeted therapy in August 2019, the patient was in good physical condition and routine follow-up showed no abnormalities.

To study the patient's genetic characteristics, informed consent was obtained from the patient. Whole exome sequencing (WES) was carried out on the tissue specimens of rectal carcinoma, esophageal cancer, GIST, and white blood cells. For sequencing, the genomic DNA was first sheared into 150-200 bp fragments using Covaris M220 Focused-ultrasonicator Instrument (Covaris, MA, United States). Next, the fragmented DNA libraries were constructed via NimbleGen SeqCap EZ Exome Library Kit (Roche,
WL, United States) according to manufacturer’s instructions. Subsequently, the captured DNA fragments were sequenced using Illumina Novaseq 6000 sequencing system at least 50× for blood cells and 100× for tumour tissue samples (Genecast, Wuxi, Jiangsu Province, China). After filtering out low quality reads, the clean reads were aligned with the human reference genome (Hg19, NCBI Build 37.5) via Burrows-Wheeler Aligner (version 0.7.17) [13]. Picard toolkit (version 2.1.0) [14] was used to make duplicates, while Genome Analysis Toolkit (version 3.7) [15] was adopted for realignment. VarDict (version 1.5.1) [16] was introduced to single nucleotide variations calling, while compound heterozygous mutations were merged with FreeBayes (version 1.2.0) [17]. All mutations were annotated through ANNOVAR [18]. Finally, the remaining mutations were annotated with pathway information [19]. Copy number variations (CNVs) were paired via software CONTRA (version 2.0.8) [20] with copy number threshold 3 for CNV gain and 1.2 for CNV loss.

The results of genetic characteristics showed that carboxyl ester lipase, mucin-16, mucin-3A (MUC3A), mucin-4 (MUC4), and zinc finger protein 88 were common mutated genes in the three lesions (Supplementary Figure 1). There were 51 unique mutated genes in intestinal tumour tissues, 13 in gastric tumour tissues, and 55 in esophageal tumour tissues (Figure 3A), among which the common mutation sites were MUC3A p.S697N and MUC3A p.T465P. Additionally, the numbers of unique mutated gene loci in intestinal tumour tissues, gastric tumour tissues, and esophageal tumour tissues were 73, 19, and 83, respectively (Figure 3B), indicating a strong heterogeneity of the three lesions, with few mutated genes and loci in common. According to gene analysis, v-Ki-ras2-Kirsten rat sarcoma viral oncogene homolog (KRAS), adenosomatous polyposis coli (APC), and mothers against decapentaplegic homolog 4 (SMAD4) gene mutations were detected in rectal adenocarcinoma sample, but not in esophageal and gastric tumour samples (Figure 3C). Furthermore, the mast/stem cell growth factor receptor (KIT) mutation was detected in GIST tissue, but not observed in intestinal and esophageal tumour specimens (Figure 3C); lysine methyltransferase 2D (KMT2D) was noticed in ESCC specimen, but not in intestinal and GIST specimens (Supplementary Figure 1). The results of CNV revealed that the three lesions were inconsistent, and the copy numbers of MUC4, family with sequence similarity 91 member A1, LOC101928884, and LOC101929060 in the rectal adenocarcinoma and two pore segment channel 2 in the ESCC samples were significantly increased, while there was no significance between gene copy numbers in the GIST tissue (Figure 3D). Therefore, since 2016, the GIST and esophageal cancer lesions of this patient developed independently, rather than as clone evolution of rectal adenocarcinoma.

**DISCUSSION**

Next generation sequencing (NGS) is considered a genetic testing that can be used to distinguish between multiple primary lung cancers and intrapulmonary metastasis. In a NGS analysis of 60 patients with multifocal tumours, researchers at Memorial Sloan-Kettering Cancer Center found that prospective histological predictions were inconsistent with the sequencing results in 17 (22%) cases, particularly intrapulmonary metastases (IPMs) (44%). In comparison with NGS, standard histopathologic approach is adequate in most cases, but has notable limitations in the recognition of IPMs [21]. Besides, the identification of multiple primary lung cancers or intrapulmonary metastasis by genomic breakpoint connections and chromosomal CNV levels in rearrangement suggested that the pedigree of paired tumours was categorized by the sequencing; however, 9 of 33 identical histological tumour pairs were misclassified, 7 were inconclusive, and 2 were metastases by histological evaluation, while categorization was accurate by genetic testing [22]. Jiang et al [23] performed WES in 84 tissue and blood samples from 26 lung adenocarcinoma patients with liver metastases or brain metastases, and they found that common driver mutations were highly consistent between paired primary and metastatic tumours, suggesting that next generation WES sequencing was a useful tool to study tumour evolution. Thus, genetic testing, especially second-generation WES sequencing, shows great promise in distinguishing intrapulmonary metastasis from independent primary clinical issues in non-small cell lung cancer due to the large number of comprehensive genes covered. In other cancer species such as intestinal cancer, there have also been some reports of using genetic testing to distinguish between primary and metastatic cancers [24, 25].

MPMN models are sometimes confused with multiple metastases from the same cancer. Genetic testing is an effective tool for studying these problems; however, the application of genetic testing to distinguish colorectal cancer, esophageal cancer, and
Figure 3 Genetic test results of three lesions. A: Venn diagram of mutant genes; B: Venn diagram of mutant gene loci; C: Patterns of common gene variants and signaling pathways; D: Copy number variation heat map. PYP161474 represents tissue specimen of colorectal adenocarcinoma, PYP20190282-10 represents tissue specimen of gastrointestinal stromal tumour, and PYP201902382-3 represents tissue specimen of esophageal cancer.

GIST in the same patient has rarely been reported. Compared with NGS panel sequencing, Sanger sequencing, or normal PCR, WES can cover a comprehensive range of genes and loci, which is more conducive to the study of tumour evolution and origin, and its detection results could provide sufficient reference information for medication. Thus, we performed next-generation WES on the tissue samples of rectal carcinoma, esophageal cancer including middle thoracic ESCC and GIST, and white blood cells to investigate the relationship between various tumours in different periods. Mutations including KRAS, APC, and SMAD4 were detected in rectal adenocarcinoma sample, which were not found in esophageal and gastric tumour samples. KRAS, APC, and SMAD4 mutations are common in colorectal cancer. In the COSMIC dataset, the mutation frequency of rectal adenocarcinoma is 32%, 73%, and 2%, respectively. The mutation hotspots of KRAS are G12, G13, and Q61\[26\]; the first two occur in the GTPase domain, and the latter interferes with the ability of NF1 to bind and regulate KRAS. Mutations in residues G12, G13, and Q61 alter RAS interactions with regulatory proteins, leading to constitutive activation\[27\]. Patients with any known KRAS mutation (exons 2, 3, and 4) or NRAS mutation (exon 2, 3, and 4) should not be treated with either cetuximab or panitumumab.

KIT p.V559D mutation was detected in GIST tissue, but not in intestinal and esophageal tumour specimens, which is located in exon 11 of KIT gene. Nearly 90% of GISTs harbour activating mutations in the KIT gene, and approximately 80% of patients with metastatic GISTs show at least some clinical response to the targeted small molecule KIT inhibitor imatinib\[28\]. In addition, KMT2D mutation was detected in ESCC specimen, which was not found in intestinal and GIST specimens. The CNV results revealed that the three lesions were inconsistent.
From the results of genetic testing, there was no dominant mutation clone in the rectal adenocarcinoma, GIST, and esophageal cancer lesions in this patient. The two lesions in 2019 did not evolve from the main clone of the lesion in 2016, and this result was supported by the favourable prognosis of the patient. After that, no pathogenic germ-line mutation was identified by WES and the patient also reported no family history of similar lesions, suggesting that the MPMNs were not triggered by genetic factors. Therefore, the cause of MPMNs in this case remains unclear.

In addition to studying the origin and evolution of tumours, the results of WES could also guide the medication for patients. The patient in the case with KRAS p.G13D should not be administrated with cetuximab. The KIT p.V559D mutation indicated that the patients might be treated with KIT inhibitor such as imatinib.

Due to limited data, this research only provides a reference for the identification of multiple primary tumours and metastatic tumours at the genetic level. For large-scale clinical application, more prospective studies with large sample size are needed to guide clinical decision-making, and the cost of detection and the economic cost of patients are also important factors that must be considered.

**CONCLUSION**

Genetic testing provides important information for the study of MPMNs. In this case, next-generation WES confirmed that ESCC and GIST did not genetically evolve from rectal adenocarcinoma resected 3 years ago, but occurred independently. Besides, the subject of this study did not have a trunk driven clone. In summary, NGS is a useful tool to study clonal evolution of tumours.

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Hypereosinophilia with cerebral venous sinus thrombosis and intracerebral hemorrhage: A case report and review of the literature

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Abstract

BACKGROUND
Hypereosinophilia (HE) is defined as a peripheral blood eosinophil count of > 1.5 \times 10^9/L and may be associated with tissue damage. The clinical presentations of HE vary; however, myocardial fibrosis and thrombosis can threaten the lives of patients with sustained eosinophilia. Cerebral venous sinus thrombosis (CVST) in the setting of eosinophil-related diseases has seldom been reported. Here, we review the literature on HE with CVST to increase knowledge and encourage early diagnosis.

CASE SUMMARY
A previously healthy 41-year-old man was admitted to hospital with diarrhea and abdominal pain. He was treated with antibiotics for suspected acute colitis. Three days later, he experienced headache and vomiting. Brain computed tomography (CT) revealed thrombosis of the left jugular vein to the left transverse sinus vein. Platelet (PLT) count decreased to 60 \times 10^9/L, and absolute eosinophil count (AEC) increased to 2.41 \times 10^9/L. He was treated with low-molecular-weight heparin. PLT count progressively decreased to 14 \times 10^9/L, and we terminated anticoagulation and performed PLT transfusion. Six days after admission, he complained of a worsening headache. Brain CT revealed right temporal lobe and left centrum semiovale intracerebral hemorrhage, and AEC increased to 7.65 \times 10^9/L. We used prednisolone for HE. The level of consciousness decreased, so emergency hematoma removal and decompressive craniectomy for right cerebral hemorrhage were performed. The patient was alert 2 d after surgery. He was treated with anticoagulation again 2 wk after surgery. Corticosteroids were gradually tapered without any symptomatic recurrence or abnormal laboratory findings.

CONCLUSION
HE can induce CVST, and we need to focus on eosinophil counts in patients with CVST.
INTRODUCTION

Cerebral venous sinus thrombosis (CVST) can occur in the early stages of hypereosinophilia (HE) and can be life-threatening if not identified early. We searched the Web of Science, Scopus, Embase, and PubMed up to December 2020 using medical subject headings of “eosinophilia/HE” and “cerebral venous thrombosis/sinus thrombosis” (limits: Full text available, clinical trials, human studies, and studies in English), and identified eight publications (Table 1) related to HE with CVST in eight cases[1-8]. Herein, we report a 41-year-old man who presented with HE-associated CVST and intracerebral hemorrhage (ICH). Blood eosinophil count decreased quickly after corticosteroid therapy, and CVST caused headache, which improved after anticoagulation therapy.

CASE PRESENTATION

Chief complaints
A 41-year-old man was admitted to the Department of Neurology of our hospital after experiencing headache and vomiting for 1 d on September 9, 2020.

History of present illness
Six days before admission, the patient presented with diarrhea (2–3 times per day) and abdominal pain with a slight fever. Self-medication with trimebutine maleate and compound Lactobacillus acidophilus showed no improvement. Three days before admission, the patient visited our hospital on emergency and was treated with antibiotics (levofloxacin) for suspected colitis. The patient achieved remission from diarrhea, but still demonstrated abdominal distension. The patient did not experience chest tightness or heart palpitations. Six days after admission, he complained of a worsening headache and developed left hemiplegia. His consciousness rapidly deteriorated with signs of brain herniation. Thirteen days after admission (2 d after surgery), he had no symptoms, but he did demonstrate acne on his skin.

History of past illness
The patient had a history of tonsillectomy, appendectomy, and kidney stones.

Personal and family history
The patient denied a past history of drug or alcohol abuse, smoking, promiscuous sexual behavior, raw food consumption, and travel. There was no family history of...
Table 1 Reported cases of cerebral venous sinus thrombosis with hypereosinophilia

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Age/sex</th>
<th>Medical history</th>
<th>Initial symptoms</th>
<th>CVST</th>
<th>ICH</th>
<th>Thrombocytopenia</th>
<th>Treatment</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schulman et al[1], 1999</td>
<td>11/M</td>
<td>None</td>
<td>Bug bites, rash</td>
<td>Straight sinus; superior sagittal sinus</td>
<td>Brain stem</td>
<td>No</td>
<td>Prednisone, heparin</td>
<td>Death</td>
</tr>
<tr>
<td>Sakuta et al [2], 2007</td>
<td>7/M</td>
<td>Seizures, taking valproate</td>
<td>HE for 10 m</td>
<td>Superior sagittal sinus</td>
<td>Right hemisphere</td>
<td>50 × 10^9/L</td>
<td>Heparin, warfarin</td>
<td>Cure</td>
</tr>
<tr>
<td>Numagami et al[3], 2008</td>
<td>76/F</td>
<td>None</td>
<td>Right mandible swelling</td>
<td>Left transverse sinus</td>
<td>Left temporal lobe</td>
<td>No</td>
<td>Prednisolone, evacuation of hematoma</td>
<td>Death</td>
</tr>
<tr>
<td>Ananth et al [4], 2016</td>
<td>17/M</td>
<td>Asthma</td>
<td>Intermittent fever, dyspnea</td>
<td>Transverse sinus</td>
<td>None</td>
<td>No</td>
<td>Prednisolone, warfarin</td>
<td>Death</td>
</tr>
<tr>
<td>Teresa et al [5], 2006</td>
<td>40/F</td>
<td>Rhinitis asthma, nasal polyps, taking contraceptives for 6 yr</td>
<td>Asthenia, myalgia, fever</td>
<td>Superior sagittal sinus</td>
<td>Bilateral parietal lobe</td>
<td>No</td>
<td>Heparin, warfarin</td>
<td>Cure</td>
</tr>
<tr>
<td>Numagami et al[3], 2008</td>
<td>7/M</td>
<td>None</td>
<td>Right lateral sinus</td>
<td>Left arm/foot paresthesia</td>
<td>Right lateral sinus</td>
<td>No</td>
<td>Heparin, warfarin</td>
<td>Death</td>
</tr>
<tr>
<td>Kanno et al [6], 2005</td>
<td>34/F</td>
<td>None</td>
<td>Lump on left thigh</td>
<td>Left transverse sinus</td>
<td>Left hemisphere</td>
<td>10.4 × 10^9/L</td>
<td>Antibiotics, corticosteroid, decompression surgery</td>
<td>Death</td>
</tr>
<tr>
<td>Chan et al [7], 2004</td>
<td>49/F</td>
<td>None</td>
<td>Headache, diplopia</td>
<td>Cavernous sinus, transverse sigmoid sinuses</td>
<td>None</td>
<td>No</td>
<td>Bilateral endoscopic sphenoidectomy, steroids, itraconazole</td>
<td>Cure</td>
</tr>
<tr>
<td>Sano et al [8], 2014</td>
<td>67/M</td>
<td>Prostatic hypertrophy</td>
<td>Slight fever</td>
<td>Superior sagittal sinus</td>
<td>Bilateral parietal lobes, right occipital lobe</td>
<td>No</td>
<td>Evacuation of hematoma</td>
<td>Cure</td>
</tr>
</tbody>
</table>

CVST: Cerebral venous sinus thrombosis; ICH: Intracerebral hemorrhage.

neurological or blood system diseases.

**Physical examination**

After admission, the patient’s body temperature was 36.7 °C, respiratory rate was 16 bpm, heart rate was 42 bpm, and blood pressure was 135/72 mmHg. There was no detectable rash, bradycardia, arrhythmia, or murmur, and both lungs sounded clear with no rales. Abdominal distension without tenderness was noted, and the patient’s neurological examination was normal.

**Laboratory examinations**

On September 6, 2020, white blood cell count was elevated (12.6 × 10^9/L) with an absolute eosinophil count (AEC) of 0.97 × 10^9/L, hemoglobin concentration of 155 g/L, platelet (PLT) count of 238 × 10^12/L, and C-reactive protein concentration of 110 mg/L. On September 9, 2020, PLT count decreased to 60 × 10^12/L, AEC increased to 2.41 × 10^9/L, D-dimer increased to 50.22 mg/L, prothrombin time (PT) was 12.8 s, and activated partial PT was 36.2 s. Total immunoglobulin E was 389.4 IU/mL, erythrocyte sedimentation rate was 21 mm/h, and glycan antigen was 125 U/mL, but a serological allergen screen was negative. Tests for parasites in the stool were negative. Anti-neutrophil cytoplasmic, antinuclear, and cardiolipin antibodies were negative. Procalcitonin, troponin, cardiac enzymes, liver and kidney function, folic acid, vitamin B12, and thyroid function were all normal.

Serology for human immunodeficiency virus, hepatitis viruses, and *Treponema pallidum* was normal. Bone marrow biopsy showed normal cellularity with increased eosinophils (35%). *FIPL1* and platelet-derived growth factor receptor (*PDGFR*) A/B gene fusion and chromosomal analysis were normal. However, AEC progressively
increased up to $7.65 \times 10^9/L$, PLT count progressively decreased to a minimum of $14 \times 10^9/L$, and D-dimer continuously increased to 69.76 mg/L (Figure 1).

**Imaging examinations**

On September 6, 2020, abdominal computed tomography (CT) revealed swelling with peripheral exudation changes in the wall of the transverse and sigmoid colon. On September 9, 2020, brain CT revealed thrombosis of the left jugular vein to the left transverse sinus vein (Figure 2A). Chest CT demonstrated inflammation in both lungs.

Electrocardiography showed significant sinus bradycardia with irregularity, sinus arrest, and frequent borderline escape, with normal myocardial enzymes and troponin. Echocardiography showed no abnormal findings. On September 15, 2020, brain CT revealed right temporal lobe and left centrum semiovale ICH (Figure 2B and C). Chest CT showed bilateral pleural effusion. Duplex ultrasonography showed bilateral intermuscular venous thrombosis of the calf.

On September 30, 2020, enhanced cranial magnetic resonance venogram showed stenosis of the left internal jugular vein, transverse sinus, sigmoid sinus, confluent sinus, straight sinus, and inferior sagittal sinus (Figure 3A).

**FINAL DIAGNOSIS**

HE induced CVST, and the cause of HE was unknown, so the diagnosis changed from HE to idiopathic HE syndrome (HES). Thrombocytopenia may have been related to consumptive reduction by thromboembolism, and ICH occurred secondarily to thrombocytopenia.

**TREATMENT**

The patient was treated with antibiotic agents due to suspected colitis, and low-molecular-weight heparin was initiated after the diagnosis of CVST. When PLT count decreased to $14 \times 10^9/L$, we terminated anticoagulation and antibiotic agents and performed PLT transfusion. We used intravenous immunoglobulin (32 g/d for 5 d) for suspected heparin-induced thrombocytopenia (HIT) and prednisolone 80 mg/day due to HE after ICH. Hematoma removal and decompressive craniectomy for right ICH were performed after PLT count increased to $80 \times 10^9/L$ after PLT transfusion. The patient was treated with anti-coagulation again (heparin and warfarin) 2 wk after surgery. Corticosteroids were gradually tapered, and the total treatment course was 3 mo. Warfarin was continued, and the patient still uses it today.

**OUTCOME AND FOLLOW-UP**

A 6-mo follow-up showed that the patient did not experience any further symptoms. However, thrombosis in the left internal jugular vein, transverse sinus, sigmoid sinus, and confluent sinus, as well as partial venous thrombosis in the straight sinus and inferior sagittal sinus, was unchanged (Figure 3B).

**DISCUSSION**

Eosinophils are multifunctional granular leukocytes that represent approximately 3%–5% of circulating blood leukocytes with an AEC in healthy adults of 0.35–0.5 × 10^9/L. Eosinophils are normally present in gastrointestinal tract, except in the squamous esophagus, and are important in homeostasis and reconstitution of tissue[9]. Eosinophilia encompasses a broad range of non-hematologic (secondary or reactive) and hematologic (primary or clonal) disorders with potential for end-organ damage[10]. HE is usually linked to allergies, infections (parasitic or fungal), drugs, neoplastic disorders, autoimmune diseases, and atopy[9,10]. When blood HE induced organ damage, the diagnosis changes from HE to HES[9].

Of the cases reported in the literature, three occurred secondarily to eosinophilic granulomatosis, one was secondary to an allergic reaction to a fungus, and three was idiopathic HES. Our case was also idiopathic HES.
Peripheral blood eosinophilia can occur in patients with inflammatory bowel disease[11-13], and peripheral blood eosinophilia may be a biomarker of disease severity. Eosinophilic colitis (EC) should be suspected in any patient with intestinal symptoms with peripheral blood eosinophilia, but EC is a rare condition[14]. When accompanied by peripheral blood HE, colitis can occur as an isolated gastrointestinal disorder or as part of HES[15]. Our patient’s colitis may be a part of HES.

Thrombosis is one of the most serious HE-related organ damage. It has been suggested that approximately one-quarter of patients with HES develop thromboembolic complications and that 5%-10% die as a result of these complications[16]; however, CVST is rare. Eosinophils release rich tissue factors (TFs)[17] and provide a procoagulant phospholipid surface that supports TF-mediated thrombin generation[18]. Eosinophil cationic protein activates factor XII, which promotes internal coagulation[19]. Major basic protein (MBP) and eosinophil peroxidase activate PLTs [20,21]. Binding of MBP to thrombomodulin inhibits anticoagulant activities[22,23]. Tissue and endothelial damages through direct cytotoxic effects or indirect recruitment and activation of other inflammatory cells increase vascular permeability, which may contribute to a procoagulant state.

Thrombocytopenia is more common than thrombocytosis in patients with HE (31% vs 16%, respectively)[24]. The mechanisms of thrombocytopenia in HE are not fully understood, but may be related to consumptive thrombocytopenia caused by thromboembolism. In a previous study, thrombocytopenia was present in five of ten patients with central nervous system involvement but no thrombosis of HE[25]. In our review, two of eight cases reported in the literature developed thrombocytopenia,
Figure 3 Magnetic resonance venogram. A: Thrombosis in the left internal jugular vein, transverse sinus, sigmoid sinus, confluent sinus, partial venous thrombosis in the straight sinus and inferior sagittal sinus; B: The thrombus was smaller than before.

which may have been underpinned by an immunological mechanism. One case of thrombotic thrombocytopenic purpura with HE was caused by an ADAMTS13 inhibitor[26]. Other cases of HE with an initial presentation of idiopathic thrombocytopenia have been reported[27]. Spontaneous HIT is rare and may be associated with antibodies against platelet factor-4, but it may occur without previous heparin exposure[28,29].

HE with ICH was accompanied by CVST in five of eight cases reported in the literature. Of these, three deaths were observed due to cerebral herniation. Multiple mechanisms may account for ICH. ICH may occur secondarily to CVST or thrombocytopenia, as a side effect of anticoagulant drugs, or due to direct endothelial injury or vasculitis caused by eosinophilic infiltration.

Corticosteroids are a first-line therapy for PDGFRA/B-negative HE[10]. HE can induce CVST, and we need to focus on eosinophil counts in patients with CVST. Early initiation of steroid therapy can potentially prevent disease progression. Persistent eosinophilia is associated with a shorter time to thromboembolism relapse[30], so the goal of therapy is to maintain the eosinophil count below 1500/μL.

CONCLUSION

HE can induce CVST, and we need to focus on eosinophil counts in patients with CVST. Corticosteroids are a useful first-line therapy for PDGFRA/B-negative HE and HES.

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Itraconazole therapy for infant hemangioma: Two case reports

Zhe Liu, Sha Lv, Shuang Wang, Sheng-Ming Qu, Gui-Yun Zhang, Yi-Tong Lin, Lei Yang, Fu-Qiu Li

BACKGROUND
Infantile hemangiomas (IHs) are the most common childhood benign tumors, showing distinctive progression characteristics and outcomes. Due to the high demand for aesthetics among parents of IH babies, early intervention is critical in some cases. β-Adrenergic blockers and corticosteroids are first-line medications for IHs, while itraconazole, an antifungal medicine, has shown positive results in recent years.

CASE SUMMARY
In the present study, itraconazole was applied to treat two IH cases. The therapeutic course lasted 80-90 d, during which the visible lesion faded by more than 90%. Moreover, no obvious side effects were reported, and the compliance of the baby and parents was desirable.

CONCLUSION
Although these outcomes further support itraconazole as an effective therapeutic choice for IHs, large-scale clinical and basic studies are still warranted to improve further treatment.

Key Words: Infant; Hemangiomas; Therapeutics; Itraconazole; Oral; Case report

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Itraconazole for infant hemangioma

**INTRODUCTION**

Infantile hemangiomas (IHs), the most common vascular tumors in infants, are caused by disorder of vascular architecture and aberrant proliferation of endothelial cells[1]. Several retrospective and prospective studies reported 1%-3% incidence of IHs among infants, 2.6%-9.9% incidence in older children, and up to 22%-30% incidence in preterm infants weighing less than 1 kg[2]. The initial onset of IHs usually appears before 4 wk of age with complete growth by 5 mo. For most IH cases, the involution begins at 12 mo and finalizes by age 4[2]. Although a large portion of IHs tend to fade spontaneously without structural or aesthetic challenges, some are accompanied by vital complications or residual disfigurement[3]. In such cases, early intervention is critical for restraining the lesion growth, reducing the risk of complications, and mitigating psychosocial stress[4].

IH intervention approaches involve medications and laser treatments, while surgery is required for patients who fail to respond to pharmacotherapy[2,3]. Orally administered propranolol or topical applied timolol, as β-adrenergic blockers, have shown clear efficacy on the superficial IHs[5]. While systemic corticosteroids are the typical first-line therapy for IHs, their distinct adverse effects limit their application in clinic[6]. Other medications, including vincristine, interferon-α, and imiquimod, are also commonly used but result in remarkable complications[2,3].

Itraconazole is an antifungal medication to treat infections caused by fungus in the lungs, mouth, throat, toenails, and fingernails in adults[7]. However, complications associated with this medicine include heart failure, liver, and kidney disease[8]. A recent study has suggested that the treatment of IH with 5 mg/kg per day itraconazole (oral) induced a substantial alleviation of lesions[9]. The underlying reasons for the success are related to angiogenesis inhibition and depressed cellular proliferation[10]. Despite this evidence, further research is still required to confirm the contribution of itraconazole. Therefore, we describe two cases in which infants presenting IHs were treated by itraconazole for 80-90 d and exhibited satisfying results without any noticeable complications. In both cases, the infants and parents showed promising compliance to the therapeutic approaches.

**CASE PRESENTATION**

**Chief complaints**

Case 1: A 4-mo-old baby presented slightly raised soft reddish-purple patches on the right hand at birth.

Case 2: A 6-mo-old baby visited the hospital for a bright red raised soft patch on the surface of the right ala nasi (Figure 1).

**History of present illness**

Case 1: Within 3 mo, the lesion grew rapidly in size and thickness, showing no fading tendency. The lesions were limited to the right palm and dorsum and exhibited a reddish-purple color, well-defined boundary, and nodular shape with slight lobulation (Figure 2).

Case 2: The lesion appeared 1 mo after birth and rapidly enlarged in size and thickness within 5 mo, showing no fading tendency. The patient had received radionuclide application therapy in another hospital 2 mo prior, which flattened the lesion slightly, but the response lasted only half a month. The lesion relapsed and thickened quickly,
Figure 1 The manifestations of infantile hemangioma affecting right ala nasi in case 2 on first visit, day 30, 60, 80, 90, and 1 year after itraconazole treatment. A: First visit; B: 30 d; C: 60 d; D: 80 d; E: 90 d; F: 1 year.

displaying a bright-red strawberry shape and clear boundary that faded upon pressing, thus was diagnosed as infantile strawberry hemangioma. The lesion extended into the nasal cavity causing vascular malformation on nasal mucosa.
Figure 2 The manifestations of infantile hemangiomas affecting the right hand in case 1 on first visit, day 43, 80, 124, and 1 year after itraconazole treatment. A: First visit; B: 43 d; C: 80 d; D: 124 d; E: 1 year.

**History of past illness**

*Case 1:* The patient showed a clear previous medical history.

*Case 2:* The previous medical history of the patient was clear.

**Personal and family history**

*Case 1:* The baby’s parents reported no special personal and family medical history.

*Case 2:* No special personal and family medical history was reported.

**Physical examination**

*Case 1:* The baby weighed 5 kg, and the physical examination revealed no abnormal signs.

*Case 2:* The baby weighed 7.9 kg, and the physical examination found no abnormality.
Laboratory examinations
Liver function was normal, and no other vital organs were involved.

Imaging examinations
Case 1: None of the imaging examinations revealed anomaly.
Case 2: All the imaging examinations were normal.

FINAL DIAGNOSIS
Case 1: All the clinical features supported the diagnosis of infantile cavernous hemangioma.
Case 2: The clinical features of this patient supported the diagnosis of IH.

TREATMENT
Case 1: With the written informed consent obtained from the baby’s parents, oral itraconazole (5 mg/kg/d, Janssen Pharmaceutical Co. Ltd) was chosen as the only treatment. The medicine (2000 mg itraconazole dissolved in milk) was fed to the baby for 80 d.

Case 2: After obtaining the written informed consent from the baby’s parents, oral itraconazole (5 mg/kg/d, Janssen Pharmaceutical Co. Ltd) was chosen as the only treatment. One of two equal parts of the 100-mg itraconazole capsule was dissolved in 5 mL of milk, which was fed to the baby once a day. The treatment included 39.5 mg/d itraconazole and lasted for 90 d, thus a total of 3600 mg itraconazole was administered to the baby.

OUTCOME AND FOLLOW-UP
Case 1: The follow-up examinations were performed on day 43, 80, 124, and 1 year after the treatment began. No biochemical anomaly was found, and normal liver function was maintained. The patient showed fine compliance. On day 43, the lesions were less raised with a slightly faded color, narrowed size, and emergence of cracks, invagination, and ruffle on the surface (Figure 2). On day 80, the size and color of lesions were reduced further (Figure 2), therefore itraconazole administration was halted. The follow-up examination at month 4 revealed flattened lesions with light pink fibrous and adipose tissues and substantially lessened vascular structures (Figure 1). At the 1-year follow-up, only a trace of light pink fibrous and adipose tissues as well as vascular structures were left (Figure 1).

Case 2: The follow-up examinations were assigned on day 30, 60, 80, and 90. The biochemical indices and liver function remained normal, and the parents did not report any discomfort of the baby. Upon visual observation on day 30, the lesion was flattened with reduced size and color, and invagination appeared on the surface of the lesion, which indicated clear fading tendency (Figure 1). The color B type ultrasonography detected a smaller vascular malformation inside the nasal cavity. After day 90, the baby’s parents decided by themselves to stop the medication and no longer visit the hospital. One year later, a photo of the baby revealed only a small light-pink scar at the original site of the IH (Figure 1).

DISCUSSION
IH is the most common benign tumor in children with distinctive progress and outcomes. Specifically, they can grow quickly in the early infancy, then fade slowly but spontaneously grow in the following years, which is characteristic of the most uncomplicated IHs. However, if IHs are present on risky sites, such as the eye, lip, nose, cheek, or central nervous system, early intervention becomes a necessity[1]. Darrow et al[2] proved that the most remarkable growth of IHs occurs 5.5 and 6.5 wk
after the onset of the disease, much sooner than previous predictions. This report also recommends early intervention before this time frame to prevent the irreversible anatomic deformation or complications[2]. While systemic corticosteroids have been the first-line option for IH therapy, propranolol was found effective in 2008[11] and demonstrated higher safety and efficacy than corticosteroids in later studies.

In 2015, Ran et al[9] reported 6 IH cases in which oral itraconazole was used as the only treatment[9]. A favorable outcome was achieved as the lesions faded by 80%-100% after 2-9 wk of itraconazole treatment (5 mg/kg/d), although minor digestive symptoms, such as diarrhea, appeared. Later, the same team reported positive results of a giant tufted angioma, which faded within 3 mo of oral itraconazole treatment[12]. The liver function and blood test were normal during the treatment, and conditions continued to improve 6 mo after withdrawal of the medication. Moreover, Li et al[13] selected specimens of 5 IHs cases and 11 capillary malformations to perform an adenosine triphosphate sensitivity assay to detect the growth inhibition activity of propranolol, rapamycin, sildenafl, and itraconazole[13]. They found that itraconazole exhibited clear inhibition on the cellular proliferation of both IHs and capillary malformations[13]. Bessar et al[14] investigated the efficacy of propranolol and itraconazole on IHs by observing the variation of serum angiopoietin-2. They reported that oral itraconazole is a promising alternative to propranolol with shorter treatment duration and higher safety[14]. We chose itraconazole for the 2 cases considering its superiority compared to propranolol, less side effects, reliance on electrocardiogram monitoring, and therapeutic capability on cardiovascular diseases[15,16]. Both the patients were satisfied with the treatment. Nonetheless, because only a few dermatologists are aware of the benefits of itraconazole to date, in the present study, the effect of itraconazole was further observed in two babies with IHs.

Patients of the two cases exhibited lesions on exposed sites. A large and rapidly growing lesion on the right hand with no fading tendency was reported in case 1. In case 2, the lesion was presented on the ala nasi, affecting the nasal cavity and creating an apparent vascular deformation. Both cases met the need for early intervention; thus, the parents of case 1 chose itraconazole as the only treatment, and the case 2 parents selected radionuclide application therapy before oral itraconazole. Currently, the 90Sr and 32P radionuclides are the most frequently used for IHs, which emit β-rays upon decay[17]. IH tissues are more sensitive to radioactive rays than the surrounding normal tissues, whereby the ionization induces swelling and necrosis of vascular endothelial cells and the subsequent occlusion and atrophy of vascular lumen. The 90Sr applicator is used often in clinic for superficial IHs since β-rays possess a 3-mm penetrating power and, thus, cannot reach deep lesions[18]. Besides, the radionuclide application therapy brings about several complications, such as skin atrophy, pigmentation or depigmentation, and scarring[17]. In case 2, the negative response to radionuclide application suggests that the lesion is located in deeper tissues, therefore the residue scan of this case could be a complication of radioactive treatment.

As for the preparation of medicine, lipophilic itraconazole is almost completely insoluble in water[19], so its bioavailability would be reduced by 40% with fasting[20]. A previous study implied that milk as a medium can improve the dissolving velocity and solubility of itraconazole[21]. Therefore, we used milk as the delivery medium in these 2 cases, during which neither baby showed any obvious adverse effect.

For more than 30 years, itraconazole has been widely acknowledged as a safe and effective treatment in clinic to treat fungal infections of infants and children[22,23]. The United States Food and Drug Administration has approved itraconazole as an inhibitor of the hedgehog pathway to treat cancers, such as basal cell carcinoma[24]. Compared to other triazole antifungal medications, itraconazole retains the endothelium in the G1 phase of the cell cycle[25] and restrains the angiogenesis through the vascular endothelial-derived growth factor signal pathway[26]. A recent study indicated that itraconazole can reduce the platelet-derived growth factor content to suppress the activation of platelet-derived growth factor-β and downstream effectors, including phosphatidylinositol-3-kiase, Akt, 4E binding protein 1, and p70S6K[27]. This discovery partly explains the therapeutic effect of itraconazole on the growth and survival of IHs cells.

CONCLUSION

In both cases, satisfying outcomes were achieved after the patients received oral administration of itraconazole, which further demonstrated the remarkable efficacy of this medication on IHs. Since there was no need for the patients and their parents to
stay in the hospital, the compliance of parents could be ensured. Considering its low price and minor side effects, itraconazole stands as a promising new therapeutic approach for IHs. Nevertheless, high-quality large-scale multicenter clinical studies and a further comparative study between itraconazole and propranolol are still needed to confirm its efficacy. In addition, considering the younger age of IH patients and the long therapeutic course of itraconazole (daily oral administration for more than 3 mo), other adverse effects, including bone growth inhibition, should be closely observed for a longer duration. Overall, more clinical and basic research regarding the effect of itraconazole on IHs are warranted.

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One-stage total hip arthroplasty for advanced hip tuberculosis combined with developmental dysplasia of the hip: A case report

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Author contributions: Zhu RT performed the surgery and wrote the manuscript; Shen LP performed the laboratory tests on the patient; Chen LL performed the pathological examination on the patient; Jin G followed up the patient and prepared the manuscript; Jiang HT contributed to the conception of the study.

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Abstract

BACKGROUND
A patient with advanced tuberculosis of the hip joint combined with Crowe type IV developmental dysplasia of the hip (DDH) and a drainage sinus is a rare condition. There are no previous reports of this condition, and it is a complex challenge for surgeons to develop a treatment scheme.

CASE SUMMARY
We report a 73-year-old male patient with severe hip pain and drainage sinus of the left hip for one month. Approximately 40 years ago, a drainage sinus occurred at the lateral left hip was healed at the local hospital with anti-infectious therapy. After the sinus healed, gradual pain occurred in the left hip for 40 years. Approximately one month prior, hip pain was sharply aggravated, and a drainage sinus reoccurred in the left hip. The X-ray and computed tomography examinations showed destruction of the head and neck of the left femur, as well as an
The results of \textit{Mycobacterium tuberculosis} antibody and Xpert were positive. Therefore, the patient was diagnosed with advanced TH combined with Crowe type IV DDH. After 22 d of treatment with anti-tuberculosis chemotherapy, the sinus healed, and the patient underwent one-stage total hip arthroplasty (THA) surgery consisting of debridement, osteotomy, and joint replacement. After surgery, the patient received anti-tuberculosis chemotherapy drugs for nine months, with no recurrent infection. After one year of follow-up, the Harris score of the patient increased from 21 pre-THA to 86.

**CONCLUSION**

Although drainage sinuses are a contraindication to one-stage THA, one-stage THA is still an effective and safe surgical method after the sinus heals.

**Key Words:** Advanced tuberculosis of the hip joint; Developmental dysplasia of the hip; Total hip arthroplasty; Drainage sinus; Anti-tuberculosis treatment; Case report

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**INTRODUCTION**

Tuberculosis of the hip joint (TH) is a severe osteoarticular tuberculosis and always results in cartilage and bone destruction, causing pain, deformity, shortening, and instability\cite{1}. In its early stages, symptoms and imaging changes are not typical, and the diagnosis is easily missed\cite{2}. When severe hip bone destruction occurs, TH has reached advanced stages\cite{1}. Total hip arthroplasty (THA) is always considered the preferred treatment option for advanced TH, which could provide a painless stable joint with normal gait and is generally divided into two-stage THA and one-stage THA\cite{3}. Although two-stage THA achieves satisfactory clinical efficacy for treating advanced TH\cite{4}, the second-step replacement surgery must be performed several months after debridement, leading to poor joint mobility (even stiffness) and muscle atrophy, increasing the difficulty of the whole treatment procedure\cite{5}. Therefore, surgeons prefer to choose one-stage THA that could attain satisfactory clinical efficacy and effectively shorten the treatment time\cite{6}, except for the presence of a drainage sinus, which is a contraindication to one-stage THA\cite{7}.

When the patient was admitted to our department for severe hip pain and a drainage sinus, we diagnosed advanced TH with Crowe type IV DDH of his left hip through a thorough examination. It was difficult for us to develop a suitable treatment scheme that could improve the function of the patient’s TH and prevent tuberculosis. Although the patient was not qualified for one-stage THA because of sinus drainage, the first step of radical debridement and cement spacer implantation could destroy the pseudarthrosis between the ilium ala and proximal femur. If so, the stability of the left hip would be destroyed, and the patient would have to be confined to bed for at least three months, which could be fatal for the senior patient because of the severe complic-
ations resulting from bed rest.

Unfortunately, there is no previous literature or report teaching us how to develop a suitable scheme. Considering the probable serious complications of two-stage THA and improving joint function, we finally decided to carry out a one-stage THA consisting of debridement, osteotomy, and THA. In this report, we introduced our treatment plan in detail and showed the complications and recovery conditions of the patient in total.

CASE PRESENTATION

Chief complaints
A 73-year-old male patient was admitted to our department for a drainage sinus at the lateral skin surface of the left hip combined with severe joint pain.

History of present illness
The sinus occurred lateral to the left hip 40 years ago and healed with anti-infective treatment and debridement at the local hospital. One month prior, the left hip pain was exacerbated and the sinus reoccurred. After ineffective anti-infective therapy (levofloxacin and ceftazidime) at the local hospital, the patient presented to our department.

History of past illness
The patient was diagnosed with tuberculosis more than 40 years ago and has been cured in a local hospital.

Personal and family history
The patient denied any other specific personal or family history of other disease.

Physical examination
The physical examination showed plenty of fresh granulation tissue in a drainage sinus (Figure 1A). The patient had severe hip pain and was unable to move actively or passively. The left lower limb was approximately 3 cm shorter than the right lower limb. The patient could walk on the ground with the help of a crutch by himself. The Harris score of the patient’s left hip was 21.

Laboratory examinations
At the time of admission, the erythrocyte sedimentation rate (ESR) was 49 mm/h, and the C-reactive protein (CRP) level was 12.12 mg/L. Although a Mycobacterium tuberculosis smear was negative, we diagnosed the patient with TH according to both positive Mycobacterium tuberculosis antibody and Xpert results.

Imaging examinations
The preoperative X-ray (Figure 2A) and computed tomography (Figure 2B and C) showed heavy destruction of the left femoral head and neck, pseudarthrosis between the proximal femur and iliac ala, and a smaller and more shallow original acetabulum. The preoperative magnetic resonance (Figure 2D and E) showed a slender localized sinus and no infective foci in the pelvic cavity.

FINAL DIAGNOSIS
The patient was eventually diagnosed with advanced tuberculosis of the hip combined with Crowe type IV developmental dysplasia of the hip.

TREATMENT
After undergoing anti-tuberculosis treatment (isoniazid, rifampin, pyrazinamide, and ethambutol) for 22 d, the sinus was almost healed (Figure 1B). Although a drainage sinus is a contraindication to THA, thinking of the healed sinus and difficulty of cement spacer placement in a severe hip malformation, we decided to carry out a one-stage THA on the patient.
Figure 1 Performance of the drainage sinus. A: There was plenty of fresh granulation tissue in a drainage sinus; B: After 22 d of anti-tuberculosis chemotherapy treatment, the sinus was almost healed.

At the beginning of the operation process, the sinus was excised entirely, and sinus tissue was obtained to investigate histological changes. The intraoperative rapid pathological diagnosis showed no apparent active infection (Figure 3A). The operating field revealed complete necrosis of the gluteus maximus and gluteus medius, disappearance of the left femoral head and neck, partial structural destruction of the iliac crest, and apparent upward movement of the proximal femur. The lesion tissue was entirely excised with bone forceps, and the destroyed bone of the proximal femur, except the more significant trochanter part, was released with a wire saw. After repeatedly washing the wound with iodophor, hydrogen peroxide, and saline, we changed the operating garment and sterile towel. Then, a subtrochanteric osteotomy was carried out to protect the sciatic nerve by lessening the leg lengthening. Finally, we chose a cementless prosthesis to complete the THA surgery. The postoperative X-ray showed that the prosthesis was in a good position (Figure 4A). The lesion tissue of the left hip was sent to for pathological examination postoperatively, and the result showed evident caseous necrosis (Figure 3B).

Postoperatively, the patient received anti-tuberculosis drugs (isoniazid, rifampicin, pyrazinamide, and ethambutol) and was asked to remain in bed for six weeks after the procedure. Unfortunately, six weeks after surgery, the patient fell when he was walking to the toilet and was sent to our hospital immediately. The X-ray showed periprosthetic fractures, no loss of the prosthesis, and no destruction of the proximal femur (Figure 4B). Therefore, we carried out reduction and internal fixation of the fracture with a plate and wire. During the surgery, there was no loss of the prosthesis or reactive tuberculosis in the surgical field. Three months after internal fixation, the X-ray of the left hip showed no recurrent bone destruction or prosthesis loss (Figure 4C and D).

After internal fixation surgery, the patient continually received anti-tuberculosis chemotherapy (isoniazid, rifampicin, pyrazinamide, and ethambutol) for nine months. Three months after internal fixation surgery, the patient could walk with a crutch, and six months after surgery, he was able to walk independently.

OUTCOME AND FOLLOW-UP

Eighty-nine days after one-stage THA, the ESR and CRP levels returned to normal, and the tests were negative three times in a row (Figure 5). At 1-year follow-up, the Harris score of the patient was 86.
DISCUSSION

This is the first report of a patient with advanced TH with Crowe type IV DDH, especially with a drainage sinus at the affected hip. It was a challenge for us to develop a suitable clinical treatment scheme, preventing tuberculosis recurrence and preserving the function of the joint. We developed a one-stage THA plan through a literature review, including perioperative anti-tuberculosis chemotherapy, intraoperative debridement, and THA. At one-year follow-up, the patient’s TH had good function, and the TH did not recur.

There are three treatment options for advanced TH: Excision arthroplasty, arthrodesis, and THA. Excision arthroplasty can offer a painless and mobile hip but finally results in hip instability and abnormal gait[8,9]. Arthrodesis offers a severely dysfunctional hip, back pain, and abnormal gait and is rarely chosen[10]. THA can provide a painless stable joint with normal gait and is generally divided into two forms: One-stage THA and two-stage THA. As a result of joint infectious disease, two-stage THA is the gold standard for treatment[4]. The first step involves radical debridement and implantation of the cement spacer. The second step is carried out after the infection is under control and involves additional debridement and implantation of the metal prosthesis. However, the second step must be performed...
several months after the first step, resulting in poor joint mobility (even stiffness) and muscle atrophy, increasing the difficulty of the whole treatment procedure[5].

The difference in pathogenic bacteria characteristics between pyogenic pathogens and tuberculosis bacilli creates the conditions for one-stage surgery. Bacteria covered by biofilms have strong resistance to antibiotics and host immune attacks, leading to severe surgical failure[11]. Contrary to common purulent pathogens, tuberculosis bacilli have unique biological characteristics, including slow growth, no adhesion to metal surfaces, and little biofilm formation[11-13]. Furthermore, one-stage surgery with metal implantation for active spinal tuberculosis has been successful[14]. Therefore, an increasing number of surgeons have applied one-stage THA to treat TH and have achieved satisfactory results[6].

In addition, it is not easy to carry out two-stage THA on Crowe type IV DDH[15-17]. After debridement of the affected TH, the pseudarthrosis between the proximal femur and ilium was destroyed, and implantation of an antibiotic-loaded cement spacer could not reconstruct the stability of the affected TH. This may lead to an extended stay in the bed and many complications for patients, such as deep venous thrombosis, myophagism, and pressure sores. Therefore, the one-stage THA method might be the best choice in patients with advanced TH combined with Crowe type IV DDH. However, many authors believe that a drainage sinus is a contraindication to one-stage THA, because the drainage sinus is often associated with a mixed infection of other common pyogenic pathogens[4,12,18]. In our report, although a drainage

Figure 3 Intraoperative rapid pathology and postoperative pathology. A: The intraoperative rapid pathological diagnosis showed no apparent active infection; B: The pathological examination of lesion tissue showed evident caseous necrosis.

Figure 4 Postoperative imaging findings. A: The postoperative X-ray showed that the prosthesis was in a good position; B: The X-ray showed periprosthetic fractures, no loss of the prostheses, and no destruction of the proximal femur; C and D: Three months after internal fixation, the X-ray of the left hip showed no recurrent bone destruction or prosthesis loss.
The trends of erythrocyte sedimentation rate and C-reactive protein level showed that erythrocyte sedimentation rate and C-reactive protein returned to normal after 89 d of anti-tuberculosis chemotherapy after one-stage total hip arthroplasty. In addition, the tests were negative three times in a row. ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein.

sinus was lateral to the left hip, when the sinus had healed and intraoperative rapid pathological examination showed no apparent active infection, we believed that it was safe and effective to carry out one-stage THA.

Moreover, regardless of the treatment method, it is essential that standard first-line anti-tuberculosis chemotherapy, including isoniazid, rifampicin, pyrazinamide, and ethambutol, be applied for every patient between 2 wk and 6 wk preoperatively and between 9 mo and 12 mo postoperatively [19,20]. Therefore, after the level of ESR and CRP returned to normal, the patient in our report continued to receive anti-tuberculosis chemotherapy until nine months after one-stage THA.

Finally, through our treatment, the patient could walk by himself six months after internal fixation surgery, and the levels of ESR and CRP returned to normal 89 d after one-stage THA. Meanwhile, the limitation of our study is obvious. First, because of the rarity of similar cases, only one case was too few to demonstrate the effectiveness of our treatment method. Second, the follow-up data in our study were only one year, and it could not prove the long-term effectiveness.

CONCLUSION

In our opinion, to reduce complications caused by bed rest and reduce mortality, one-stage THA is more suitable for patients with advanced TH combined with Crowe type IV DDH. Moreover, although the drainage sinus was a contraindication for one-stage THA, when the sinus had healed and intraoperative rapid pathological examination showed no apparent active infection, we believed it was safe and effective to carry out one-stage THA.

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CASE REPORT

Pneumocystis jirovecii and Legionella pneumophila coinfection in a patient with diffuse large B-cell lymphoma: A case report

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Author contributions: Li X and Pan HY designed the research study; Wu WH, Hui TC, and Wu QQ performed the research; Xu CA, Zhou ZW, and Wang SH contributed new reagents and analytic tools; Yin QQ analysed the data; and Wu WH wrote the manuscript; all authors have read and approved the final manuscript.

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Abstract

BACKGROUND

Diffuse large B-cell lymphoma (DLBCL) is a common non-Hodgkin's lymphoma. R-CHOP is a protocol for long-term chemotherapy for DLBCL patients. Long-term chemotherapy can lead to low immunity and increase the risk of opportunistic pathogen infections in immunocompromised patients.

CASE SUMMARY

We report a case of coinfection with Pneumocystis jirovecii (P. jirovecii) and Legionella pneumophila (L. pneumophila) in a patient with DLBCL. The patient was a 40-year-old female who was diagnosed with DLBCL and was admitted due to pulmonary infection. P. jirovecii and L. pneumophila were detected in her bronchoalveolar lavage fluid by hexamine silver staining, isothermal amplification and metagenomic sequencing.

CONCLUSION

To the best of our knowledge, this is the first case of P. jirovecii and L. pneumophila coinfection found in a DLBCL patient. Clinicians should be aware of the risk of complicated infection in patients undergoing long-term chemotherapy.

Key Words: Legionella pneumophila; Pneumocystis jirovecii; Next-generation sequencing; Diffuse large B-cell lymphoma; Case report
revised according to the CARE Checklist (2016).

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**Core Tip:** Coinfection of Pneumocystis and Legionella is very rare. This is the first case of such infection in a patient with diffuse large B cell lymphoma. This case is significant for the detection of pathogens and the diagnosis and treatment of related diseases.

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**INTRODUCTION**

Diffuse large B-cell lymphoma (DLBCL) is a common type of non-Hodgkin’s lymphoma. R-CHOP is a protocol for long-term chemotherapy for DLBCL patients[1]. The common complications of R-CHOP include febrile neutropenia, neutropenia, thrombocytopenia, cardiotoxicity, peripheral neuropathy and so on. Long-term chemotherapy can also reduce the immunity of patients, which increases the possibility of the development of complex infections that are difficult to treat[2]. A variety of pathogenic microorganisms, such as bacteria, fungi and viruses, may cause infection in these patients. Immunocompromised populations are susceptible to *Legionella* and *Pneumocystis* infection, but *Pneumocystis* and *Legionella* coinfection in a patient is extremely rare. To date, only two studies have reported coinfection caused by *Pneumocystis* and *Legionella* in patients. Concurrent infection with *Pneumocystis* and *Legionella* was reported in a patient with adult T cell leukaemia in Japan[3]. *Pneumocystis* and *Legionella* coinfection was also reported in an infant with infantile spasms in Israel[4]. It is a major challenge for clinicians to correctly diagnose and treat diseases caused by coinfection with these two pathogens. Here, we report for the first time a case of severe pneumonia caused by *Pneumocystis jirovecii* (*P. jirovecii*) and *Legionella pneumophila* (*L. pneumophila*) coinfection in a patient with DLBCL.

**CASE PRESENTATION**

**Chief complaints**
The patient was a 40-year-old female who presented with high fever six months prior to admission.

**History of present illness**
Her medical history was notable for DLBCL. After two R-CHOP treatments, the patient still had symptoms of fever.

**History of past illness**
The patient was diagnosed with DLBCL in a local hospital two months before admission.

**Personal and family history**
She was treated with the R-CHOP regimen (rituximab 600 mg day 0 +, cyclophosphamide 1.1 g day 1 +, doxorubicin 40 mg day 1 +, vincristine 4 mg day 1+ and prednisone 100 mg days 1-5) for two cycles.

**Physical examination**
The body temperature was 37.8 °C, the blood pressure was 162/104 mmHg, the pulse was regular at 147 beats per minute (bpm), and the respiratory rate was 28 breaths/min. The patient had shortness of breath, and moist rales could be heard in both lungs.
Laboratory examinations

Laboratory tests showed a white blood cell count of $7.17 \times 10^9/L$, red blood cell count of $2.86 \times 10^12/L$, haemoglobin level of 95 g/L, platelet count of $403 \times 10^9/L$, and C-reactive protein (CRP) level of 277.6 mg/L. Bone marrow cytology showed that the proliferation of nucleated cells in the bone marrow was obviously active, and the proportion of granulocyte red cells was inverted. Lymphoid malignant tumour cells accounted for 22.5% of the total cells. Bone marrow immunohistochemistry showed that the patient was CD20 (+) and TDT (-).

After anti-infective treatment, the body temperature was 36.5 °C, oxygen saturation was 91.3%, white blood cell count was $12.32 \times 10^9/L$, lymphocyte classification was 1.0%, monocyte classification was 1.0%, neutrophil classification was 97.0% and CRP level was 79.0 mg/L.

For comparison, the normal values are as follows: the white blood cell count is 4.0-10.0 $\times 10^9/L$, red blood cell count is 3.5-5.0 $\times 10^{12}/L$, haemoglobin level is 110 g/L, platelet count is 100-300 $\times 10^9/L$, CRP level is 0-10 mg/L, lymphocyte classification is 20%-30%, monocyte classification is 3%-8% and neutrophil classification is 50%-70%.

Imaging examinations

Chest computed tomography (CT) indicated multiple consolidation shadows and plaques in both lungs, and pulmonary oedema with inflammation was considered (Figure 1). After anti-infective treatment, chest CT showed that the consolidation of the lung disappeared slightly (Figure 2).

Microbiology examinations

Pneumocystis was found in the patient’s bronchoalveolar lavage fluid by hexamine silver staining (Figure 3). The patient’s bronchoalveolar lavage fluid was sent to a third-party medical laboratory for next-generation sequencing because the present laboratory does not routinely carry out the molecular detection of pathogens. Sequence results showed that another pathogen, L. pneumophila, was also present in the patient’s bronchoalveolar lavage fluid. The previous diagnosis of P. jirovecii infection was also verified (Table 1). To verify the results of metagenome sequencing, Legionella culture and isothermal chip amplification were used to identify Legionella and Pneumocystis (Figure 4). After four days of bacterial culture, L. pneumophila grew on BCYE medium and was identified by the MALDI-TOF MS system (Figure 5).

FINAL DIAGNOSIS

P. jirovecii and L. pneumophila coinfection with DLBCL.

TREATMENT

The patient was given imipenem 1 g q6h+, tigecycline 100 mg q12h+, and carprofen 5 mg qd for empirical anti-infective therapy. After the pathogens were identified as P. jirovecii and L. pneumophila, intravenous injection of 100 mL of levofloxacin was added to the treatment regimen, and compound sulfamethoxazole tablets (0.96 g q6h) were given orally. Since the patient’s blood oxygen saturation fluctuated between 40% and 90%, she was given an endotracheal intubation ventilator to assist in breathing.

OUTCOME AND FOLLOW-UP

The patient’s condition improved after anti-infective treatment. However, the patient developed septic shock, considered to be a result of poor health status. B-ultrasound showed that her pancreas was enlarged with echo changes, which was considered drug-induced pancreatitis caused by long-term immunosuppression and the use of large-dose antibiotics. After one month of treatment in the intensive care unit, the patient finally died.
Table 1 Results of next-generation sequencing: Pneumocystis jirovecii and Legionella pneumophila were detected from patient’s bronchoalveolar lavage fluid

<table>
<thead>
<tr>
<th>Types of pathogens</th>
<th>Number of sequences</th>
<th>Relative abundance</th>
</tr>
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<tbody>
<tr>
<td>Legionella pneumophila</td>
<td>363</td>
<td>64.82%</td>
</tr>
<tr>
<td>Pneumocystis jirovecii</td>
<td>4758</td>
<td>99.69%</td>
</tr>
</tbody>
</table>

Figure 1 Chest computed tomography indicated multiple consolidation shadows and plaques in both lungs, and pulmonary edema with inflammation was considered.

DISCUSSION

In this case, the patient suffered from diffuse large B-cell lymphoma. During long-term chemotherapy, the patient's immunity declined seriously, resulting in a complex infection. Through traditional staining and culture techniques combined with molecular diagnostic techniques, the pathogens responsible for the infection were finally identified as P. jirovecii and L. pneumophila.

Pneumocystis is a relatively primitive fungus in Ascomycota. Pneumocystidomycetes has only one order, one family and one genus. First discovered in the early 20th century, Pneumocystis lives in the lungs of humans and mammals. The first species identified was P. caterinii, thought to be a protozoan found in the lungs of mice. It was later found that P. jirovecii, which resides in human lungs, could cause Pneumocystis pneumonia in humans. Pneumocystis pneumonia is the most common disease in people with AIDS and in those with weakened immune systems[5]. Bronchoalveolar lavage fluid smear microscopy is the gold standard for the diagnosis of Pneumocystis pneumonia. At present, empirical medicine has a great influence on the detection of Pneumocystis by hexamine silver staining. It is easy for Pneumocystis to be missed during detection in clinical laboratories after empirical therapy. In the present study, we found very few cases of Pneumocystis by microscopy after empirical treatment was performed. Compared with microscopy, molecular detection is a more efficient...
method for the diagnosis of Pneumocystis pneumonia. We further confirmed the presence of *P. jirovecii* in this patient by next-generation sequencing and isothermal chip amplification.

*Legionella* is a genus of gram-negative bacteria, and the most common and most virulent species in this genus is *L. pneumophila*, which was first discovered in 1976. *Legionella* spp. are mainly found in sewage and in the soil. *Legionella* spreads through the air and can lead to severe lung infections accompanied by systemic damage. Approximately 5%-15% of patients with severe pneumonia have an *L. pneumophila* infection[6]. Bacterial culture, urinary antigen detection and targeted PCR are common methods for *Legionella* detection. In China, the use of *Legionella* urinary antigen is limited, while targeted PCR is not available in most hospital laboratories. Bacterial culture, although effective, requires at least 72 h of culture time and may delay the treatment of critically ill patients. In this case, the presence of *Pneumocystis* was confirmed by hexamine silver staining. However, after anti-infection treatment, the patient still had lung symptoms. To further exclude other pathogenic bacterial infections, next-generation sequencing was performed. Notably, the results of next-generation sequencing confirmed coinfection caused by *Pneumocystis* and *Legionella*.

Sanger sequencing is considered to be a first-generation gene sequencing technology. A series of sequencing technologies developed since 2004 are known as next-generation sequencing technologies[7]. Next-generation sequencing can quickly provide a large amount of gene sequence data, which can be used to quickly sequence the whole genome, enabling broad identification of known and unexpected pathogens or even the discovery of new organisms[8]. Due to the lack of a unified standard, next-generation sequencing has not yet become a clinically recommended diagnostic technique. However, we can still use this method to aid disease prevention and diagnosis. Next-generation sequencing has played an important role in the early detection and prevention of infectious diseases. In 2011, there was an outbreak of haemorrhagic intestinal infection in Europe. Through genome sequencing, the

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**Figure 2** After anti-infection treatment, the consolidation of the lung disappeared slightly.
Wu WH et al. *P. jirovecii* and *L. pneumophila* coinfection

**Figure 3** *Pneumocystis* was found in the patient's bronchoalveolar lavage fluid by hexamine silver staining.

**Figure 4** Isothermal chip amplification were used to verify *Legionella* and *Pneumocystis*.

pathogen was identified as *Escherichia coli* O104:H4, and its pathogenesis and transmission mechanisms were deduced through sequence analysis, which provided an important basis for clinical diagnosis and treatment[9]. In this case, we used metagenomic next-generation sequencing (mNGS) to detect pathogens. The sequencing platform was Illumina NextSeq 550, and the sequencing strategy was SE75. mNGS is a technology that does not rely on microbial culture, directly extracts nucleic acids from clinical samples for pathogen detection, and can provide results within 36 h. The Illumina NextSeq 500 sequencing platform uses the SE75 sequencing strategy and can provide 400 M high-quality reads within 11 h. A total of 13832333 DNA sequences (13.8 M reads, each 75 bp in length) were obtained, and 37984 sequences were obtained after removing the sequences derived from humans. The pathogenic microorganism database is a nonpublic database organized by the laboratory. The results showed that the number of sequences from *P. jirovecii* was 4758, and the relative abundance was 99.69%. The number of sequences from *L. pneumophila* was 363, and the relative abundance was 64.82%.

**CONCLUSION**

Our case is notable for several reasons. First, this is the first case report of *P. jirovecii* and *L. pneumophila* coinfection in a DLBCL patient. Second, this case reminds us to be aware of the possibility of mixed infection in immunosuppressed patients. Finally,
next-generation sequencing has an important role in the diagnosis and treatment of mixed infections in immunodeficient patients. When the commonly used test methods cannot identify the causative pathogen of infections, next-generation sequencing can help clinicians save the lives of critically ill patients in a timely manner.

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Delayed massive cerebral infarction after perioperative period of anterior cervical discectomy and fusion: A case report

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Abstract

BACKGROUND
Cerebral infarction is an extremely rare postoperative complication of anterior cervical discectomy and fusion (ACDF), particularly in the delayed setting. We present a case who had a sudden stroke on day 18 after surgery. By sharing our experience with this case, we hope to provide new information about stroke after anterior cervical surgery.

CASE SUMMARY
We present the case of a 61-year-old man with more than 20 years of hypertension and 14 years of coronary heart disease who had suffered a stroke 11 years ago. The patient was admitted for a multiple ACDF due to symptoms of cervical spondylotic myelopathy and had a sudden stroke on day 18 after surgery. Imaging findings showed a large-area infarct of his left cerebral hemisphere and thrombosis in his left common carotid artery. With the consent of his family, the thrombus was removed and a vascular stent was implanted through an interventional operation. Forty days later, the patient was transferred to a rehabilitation hospital for further treatment. He had normal consciousness but slurred speech at the 1-year follow-up evaluation. The motor and sensory functions of his hemiplegic limbs partially recovered.

CONCLUSION
This case illustrated that a postoperative stroke related to anterior cervical surgery may be attributed to prolonged carotid retraction and might have a long silent period. Preventive measures include careful preoperative and postoperative examination for high-risk patients as well as gentle and intermittent retraction of carotid artery sheath during operation.

Key Words: Anterior cervical discectomy and fusion; Cerebral infarction; Carotid artery; Postoperative complication; Case report
Anterior cervical discectomy and fusion (ACDF) is an important surgical option in the treatment of cervical degenerative disease, which has a good clinical efficacy and safety with a low incidence of complications[1]. However, since the anterior cervical approach requires intraoperative retraction of carotid artery sheath to expose adequate surgical field, it may affect the hemodynamics of carotid artery and even cause some serious complications in atherosclerotics[2]. In fact, the references from the academic search were limited and insufficient to explain the incidence and timing of cerebral infarction after ACDF. There are only three previous case reports on postoperative cerebral infarction related to cervical spine surgery. Two reports showed cases of stroke occurring immediately after surgery, and the remaining one reported the occurrence at postoperative day 3[3-5]. There has been no report about delayed cerebral infarction occurring after the whole perioperative period of an ACDF.

Herein, we report a case who had a sudden stroke on day 18 after a multilevel ACDF. To the best of our knowledge, this is the first case of massive brain infarction reported after a whole perioperative period. We remind surgeons of this causal relationship segmented by time intervals, discuss the etiology of this rare entity, and report notes on the management.

CASE PRESENTATION

Chief complaints
A 61-year-old man was sent to the emergency room (ER) due to aphasia and right limb dyskinesia when he was doing exercises at home in the early morning.

History of present illness
Eighty days ago, the patient sought treatment for a chief complaint of discomfort in the neck and shoulders accompanied with weakness of both upper and lower limbs. The symptoms did not relieve after a full rest. On physical examination, no obvious tenderness but dysfunction of flexion was found in his neck. Pain and hypoesthesia were found in C4, C5, and C6 dermatomes. The muscle strength of scapula stabilization, shoulder abduction, elbow flexion and extension, wrist flexion and extension, were all grade 3 according to the ASIA Grading System. Bilateral Hoffmann’s sign was positive and knee tendon reflex was hyperactive. No significant abnormal findings were noted in blood tests. Magnetic resonance imaging (MRI) showed herniated C3-7 discs and hypertrophy of the ligamentum flavum at the C3-6 levels with a wasp-waisted spinal cord (Figure 1A and B). No preoperative vascular examination of the head and neck was performed because it was not a routine item. As a patient with cervical spondylotic myelopathy, he was hospitalized for cervical spine surgery. A multilevel ACDF was performed at the C3-4, C4-5, and C5-6 segments.
During operation, the patient lied in supine position with cervical mild extension, then a left anterior transverse incision at the level of thyroid cartilage was made. After adequate exposure, responsible segments were confirmed with C-arm X-ray images and discectomy was performed with curets and rongeurs. Appropriate cages were implanted into the corresponding disc spaces after sufficient decompression and an anterior cervical plate system was applied. Anterior retraction system was used constantly during the operation. The retractors (self-retaining retractors, WEGO, China) were not always stable at their positions and were adjusted three times. No neurophysiological monitoring techniques were used. Blood pressure, heart rate, and other vital signs were stable during the operation. The operating time was 2 h and the blood loss was about 200 mL.

Postoperatively, the rehabilitation process was satisfactory and the patient was free of complaints about cervical discomfort, but his muscle strength did not recover significantly. The Japanese Orthopaedic Association (JOA) score increased from 8 to 13. Radiographs showed a good cervical curvature and well-positioned internal fixations (Figure 1C and D). No complications developed during his hospital stay. Antihypertensive drugs, aspirin, and low molecular weight heparin were given regularly from the second day after surgery.

At postoperative day 18, when the patient was exercising at home in the early morning, he suddenly developed aphasia, deviated mouth, weakness of the right limbs, urinary incontinence, and unresponsiveness without obvious inducement. There was no headache, dizziness, cough, unconsciousness, or convulsion. Then he was rushed to the emergency room.

**History of past illness**

The patient had more than 20 years of hypertension while the blood pressure was said to be stable (130-140 mmHg/70-90 mmHg) for years. Besides, he had a 14-year history of coronary heart disease and underwent coronary stent implantation 13 years ago. He took aspirin tablets regularly and was ranked in New York Heart Association (NYHA) class I. The patient had also suffered a cerebral stroke 11 years ago but did not have obvious residual sequelae. Aspirin was stopped after his initial admission.

**Personal and family history**

The patient denied any other relevant personal or family history.

**Physical examination**

The patient was urgently sent to the ER for evaluation and was found to have a score of 15 on the NIH Stroke Scale. His left internal carotid pulse became weak and a vascular murmur was audible on auscultation. His blood pressure was 160/100 mmHg and speech was slurred. He was conscious but unresponsive. The right nasolabial fold was shallow and the tongue was deviated to the right on extension. The muscle strength of the right limbs decreased significantly, accompanied by superficial hypoesthesia. Hypertonia appeared on his right side. Bilateral Kernig’s sign, Brudzinski’s sign, and Babinski’s sign were all negative.
**Laboratory examinations**
During the ER treatment period, his counts of white blood cells, red blood cells, and platelets as well as the level of blood glucose were normal. The serum test results were: Homocysteine, 15.65 μmol/L; triglycerides, 2.12 mmol/L; low-density lipoprotein, 4.23 mmol/L; and total cholesterol, 6.42 mmol/L. His D-dimer was 3.92 mg/L and fibrinogen was 4.24 g/L, which were higher than the reference range.

**Imaging examinations**
A brain computed tomography (CT) scan showed a diffuse low-density region in his left hemisphere with a periventricular high-density hemorrhage focus (Figure 2A). The patient's condition worsened over time, so a carotid angiography was performed, which showed severe stenosis at the initial segment of his left common carotid artery. The contrast agent could not pass through the stenotic site to the distal end (Figure 2B). The percentage of arteriostenosis was reported at 92% and thrombosis of the left common carotid artery was reported.

**FINAL DIAGNOSIS**
Based on the above findings, a diagnosis of common carotid artery thrombosis and a new left hemispheric infarct after cervical spine surgery was established.

**TREATMENT**
With the consent of his family, the thrombus was removed and a vascular stent was implanted with an emergency interventional operation.

**OUTCOME AND FOLLOW-UP**
Forty days later, the patient was transferred to a rehabilitation hospital for further treatment and exercise. He had normal consciousness but slurred speech at the 1-year follow-up evaluation. The motor and sensory functions of his hemiplegic limbs were partially restored.

**DISCUSSION**
We present a case of massive cerebral infarction that occurred 18 d after a multilevel ACDF. It is clear that he had several risk factors for cerebral infarction, including atherosclerotic lesion in the carotid artery, hypertension, coronary heart disease, and previous stroke history[6-9]. On the basis of these factors, discontinuation of aspirin, surgical stress, acute dehydration, and blood pressure fluctuation might collectively precipitate the carotid thrombosis[10,11]. According to the Essen-Stroke-Risk-Score (ESRS) system, the patient should be quantified as median risk (7/9) based on his preoperative status[8,12]. Theoretically, prolonged retraction of the atherosclerotic carotid artery would influence the stability of plaques or even damage the fibrous caps of atheromas, which eventually brought about serious cerebrovascular accidents[13-15]. This is an obvious defect of a long-standing anterior cervical spine surgery. Retraction could also cause changes in carotid artery hemodynamics by reducing cross-sectional area of local vessels but increasing turbulent blood flow[2]. Coupled with perioperative hypercoagulability, all three factors of Virchow were present on one patient and caused the carotid thrombosis[16]. Therefore, we thought that gentle manipulation and intermittent relaxation of retraction should be given in surgery to avoid excessive mechanical stimulation on vessels.

According to the search results of Google Scholar, only three case reports of acute cerebral infarction following cervical spine surgery have been published[3-5]. Afana et al[3] deemed that intraoperative surgical manipulation, hypotensive anesthesia, and prolonged neck hyperextension might contribute to their patients’ stroke. Graffeo et al [5] expressed similar sentiments and speculated that the true incidence of cerebral ischemia might be underestimated by current reports, particularly in the delayed
Figure 2 Representative images of the patient after an episode of cerebral infarction. A: Axial computed tomography image showing a massive low-density region in the left hemisphere and a high-density focus beside the left ventricle, indicating that a large-area ischemic cerebral infarct occurred with a focal hemorrhagic cerebral infarct; B: Carotid angiography showed that the right common carotid was present (arrow) but the left common carotid artery was invisible, indicating that the vascular occlusion was at the initial segment of the left common carotid artery.

setting. Perhaps that was the fact - to the best of our knowledge, this is the first report of cerebral infarction occurring 2 wk after a cervical spine surgery. It cannot be concluded with certainty that the cerebral infarction was due to mechanical stimulation during the operation, but available evidence tended to prove the point. The angiographic images showed that the thrombus was at the initial segment of the patient’s left common carotid artery, which was exactly the site of intraoperative retraction. It was not the common multiple lacunar infarcts that caused the stroke in this patient but a massive infarct of the left hemisphere. In addition, the case illustrated that a stroke related to anterior cervical spine surgery might have a long silent period during which a carotid thrombus had formed. Patients were at high risk of strokes with few symptoms in this stage and blood pressure fluctuation might play the role of trigger. Besides, the rise of blood pressure could also lead to hemorrhagic strokes with severe symptoms equally[17].

Several studies have shown that aspirin should not be suspended before surgery in patients who have been taking aspirin for a long time, because aspirin has no significant effect on intraoperative and postoperative bleeding[18,19]. Perioperative discontinuation of aspirin may affect coagulation status, thereby increasing the incidence of cardiovascular and cerebrovascular accidents, especially in patients with previous coronary heart diseases or strokes[20]. Perioperative use of anticoagulants such as low molecular weight heparin may also be useful in preventing serious complications[21]. In addition, lipid-lowering drugs can stabilize atheromatous plaques and limit the formation and expansion of thrombosis[22,23]. Preoperative coagulation tests are valuable in evaluating the coagulation status of patients. Adequate preoperative risk assessment and examination can help identify risk factors for stroke and screen out patients with atherosclerosis. Carotid, transcranial, and cardiac Doppler ultrasound should be performed in high-risk patients before cervical spine surgery to assess the condition of their vessels and the possibility of stroke[24]. If it is clear that there exists severe atherosclerosis unilaterally, an incision from the contralateral side or the feasibility of posterior approach should be considered.

The case has certain warning significance on the postoperative course. The use of antihypertensive agents, lipid-lowering drugs, and anticoagulants should be promptly resumed after surgery[7,21-23]. For patients with definite carotid atherosclerosis, carotid ultrasound can be repeated after surgery to determine the presence of thrombus. For high-risk patients with dizziness, headache, or nausea after surgery, relevant examinations should be performed to exclude cerebral ischemia or infarction. Once it is clear that a patient has carotid thrombosis, aggressive interventions such as thrombectomy or thrombolytic therapy should be used to avoid the occurrence of subsequent stroke with poor clinical outcome[25,26].

**CONCLUSION**

This case illustrated that a postoperative stroke related to anterior cervical surgery
may be attributed to prolonged carotid retraction and might have a long silent period during which a carotid thrombus had formed at the surgical site. Preventive measures include careful preoperative and postoperative examination for high-risk patients as well as gentle and intermittent retraction of carotid artery sheath during surgery.

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Cortical bone trajectory fixation in cemented vertebrae in lumbar degenerative disease: A case report

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Abstract

BACKGROUND
Percutaneous vertebroplasty (PVP) has been widely used in osteoporotic vertebral compression fracture (OVCF). Following surgery, the bone cement would be positioned permanently. However, in some cases of lumbar degenerative disease, the cemented vertebrae needs to be fixed after decompression and fusion procedure. It is difficult to implant traditional pedicle screws into the cemented vertebrae because of the bone cement filling. At present, the main treatment strategy is to skip the cemented vertebra and conduct a long segment fixation. This article presents a cortical bone trajectory (CBT) fixation technique for cemented vertebrae.

CASE SUMMARY
PVP involving the L3 and L4 was performed in an 82-year-old man due to OVCF. During the surgery, bone cement leakage occurred, resulting in compression of the root of the right L3 nerve. We performed a partial facetectomy to retrieve the leaked bone cement and to relieve the patient’s neurological symptoms. After 3 mo, the patient developed lumbar disc herniation in L3/4, potentially due to instability caused by the previous surgery. Therefore, it was necessary to perform intervertebral fusion and fixation. It was difficult to implant traditional trajectory pedicle screws in L3 and L4 because of the bone cement filling. Hence, we implanted CBT screws in the L3 and L4 vertebrae. As a result, the patient’s symptoms resolved and he reported satisfaction with the surgery at follow-up after 8 mo.

CONCLUSION
It is feasible to utilize CBT in cemented vertebrae for the treatment of lumbar degenerative disease.

Key Words: Cortical bone trajectory; Cemented vertebrae; Lumbar degenerative disease; Spinal fixation; Bone cement leakage; Case report
Core Tip: It is difficult to implant traditional trajectory (TT) pedicle screws in the cemented vertebrae. Cortical bone trajectory (CBT) may be a feasible method because of short implantation depth and location at the rear of the vertebrae. We successfully implanted CBT screws in the cemented vertebrae. The application of CBT provides a new method for the fixation of the cemented vertebrae and expands the indication for CBT. Meanwhile, we used two tips to decrease the rod curvature and simplify assembly in the hybrid screw technique for which CBT and TT were used in the same set.

INTRODUCTION

Percutaneous vertebroplasty (PVP) has been widely applied for the treatment of osteoporotic vertebral compression fracture (OVCF)[1]. Polymethylmethacrylate (PMMA) is used as the bone cement, which is permanently implanted into the vertebral body[2]. However, several elderly patients have concomitant lumbar degenerative disease and severe osteoporosis[3,4]. In such patients, we prefer to perform a minimally invasive PVP if they experience OVCF. Subsequently, several patients may require decompression and fixation if there is a deterioration in lumbar degenerative disease. However, it is difficult to utilize traditional trajectory (TT) screws to fix the cemented vertebrae because of the bone cement filling. At present, the main treatment strategy is to skip the cemented vertebra and conduct a long segment fixation, which may not provide sufficient stability, especially for successive vertebrae.

Herein, we report the case of a patient with lumbar disc herniation who underwent PVP of two successive vertebrae. During the surgery, bone cement leakage occurred, and open decompression was performed to remove the leaked bone cement. After 3 mo, lumbar disc herniation occurred at the decompressed segment, and a cortical bone trajectory (CBT) pedicle screw was used to fix the cemented vertebrae.

CASE PRESENTATION

Chief complaints

An 82-year-old man complained of serious backache accompanied by radiating pain to the right lower extremity.

History of present illness

The patient presented to a local hospital for acute exacerbation of chronic lower back pain 3 mo ago. Magnetic resonance imaging (MRI) revealed a high signal area in T2-weighted images of the vertebral bodies of L3 and L4, with the L2/3 presenting corresponding segment canal stenosis (Figure 1). However, the patient did not exhibit any obvious lower extremity neurological symptoms. Therefore, PVP was performed based on the diagnosis of OVCF (L3, L4). Unfortunately, bone cement leakage occurred during the surgery, which led to severe neurological symptoms. Computed tomography (CT) revealed that the right intervertebral foramen of L3/4 had a high density shadow (Figure 2). Leaked bone cement compressed the root of the L3 nerve, which caused a stabbing pain radiating to the skin of the anterior-lateral thigh. A local surgeon administered an epidural steroid injection that can temporarily alleviate neurological symptoms. However, after 2 d, the patient’s pain recurred and was unbearable. The patient was transferred to our hospital and complained of lower back pain accompanied by radiating pain in the right thigh. The patient was maintained in bedridden status because even light activity resulted in unbearable pain. We therefore performed a partial facetectomy to retrieve the leaked bone cement using a posterior approach. Following this procedure, the neurological symptoms completely resolved.
although slight backache persisted. The patient was subsequently discharged from the hospital.

After 3 mo, the patient experienced serious backache accompanied by radiating pain to the right lower extremity and revisited our hospital. The radiating pain was mainly located from the back of the thigh to the inner side of the shin. The visual analog scale score was 8.

**History of past illness**

The patient had a previous diagnosis of high blood pressure and coronary heart disease.

**Personal and family history**

The patient had been drinking for about 20 years, intaking about 200 mg per day. He had no history of smoking and no significant family history.
Physical examination
Numbness and hypoesthesia at the medial lateral of the right shin skin, and the muscle strength of the dorsiflexion ankle decreased to level 4. A positive Lasègue’s sign on the right lower extremity was noted. Bilateral patellar and Achilles tendon reflex could not be evoked. Perianal sensation and anal sphincter muscle strength were normal. Babinski sign was negative.

Laboratory examinations
Troponin-T and N-terminal pro-brain natriuretic peptide were normal. Arterial blood gas analysis revealed partial pressure of blood oxygen was 81.7 mmHg.

Imaging examinations
MRI revealed a right lumbar disc protrusion located at L3/4 and spinal canal stenosis at L2/3 (Figure 3).

FINAL DIAGNOSIS
This patient was diagnosed with lumbar disc herniation (L3/4) which compressed the root of the L4 nerve.

TREATMENT
Since sciatica was the patient’s main symptom, discectomy and nerve root decompression were the principal objectives to alleviate acute pain. Moreover, considering the potential spinal instability caused by the previous decompression, performing intervertebral fusion and fixation to ensure long-term surgery efficacy was inevitable.

The surgery scheme was designed to include discectomy, intervertebral fusion, pedicle screw fixation, and a topping-off strategy. It was difficult to implant TT pedicle screws into L3 and L4 because of the bone cement filling. We therefore applied CBT screws to fix the cemented vertebrae. The entry point was set in the lateral point of the pars interarticularis. The angle projected from 5-o’clock to 11-o’clock in the left pedicle and from 7-o’clock to 1-o’clock in the right pedicle (Figure 4). The right isthmus of the L4 Lamina had an iatrogenic defect from the previous surgery, so it was not suitable for implantation of the pedicle screw. Subsequently, TT screws were implanted into L2 and L5. Furthermore, considering the fusion of multiple segments in the lumbar spine, an interspinous stabilization device was placed between L1 and L2 to avoid adjacent segment disease (ASD).

OUTCOME AND FOLLOW-UP
After surgery, the symptom of the right lower extremity radiating pain immediately resolved. On postoperative day 5, the patient left the bed and walked around the room with the use of a waist brace. At 8 mo after surgery, the patient could take care of himself without assistance, and reported satisfaction with the surgery at the outpatient clinic follow-up. The CT reconstruction images are shown in Figure 5. No related complications occurred.

DISCUSSION
PVP has been an effective measure for the treatment of OVCF[1]. PVP has been widely used in clinical practice since it immediately enhances vertebral stability and quickly relieves pain. The most common filling material is PMMA cement, which rapidly solidifies after being injected into the vertebrae and remains in the body permanently without degradation[2]. In many cases, people who experienced PVP also have concomitant lumbar degenerative disease[3]. Subsequently, several patients may need surgery for further decompression and fixation owing to severe degeneration. However, it is challenging to fix the cemented vertebrae due to the bone cement filling. Moreover, long segment instrumentation in the method of skipping the cemented vertebrae, especially for successive vertebrae, cannot achieve the lumbar stability of...
internal fixation. In addition, elderly patients with osteoporosis may have comorbid conditions and be intolerant of major surgeries. Therefore, choosing a suitable fixation method is crucial.

We therefore applied CBT screws to fix the cemented vertebrae. Santoni first reported the application and related biomechanical study of CBT in 2009[6]. CBT was initially designed for improving the fixation strength in patients with osteoporosis. Compared to the TT screw, the implantation of the CBT screw does not require exposure of the facet joint and is minimally invasive. Therefore, less dissection and an inferior entry point expanded the indications of CBT[7,8]. Moreover, CBT is also used in revision patients with ASD and can be considered as a rescue technique using TT screws[9,10]. Pacione reported on an 83-year-old female diagnosed with L4 OVCF and lumbar spinal stenosis (L3/4) who was treated with PVP (L4) and decompression (L3/4). CBT screws were applied in L3 and L5 for spinal stability. After 3 mo, the patient experienced an adjacent segment fracture in L3 and underwent PVP with a common procedure negating impediment of CBT[11]. Shi published the application of CBT in spinal tuberculosis in which CBT screws were implanted in diseased vertebrae to strengthen the stabilization and reduce instrumented segments. The method is suitable for diseased vertebrae fixation because of the short implantation depth and location at the rear of the vertebrae[12].

The internal fixation stabilization is essential for spine fusion in osteoporosis patients. It has been reported that CBT improved the pullout strength by 30% and the insertional torque was 1.7 times higher than that of the TT screw[6,13]. Moreover,
Figure 5 Morphology and location of implants from three-dimensional reconstruction images. A: Anteroposterior image; B: Lateral image.

double fixation can also increase instrumentation stability in osteoporosis patients. Ueno reported on a 64-year-old female with severe osteoporosis who underwent spinal fixation and fusion using two sets of screw systems (CBT and TT) to enhance stability; every pedicle was implanted with two different screws.[14]

In our case, an interspinous stabilization device was used to prevent ASD after multiple lumbar spine fusion (topping-off). The increasing activity in the adjacent segment due to fusion of distal segments would lead to further disc degeneration. Therefore, an interspinous stabilization device, which limits the range of the adjacent segment and reduces the disc stress, can effectively decrease the incidence of ASD.[15, 16]

In the present case, we applied a hybrid screw technique in which CBT and TT were used in the same set. The placement of a rod could be difficult because the entry points are located in different sagittal planes. Therefore, we used two tips to decrease the rod curvature and simplify assembly. First, the CBT screws should be implanted in successive vertebrae in the hybrid screw technique. Second, the entry points in the region of the junction of the TT and CBT should be adjusted in the controllable area. In our patient, for example, the TT screw implantation in L5 can be downward and the CBT screw in L4 can be upward in the normal range. Therefore, it is feasible to reduce the curvature of the rod at the junction of the TT and CBT. However, not all cemented vertebrae can be fixed using CBT, particularly for the cement existing in the pedicle. Therefore, it is necessary to perform preoperative CT to evaluate and program the screw implantation trajectory. The limitations of this study were the limited number of cases and the short follow-up time. In the future study, more patients should be included and a longer follow-up time should be applied.

CONCLUSION

It is feasible to utilize CBT in cemented vertebrae in the treatment of lumbar degenerative disease. The application of CBT provides a new method for the fixation of the cemented vertebrae and expands the indication for CBT.

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Primary intramedullary melanocytoma presenting with lower limbs, defecation, and erectile dysfunction: A case report and review of the literature

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Abstract

BACKGROUND
Primary intramedullary melanocytoma is an exceedingly rare type of primary melanocytic tumor in the central nervous system. Unfortunately, primary intramedullary melanocytoma lacks specificity in clinical symptoms and imaging features and there is currently no standard strategy for diagnosis or treatment.

CASE SUMMARY
A 52-year-old male patient suffered from weakness and numbness involving the bilateral lower limbs for 18 mo, and defecation and erectile dysfunction for 6 mo. Furthermore, these symptoms started to worsen for the last 3 mo. Preoperative magnetic resonance imaging (MRI) revealed an intramedullary tumor located at the T9-T10 level. In subsequently surgery, the maximal safe resection extent approached to 98%. The lesion was confirmed to be melanocytoma by pathological examination. In addition, the possibility of original melanocytoma outside the spinal cord was excluded after the examination of the whole body. Therefore, a diagnosis of primary intramedullary melanocytoma was established. The patient refused to accept radiotherapy or Gamma Knife, but MRI examination on July 28, 2020 showed no sign of development. In addition, on April 10, 2021, the recent review showed that the disorder of defecation and lower limbs improved further but erectile dysfunction benefited a little from the surgery.
CONCLUSION
After diagnosing intramedullary melanocytoma by postoperative pathology, the inspection of the whole body contributed to excluding the possibility of metastasis from other regions and further suggested a diagnosis of primary intramedullary melanocytoma. Complete resection, adjuvant radiation, and regular review are critical. In addition, maximal safe resection also benefits prognosis while the tumor is difficult to be resected totally.

Key Words: Primary intramedullary melanocytoma; Diagnosis; Treatment; Prognosis; Case report

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Core Tip: Primary intramedullary melanocytoma is an extremely rare kind of primary melanocytic tumor within the spinal cord. The features in imaging are nonspecific depending on the degree of melanization, intra-tumoral hemorrhage, and duration of bleeding. Therefore, diagnosis confirmation consists of two key points: (1) Pathological test; and (2) excluding the possibility of metastases from other melanocytomas outside the spinal cord using the positron emission tomography–computed tomography scanning and physical examination of the whole body. The recommended therapy strategy includes complete resection and subsequent adjuvant radiation or Gamma Knife radiosurgery. Besides, maximal safe resection is also beneficial for cases with difficulty to be resected totally. More case studies are needed to determine the optimal management strategy due to its rarity.

INTRODUCTION
Primary melanocytic tumors can be generally divided into diffuse melanocytosis, melanocytoma, malignant melanoma, and meningeal melanomatosis according to the 2007 World Health Organisation (WHO) classification of tumors in the central nervous system (CNS)[1]. Besides, primary melanocytoma in the CNS derived from melanocyte of the leptomeninges instead of meningothelial cells is a rare type of neoplasm with an incidence of 1 per 10 million[2]. In general, melanocytomas are classified as intermediate grade melanocytic tumors and are usually located in the posterior fossa and spinal cord. In addition, the distribution percentage of primary intramedullary melanocytoma at the cervical, thoracic, and lumbosacral levels is 28.3%, 52.8%, and 18.9%, respectively[2].

Melanocytomas have been historically considered as benign neoplasms with mild cytology, but an increasing body of evidence has indicated the latent tendency of melanocytomas to relapse, metastasize, or transform to malignant melanocytic neoplasms[3]. Given the potential malignancy of melanocytomas, gross total resection and following radiotherapy may be the preferable treatment in an attempt to have a better prognosis of the disease[3]. Here, we describe the case of a 52-year-old man with primary intramedullary melanocytoma and furthermore discuss the diagnosis and therapy by combining the relevant background literature and the present case.

CASE PRESENTATION

Chief complaints
A 52-year-old male patient was admitted for weakness and numbness involving the bilateral lower limbs for 18 mo, and disorder of defecation and erectile dysfunction for...
6 mo. For the last 3 mo, these symptoms started to worsen.

**History of present illness**
The patient started to present disorders of bilateral lower limbs in January 2016, and defecation and erectile dysfunction in January 2017. Subsequently, he received magnetic resonance imaging examination at a local hospital, which suggested an intramedullary mass located at the level of T9-T10. However, he did not take any cure. In April 2017, the clinical symptoms began to worsen. Therefore, the patient was admitted to our department on July 13, 2017 for further treatment.

**History of past illness**
The patient underwent an appendectomy in 1984, and had suffered from diabetes for 7 years and hypertension for 2 years. He had been taking nimodipine, metformin, and gliclazide to control the blood pressure and blood glucose levels under the supervision of local doctors.

**Personal and family history**
Neither he nor anyone in his family had a history of primary intramedullary melanocytoma.

**Physical examination**
Neurologic examination presented that the myodynamia of the right lower limb was grade 3 and left lower limb was grade 4. Besides, the superficial and deep sense in the right lower limb was clearly worse than that of the left lower limb and these dysfunctions in distal lower limbs were more severe than those of proximal lower limbs as well. Moreover, achilles tendon reflex and patellar tendon reflex were brisk with absence of ankle and patellar clonus. Babinski sign was positive in the right lower limb. Anal reflex revealed a mild decrease and the Romberg sign was positive.

**Laboratory examinations**
Total protein was slightly low (63.2 g/L). Triglyceride (1.75 mmol/L) and low density lipoprotein (3.47 mmol/L) were a little high. Color doppler ultrasound of the stomach and pelvis indicated a single gallbladder polyp (3 mm × 3 mm) and gallstone (5 mm × 4 mm), and benign prostate hyperplasia with multiple calcifications. The routine blood, urine, and stool tests were normal. Electrocardiogram, chest X-ray, cardiac color Doppler ultrasound, pulmonary ventilation function, and blood glucose were also normal.

**Imaging examinations**
Magnetic resonance imaging (MRI) revealed an intramedullary tumor located at the T9-T10 level with oval borders and a size of 5.5 cm × 1.2 cm × 1.2 cm. The mass was slightly hyperintense on T1-weighted images (T1WI) ([Figure 1A](#)) and hypointense on T2-weighted images (T2WI) ([Figure 1B](#)). Contrast-enhanced MRI of the tumor showed mildly inhomogeneous enhancement after gadolinium administration ([Figure 1C](#) and C). The secondary lesions like syringomyelia induced by the intramedullary tumor were hypointense on T1WI ([Figure 1A](#)) and hyperintense on T2WI ([Figure 1B](#)) with mild enhancement after gadolinium management at the T5-T8 level ([Figure 1C](#)).

**FINAL DIAGNOSIS**
The lesion was confirmed to be melanocytoma by histopathological examination with typical characteristics of primary melanocytic tumors like positive manifestation of sex determining region Y box 10 (SOX10) protein, human melanoma black 45 (HMB-45), and antimelanoma antibody, and negative presence of epithelial membrane antigen (EMA) and glial fibrillary acidic protein (GFAP). The proliferative index (Ki 67) was almost equal to 3% ([Figure 2](#)). The possibility of original melanocytoma outside the spinal cord was excluded after the examinations of postoperative positron emission tomography–computed tomography (PET-CT) scanning, ophthalmological test, and gastrointestinal and dermatological inspection ([Figure 3A-C](#)). Accordingly, the final diagnosis of the patient was primary and intramedullary intermediate grade melanocytoma at the T9-T10 level.
Figure 1 Preoperative and postoperative magnetic resonance imaging. A: Sagittal T1-weighted image (T1WI); B: Sagittal T2-weighted image (T2WI); C: Sagittal T1WI with gadolinium enhancement; D: Sagittal T1WI; E: Sagittal T2WI; F: Sagittal T1WI with gadolinium enhancement at the T10 level; G: Axial T1WI with gadolinium enhancement at the T10 level; H: Axial T1WI with gadolinium enhancement at the T10 level. A-C and G: Intramedullary melanocytoma (white solid arrows) and syringomyelia (white dashed arrows) were located at the T9-T10 level and T5-T8 level, respectively; D-F and H: An approximate gross total resection of the intramedullary melanocytoma was achieved in spite of tiny residual (orange arrow).

**TREATMENT**

The patient underwent surgical operation with approximately gross total resection on July 19, 2017. The resection extent reached to 98%. During the operation, clear cerebrospinal fluid was visible in the intramedullary cavity with golden yellow substance adhering to the wall of chamber at the T5-T8 level. At T9-T10, some stale blood clots were observed. After removing these blood clots, the mass was found in the right of T9-T10 without capsule. The mass was well-circumscribed, but it possessed abundant vascularity. Furthermore, a tiny part adhered to the normal spinal cord closely, so we only performed the maximal safe resection with minimal residual (1.5 cm × 0.4 cm × 0.3 cm) to ensure patient’s life quality. The duration of surgery lasted for 5 h and the blood loss was 300 mL. The patient did not receive blood transfusion.
Figure 2 Postoperative pathology images showing the typical features of melanocytoma. A: Hematoxylin and eosin (HE) staining (400 ×) revealed spindle and epithelioid cells containing melanin pigment in the cytoplasm assembled to form sheets, bundles, nests, or whirls surrounded by reticulin fibres (yellow arrow); B: HE staining (400 ×) after removing melanin pigment in the cytoplasm; C-H: Immunohistochemical staining (400 ×) demonstrated human melanoma black 45 (C), antimelanoma antibody (D), and sex determinant region Y box 10 protein (E) were positive. Besides, epithelial membrane antigen (F) and glial fibrillary acidic protein (G) were negative, and the proliferative index was only 3% (H).

OUTCOME AND FOLLOW-UP

The hospital stay was 15 d and there was no hospital stay related issues. Postoperative MRI revealed that a small piece of tumor remained with heterogeneous enhancement before discharge (Figure 1D-F and H). The patient refused to accept radiotherapy or Gamma Knife radiosurgery. Follow-up examination on July 28, 2020 showed no sign of further growth of the lesion with heterogeneous enhancement, compared to the previous MRI scans (Figure 3D-G). On April 10, 2021, the patient received regular review at a local hospital without performing MRI scan. As for clinical symptoms, the weakness involving the bilateral lower limbs got significant improvement from rehabilitation, as the myodynamia of the right lower limb was grade 4 and left lower
Figure 3 Postoperative positron emission tomography-computed tomography images and the latest review of magnetic resonance imaging. A and B: Coronal positron emission tomography–computed tomography (PET-CT) images; C: Sagittal PET-CT image; D: Sagittal T1-weighted image (TIWI); E: Sagittal T2-weighted image; F: Sagittal TIWI with gadolinium enhancement; G: Axial TIWI with gadolinium enhancement at the T10 level. A-C: There were no abnormal regions with significant hypermetabolism in the whole body; D-G: The tiny residual (orange arrow) maintained stable. The heterogeneous enhancement of residual did not grow up, but the local edema of the spinal cord mitigated apparently.

DISCUSSION

The designation “meningeal melanocytoma” in the primary melanocytic tumors of the CNS was confirmed for the first time in 1972, which frequently tended to occur in the veutro of medulla or the upper segments of the spinal cord, but the term “melano-
Primary intramedullary melanocytoma from recurrent melanocytoma in the spinal cord after first surgical operation are otherwise difficult to be resected. 22% at 5 years compared to incomplete tumor resection. Complete tumor resection remarkably decreased the recurrence rates at 3 years and 5 years. Therefore, it is crucial to parse primary melanocytomas from metastasis melanocytomas. However, there has been no standard strategy of diagnosis and treatment for primary melanocytomas in the CNS so far due to the insufficient data available. Nonetheless, the criteria proposed by Hayward might be helpful to diagnose primary CNS melanocytic tumors: (1) No malignant melanoma tumor outside the CNS; (2) Involvement of the leptomeninges (spinal or cranial); (3) Intramedullary spinal lesions; (4) Hydrocephalus; (5) Tumor in the pituitary or pineal gland; and (6) a single intracerebral lesion.

Preoperative diagnosis of melanocytomas in the CNS on radiologic examinations is also a dilemma, as the imaging features are nonspecific depending on the degree of melanization, intra-tumoral hemorrhage, and duration of bleeding. Besides, paramagnetic free radicals in melanin were considered to be responsible for shortening the relaxation times of T1 and T2 by the proton-electron dipole-dipole proton relaxation enhancement mechanism. The MRI appearance mainly was hyper-intensity on T1WI and hypo-intensity on T2WI with homogenous enhancement after gadolinium enhancement. As for this case, the presence of inhomogeneous enhancement may be caused by intratumoral hemorrhage.

Pathological examination is an accurate and indispensable way to confirm the explicit diagnosis of melanocytomas in the CNS. The characteristics of primary melanocytic tumors are spindle or epithelioid cells arranged in the formation of sheets, bundles, nests, or whorls surrounded by reticulin fibres, which contain various degrees of melanin pigment in the cytoplasm. The appearance of melanocytomas includes low mitotic activity and absence of necrosis, nuclear atypia, and microvascular invasion. By contrast, the presence of primary malignant melanocytic tumors such as melanomas generally reveals a high proliferation index (Ki 67 > 5%) [11,12]. The mean rate of soluble protein-T100 (S-100), HMB-45, and antimelanoma antibody to diagnose melanocytic tumors was 95%, 86%, and 84% respectively. In addition, HMB-45 was considered to be more specific but less sensitive than S-100 protein [13]. SOX10 protein, a transcription factor, encoded by a gene located on chromosome 22q13.1, could regulate the differentiation of neural crest-derived melanocytes by affecting the expression of microphthalmia transcription factor [14]. Compared with S-100, SOX10 was recognized as having a higher sensitivity and/or specificity for melanocytic tumors, as S-100 protein was positively expressed in multiple types of tumors in spite of high sensitivity [14]. Therefore, SOX10 identification was adopted instead of S-100 in this case. The negative expression of GFAP and EMA is helpful to differentiate melanocytic tumors from gliomas and meningiomas [15,16]. In combination with previous studies, the diagnostic criteria for melanocytomas were proposed on the basis of positive manifestation of S-100 and/or SOX10 protein, Vimentin, HMB-45, and antimelanoma antibody and negative presence of EMA, GFAP, and neuron specific enolase [11,12,14]. As for our case, the PET-CT and physical examination of whole body helped to exclude the malignant melanoma tumor outside the spinal cord, and the confirmation of pathological examination further validated the diagnosis of primary intramedullary melanocytoma.

Surgical resection plays a crucial role in the treatment of melanocytomas in the CNS. Complete tumor resection remarkably decreased the recurrence rates at 3 years and 5 years compared to incomplete tumor resection [17]. Owing to the extensive growth of melanocytomas, surgical resection could relieve pain symptoms immediately, but neurological deficits might need more time to recover. To date, the standard adjuvant therapy for melanocytomas has not yet proposed due to its rarity. Adjuvant radiation therapy and Gamma Knife radiosurgery for incomplete tumor resection should be taken into account, as these strategies were helpful to control tumor growth and improve the clinical outcome [18]. Even for the patients who underwent complete tumor resection, adjuvant radiation therapy could diminish the recurrence rates to 22% at 5 years [19,20]. Moreover, irradiation could be used to treat these tumors which are otherwise difficult to be resected [21,22]. Verma et al. [23] treated a patient suffering from recurrent melanocytoma in the spinal cord after first surgical operation.
## Table 1 Reported cases of primary intramedullary melanocytomas

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Ref.</th>
<th>Time (yr)</th>
<th>Age</th>
<th>Sex</th>
<th>Location</th>
<th>EOR</th>
<th>RT</th>
<th>Relapse</th>
<th>MT</th>
<th>Metastasis</th>
<th>Treatment</th>
<th>Follow-up</th>
<th>Comment</th>
</tr>
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<tr>
<td>1</td>
<td>Verma et al[23]</td>
<td>1979</td>
<td>71</td>
<td>F</td>
<td>T2-T3</td>
<td>Subtotal</td>
<td>Yes</td>
<td>Yes</td>
<td>NG</td>
<td>No</td>
<td>Re-resection and chemotherapy</td>
<td>53 mo</td>
<td>PFS is 15 mo after the second therapy</td>
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<tr>
<td>2</td>
<td>Litofsky et al[26]</td>
<td>1992</td>
<td>32</td>
<td>M</td>
<td>Clivus - C5</td>
<td>Total</td>
<td>No</td>
<td>No</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>40 mo</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Ibáñez et al[22]</td>
<td>1997</td>
<td>44</td>
<td>F</td>
<td>T11</td>
<td>Total</td>
<td>No</td>
<td>No</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>54 mo</td>
<td></td>
</tr>
<tr>
<td>4</td>
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<td>1998</td>
<td>48</td>
<td>M</td>
<td>T8-T9</td>
<td>Total</td>
<td>No</td>
<td>No</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>12 mo</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Rades et al[17]</td>
<td>2001</td>
<td>23</td>
<td>F</td>
<td>T4-T7</td>
<td>Subtotal</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Re-resection and RT</td>
<td>54 mo</td>
<td>Died from brain metastases</td>
</tr>
<tr>
<td>6</td>
<td>Das et al[28]</td>
<td>2001</td>
<td>50</td>
<td>M</td>
<td>T10</td>
<td>Yes</td>
<td>Yes</td>
<td>NG</td>
<td>Yes</td>
<td>-</td>
<td>-</td>
<td>30 mo</td>
<td>Died from aspiration pneumonia</td>
</tr>
<tr>
<td>7</td>
<td>Iida et al[29]</td>
<td>2002</td>
<td>42</td>
<td>M</td>
<td>T8-T10</td>
<td>No</td>
<td>No</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>4 mo</td>
<td>Died from a urinary tract infection</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Iida et al[29]</td>
<td>2002</td>
<td>52</td>
<td>M</td>
<td>C2</td>
<td>Subtotal</td>
<td>No</td>
<td>No</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>24 mo</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Turhan et al[7]</td>
<td>2004</td>
<td>64</td>
<td>M</td>
<td>T12-L2</td>
<td>Total</td>
<td>No</td>
<td>No</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>24 mo</td>
<td></td>
</tr>
<tr>
<td>10</td>
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<td>2004</td>
<td>19</td>
<td>F</td>
<td>T8</td>
<td>Total</td>
<td>No</td>
<td>No</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>36 mo</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Wang et al[30]</td>
<td>2007</td>
<td>57</td>
<td>M</td>
<td>L5-S1</td>
<td>Total</td>
<td>No</td>
<td>Yes</td>
<td>NG</td>
<td>No</td>
<td>Re-resection and RT</td>
<td>17 mo</td>
<td>5 mo after the second surgery, metastases were found in the liver and the left ninth rib</td>
</tr>
<tr>
<td>12</td>
<td>Chacko et al[31]</td>
<td>2008</td>
<td>22</td>
<td>M</td>
<td>T6-T11</td>
<td>Total</td>
<td>No</td>
<td>No</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>96 mo</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Karikari et al[10]</td>
<td>2009</td>
<td>32</td>
<td>F</td>
<td>T10</td>
<td>Total</td>
<td>No</td>
<td>No</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3 mo</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Karikari et al[10]</td>
<td>2009</td>
<td>20</td>
<td>M</td>
<td>T12</td>
<td>Total</td>
<td>No</td>
<td>No</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>6 W</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Caruso et al[32]</td>
<td>2009</td>
<td>62</td>
<td>M</td>
<td>T11</td>
<td>Total</td>
<td>No</td>
<td>No</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>24 mo</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>Perrini et al[3]</td>
<td>2010</td>
<td>79</td>
<td>F</td>
<td>T10-T11</td>
<td>Subtotal</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Re-resection</td>
<td>30 mo</td>
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<tr>
<td>17</td>
<td>Eskandari et al[33]</td>
<td>2010</td>
<td>45</td>
<td>M</td>
<td>T11</td>
<td>Total</td>
<td>No</td>
<td>Yes</td>
<td>NG</td>
<td>No</td>
<td>RT</td>
<td>36 mo</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>Wagner et al[34]</td>
<td>2015</td>
<td>63</td>
<td>M</td>
<td>C2-C3</td>
<td>Total</td>
<td>No</td>
<td>Yes</td>
<td>NG</td>
<td>No</td>
<td>RT</td>
<td>18 mo</td>
<td>Neurological stabilization for 15 mo after radiotherapy</td>
</tr>
<tr>
<td>19</td>
<td>Wang et al[35]</td>
<td>2016</td>
<td>60</td>
<td>M</td>
<td>T1; T3-T4</td>
<td>Total</td>
<td>No</td>
<td>No</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>19 mo</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>Retov et al[36]</td>
<td>2016</td>
<td>28</td>
<td>F</td>
<td>C1-C2</td>
<td>Total</td>
<td>No</td>
<td>No</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>24 mo</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>Lee et al[12]</td>
<td>2017</td>
<td>45</td>
<td>M</td>
<td>C1</td>
<td>Total</td>
<td>No</td>
<td>No</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>6 mo</td>
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<tr>
<td>22</td>
<td>Gupta et al[37]</td>
<td>2017</td>
<td>20</td>
<td>M</td>
<td>C1-C2</td>
<td>Total</td>
<td>Yes</td>
<td>No</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>12 mo</td>
<td></td>
</tr>
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</table>
F: Female; M: Male; EOR: Extent of resection; RT: Radiotherapy; MT: Malignant transformation; NG: Not given; PFS: Progression free survival.

(approximate 95%) and then radiation therapy followed by a second partial excision (approximate 90%) and adjuvant therapy with corynebacterium parvum, dactinomycin, dacarbazine, and the progression free survival was 15 mo. Koch et al[24] treated a patient with recurrent melanocytoma in the cerebello-pontine angle with intracerebral and spinal meningeal seeding after first resection by radiotherapy in combination with chemotheraphy (oral temozolomide), but the patient died after 5 mo. The two cases indicated that the recurrent tumor might not respond to a combined radiotherapy and chemotherapy. The same result was also reported by Roser et al[25]. In fact, the role of radiochemotherapy in the treatment of melanocytomas needs further research. In terms of the present case, after approximately complete resection, the clinical symptoms induced by extensive growth of tumor was ameliorated remarkably and no relapse or aggression was discovered in spite of not getting radiochemotherapy. In addition, to now, the patient has been receiving regular review every 6 to 12 mo in order to avoid neglecting potential malignant transformation and metastasis. Some previous studies about primary melanocytomas in the spinal cord are summarized in Table 1.

In summary, the 5-year survival rate of primary melanocytomas in the spinal cord is more than 90% after surgical operation, but it is vital for doctors and patients to pay more attention to the potential malignance of primary melanocytomas such as local recurrence, adjacent structure invasion, cerebrospinal fluid spread, and distant metastases[6].

CONCLUSION

We report a case of primary intramedullary melanocytoma at the T9-T10 level presenting with lower limbs, defecation, and erectile dysfunction. In addition, the postoperative progression free survival had reached to 45 mo till the latest follow-up. The main therapy strategy includes gross total resection and adjuvant radiation. This case proves evidence that maximal safe resection can provide benefits to prognosis and improve the quality of life, when complete resection is difficult to achieve. Considering the potential malignancy, postoperative examination of whole body regions, after the pathological diagnosis of intramedullary melanocytoma, can help exclude the probability of metastasis from other regions. Therefore, it is reasonable to confirm the diagnosis of primary intramedullary melanocytoma. Based on this case, we would recommend patients to receive adjuvant radiation, which can prolong their progression free survival. Notably, regular follow-up is crucial, as physical examination and MRI scan can help find early progression or relapse.
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