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Management of acute kidney injury in gastrointestinal tumor: An overview

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Abstract
Gastrointestinal tumors remain a global health problem. Acute kidney injury (AKI) is a common complication during the treatment of gastrointestinal tumors. AKI can cause a decrease in the remission rate and an increase in mortality. In this review, we analyzed the causes and risk factors for AKI in gastrointestinal tumor patients. The possible mechanisms of AKI were divided into three groups: pretreatment, intrafraction and post-treatment causes. Treatment and prevention measures were proposed according to various factors to provide guidance to clinicians and oncologists that can reduce the incidence of AKI and improve the quality of life and survival rate of gastrointestinal tumor patients.

Key Words: Gastrointestinal tumor; Acute kidney injury; Risk factors; Treatment; Preventive measures; Enhanced recovery pathways

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Core tip: This review analyzed the causes and risk factors for acute kidney injury (AKI) in gastrointestinal tumor patients, and possible mechanism of AKI were divided into three groups: pretreatment, intrafraction and post-treatment causes. In response to these possible causes of AKI, treatment and preventive measures have been proposed based...
on the latest developments. This article intends to provide guidance of AKI during the treatment of gastrointestinal tumor patients to clinicians and oncologists.

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INTRODUCTION

In the past 10 years, with the advancement of medical technology and the vigorous development of tumor-related disciplines, the emergence of related new drugs, and the popularization of cancer screening, cancer patients’ survival rate has increased significantly. The rates of related side effects and kidney involvement during tumor treatment have also increased significantly. Acute kidney injury (AKI) is a common complication in cancer patients that can decrease the remission rate, increase mortality, extend hospital stays, and increase costs[1,2]; furthermore, it is associated with poor long-term prognosis[3]. Gastrointestinal cancer is a global health problem with an estimated 3.4 million newly diagnosed cases worldwide in 2018[4]. According to a nationwide study in China, among 1418 cases of malignancy-related AKI (MR-AKI), gastrointestinal cancer was the most common malignancy (50.1%)[5], and the occurrence of MR-AKI increased hospitalization costs and length of stay and significantly increased the medical burden[6].

Therefore, in this review, we analyzed the causes and risk factors for AKI in gastrointestinal tumor patients to determine how to promptly diagnose and prevent AKI and provide guidance for nephrologists and oncologists.

EPIDEMIOLOGY

The incidence of tumor-related AKI is related to the nature, location and severity of the tumor; the presence or absence of complications; the course of the disease; the use of chemotherapy and targeted biological therapy; and the diagnostic criteria for AKI that are adopted[7,8]. The incidence in patients with tumor-related AKI is 7.5%–18.4%[5,9,10]. A population study in Denmark followed 37,267 new cancer patients from 1999 to 2006 and reported 1-year and 5-year risks of AKI of 17.5% and 27%, respectively[11]. In total, 5.1% of patients required renal replacement therapy (RRT) within 1 year of the occurrence of AKI. Jin et al[5] found that among patients with tumor-related AKI, gastrointestinal cancer (50.1%) was the most common malignancy. Approximately half of the patients (50.3%) were treated with RRT[5]. Li et al[12] concluded that the proportions of esophageal cancer, gastric cancer and bowel cancer patients with AKI were 20.5%, 13.9% and 12.5%, respectively[12]. A smaller study concluded that the incidences of postoperative AKI after gastric cancer and colorectal cancer (CRC) were 14.4%[13] and 11.8%[14], respectively. However, most articles concluded that AKI increased tumor patients’ risk of death[11,13].

RISK FACTORS FOR TUMOR-RELATED AKI

The risk factors for AKI in patients with gastrointestinal tumors can be divided into pretreatment, intrafraction and post-treatment causes. Widely recognized risk factors for AKI in cancer patients include the use of nephrotoxic drugs, angiotensin-converting enzyme inhibitors (ACEIs), chemotherapeutics, antibiotics, and nonsteroidal anti-inflammatory drugs (NSAIDs)[15,16]. Risk factors also include age > 65 years[17], pre-existing chronic kidney disease (CKD), and comorbid diseases (such as diabetes and cardiovascular disease)[17,18], sepsis[16], contrast nephropathy[19], low blood volume, preoperative dehydration[20-22], low serum albumin levels[17,20], tumor size[23], anemia[23], heavy tumor burden or extensive metastasis, extensive surgery, surgical methods, intraoperative bleeding, operation time[17,24-28], and
MECHANISMS OF AKI IN PATIENTS WITH GASTROINTESTINAL TUMORS

Drug-related AKI in gastrointestinal tumor patients

Chemotherapeutic drugs can affect the glomeruli, renal tubules, renal interstitial tissue, or the renal microvascular system. The clinical manifestations can range from the asymptomatic elevation of serum creatinine to acute renal failure (ARF).

Cytotoxic drugs

Chemotherapy for gastrointestinal tumors mainly included neoadjuvant chemotherapy, postoperative adjuvant chemotherapy, and palliative chemotherapy. Traditional treatments are mainly divided into cytotoxic drugs and targeted therapy. In recent years, the use of novel targeted anticancer agents has led to an overall improvement in the prognosis of many patients affected by various malignancies. In recent years, the effectiveness of newly developed drugs has been confirmed for different types of solid tumors, and the survival period has been prolonged. Nevertheless, the incidence of AKI in hospitalized cancer patients seems to be increasing because of aggressive cancer therapies[30]. In Japan, cohort studies have reported drug treatment as the reason for the onset of AKI in 14.4%–25.7% of adult patients[31,32]. Therefore, drug therapy as a cause of AKI in cancer patients cannot be ignored.

The standard drug treatment for gastric cancer is combination chemotherapy with S-1 (tegafur/gimeracil/oteracil), 5-fluorouracil (5-FU), capecitabine plus cisplatin or oxaliplatin as adjuvant chemotherapy for stage II/III disease. S-1 plus cisplatin is administered as the primary treatment for human epidermal growth factor receptor type 2 (HER2)-negative, advanced, recurrent gastric cancer[33]. The standard drug treatments for colon cancer include FOLFOX (oxaliplatin, fluorouracil and leucovorin), CAPOX (capecitabine and oxaliplatin), FOLFIRI (5-FU, folinic acid and irinotecan), etc.

Cisplatin, a platinum compound that is mainly eliminated by the kidneys, is a factor that can cause AKI that has been widely studied and verified[34-36]. Cisplatin mainly damages the S3 segment of the proximal tubule, resulting in a decrease in the glomerular filtration rate (GFR). Cisplatin is associated with many mechanisms involved in renal insufficiency. The exposure of renal tubular cells to cisplatin activates complex signaling pathways, leading to renal tubular cell damage and cell death in the proximal tubules. Cisplatin selectively damages proximal tubule cells (indicated by necrosis and apoptosis), and multiple signaling pathways contribute to cisplatin-induced injury and death of renal tubular cells[34,37]. In addition, cisplatin can increase the expression of proinflammatory cytokines [tumor necrosis factor (TNF)-α, interleukin-6, and interferon-γ] and promote the differentiation, maturation, and activation of neutrophils, T cells, and other components in the cellular inflammatory response[38,39]. The severity of AKI in mice with defective inflammatory pathways after exposure to cisplatin was relatively mild, illustrating the potential importance of these mediators[38-41]. Prominent inflammation and damage to the renal vascular system can cause vasoconstriction, decreased blood flow, and ischemic damage. These changes collectively lead to AKI[42]. Furthermore, there is a cisplatin-mediated decrease in the expression and function of sodium-dependent glucose and amino acid transporters[43], which increases the risk of AKI.

Oxaliplatin, however, carries a reduced risk of AKI compared to the previously described platinum agents, including cisplatin and carboplatin. Several cases of oxaliplatin-induced acute tubular necrosis (ATN) have been reported[44-46]; however, only one case has been histopathologically confirmed as acute tubulointerstitial nephritis (ATIN). Here, we present a biopsy-confirmed and dialysis-dependent ATIN case study that shows that oxaliplatin rarely causes acute interstitial nephritis (AIN) [47,48]. Similar to cisplatin, oxaliplatin localizes to the vascular basolateral membrane and is actively transported by human organic cation transporter 2 (OCT2), which mediates the uptake of the drug into the kidneys. Cisplatin is minimally excreted by multidrug and toxin extrusion protein (MATE) 1 on the brush border membrane after its transfer into the cell. However, oxaliplatin is strongly susceptible to cellular transport via MATE2-K on the brush border membrane. It is strongly suggested that its nephrotoxicity is weak due to low tissue accumulation in renal tubular epithelial cells [49-51]. However, nephrotoxicity can be considered the result of oxaliplatin in cases of repeated exposure[52]. Carboplatin is known for its low nephrotoxicity, but only case reports have confirmed that carboplatin can cause biopsy-proven AIN[51,53,54].
**Table 1 Risk factors for acute kidney injury in gastrointestinal tumor patients**

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ACEI: Angiotensin-converting enzyme inhibitor; CKD: Chronic kidney disease; IAH: Intraperitoneal hypertension; ICIs: Immune checkpoint inhibitors; ICU: Intensive care unit; NSAIDs: Nonsteroidal anti-inflammatory drugs.

On the other hand, in addition to drug-related AKI, the side effects of chemotherapy drugs, such as nausea, vomiting, dehydration, and anorexia, can lead to prerenal AKI.

**Targeted therapy**

Targeted agents can improve the survival rate of tumor patients by targeting the molecular mechanisms underlying cancer growth. Recognition of the adverse renal effects of these agents is extremely important for patient care. At present, the targets for gastrointestinal cancer mainly include epidermal growth factor receptor (EGFR), HER-2, vascular endothelial growth factor (VEGF), VEGF receptor (VEGFR), mTOc-MET and hepatocyte growth factor. The following is a brief overview of commonly used targeted drugs.

**Anti-EGFR monoclonal antibody:** Cetuximab is a human mouse chimeric IgG1 monoclonal antibody that specifically binds to the extracellular domain of EGFR and kills tumor cells through antibody-dependent cell cytotoxicity (ADCC). It is often used in combination with chemotherapy for metastatic CRC and can effectively improve the survival rate. Cetuximab can also have nephrotoxic effects, including AKI\(^{[35,56]}\). EGFR is mainly expressed in distal and collecting tubules and is involved in maintaining the integrity of renal tubules. EGFR activation can cause the growth and production of renal tubular epithelial cells during AKI. For patients who are prone to renal injury, anti-EGFR drug therapy may be a second source of AKI. However, the prescribing information from the United States does not provide related dose guidance.
Panitumumab is a humanized IgG2 monoclonal antibody against EGFR that can prevent the activation of autophosphorylation and receptor-associated kinase by binding to EGFR and can effectively improve the prognosis of patients with CRC. AKI was the most common renal adverse event reported in 100 patients treated with pertuzumab[55]. The dose of the drug does not appear to be different for patients with renal insufficiency. For patients with mild to moderate renal injury, there is no need to adjust the dose of pertuzumab, and the clearance of drugs in patients with severe renal injury [creatinine clearance (CrCL) < 30 mL/min] has not been studied.

Nimotuzumab is the first EGFR-targeted drug synthesized in China. It mainly inhibits tumor cell proliferation and angiogenesis through ADCC and complement-dependent cytotoxicity. There is no related AKI report for this drug.

**EGFR tyrosine kinase inhibitors:** Tyrosine kinase inhibitors (TKIs) can compete for the Mg-ATP binding site on the catalytic region of EGFR-TKIs, block signal transmission, inhibit the activation of mitogen-activated protein kinase, and promote apoptosis. The main drugs for this target are erlotinib and gefitinib. According to the results of relevant clinical studies, the use of gefitinib in patients with advanced esophageal cancer or gastroesophageal junction cancer that progressed after chemotherapy failed to improve overall survival, but the patients’ self-reported results suggest that gefitinib may have some palliative benefits[57]. At present, only one study has confirmed that gefitinib causes AKI during treatment of lung cancer[58]. Further study of AKI caused by gefitinib in gastrointestinal cancer is necessary in the future.

**Anti-HER-2 monoclonal antibody:** Trastuzumab is a recombinant humanized anti-HER-2 IgG1 monoclonal antibody that specifically acts on the extracellular domain of HER-2, inhibiting the activation of HER-2 and the signaling pathway mediated by HER-2, thereby playing a role in gastrointestinal tumors. In recent years, there have been numerous reports of related renal adverse events, and the most frequently reported events include proteinuria and AKI[55]. The US prescribing information for trastuzumab includes dose adjustments for patients with renal impairment (including those undergoing dialysis). For patients with mild to moderate renal injury, there is no need to adjust the dose of pertuzumab, and the drug clearance of patients with severe renal injury (< 30 mL/min) has also not been studied. Trastuzumab emtansine (T-DM1) is a conjugate of trastuzumab and cytotoxic substances. Although there are no reports of T-DM1-related AKI, it is still necessary to pay attention to the possible side effects.

**HER-2/TKI:** Lapatinib is an oral EGFR/HER-2 dual receptor TKI that mainly inhibits the phosphorylation and activation of tumor cells by inhibiting the ATP-binding sites of HER-2 and EGFR. The FDA Adverse Event Reporting System (FAERS) report found that 48 cases of AKI were reported between 2011 and 2015[55]. The US prescribing information on lapatinib does not propose dose adjustments for patients with renal injury, but it may not be necessary to adjust the dose due to the drug’s low renal clearance rate.

Afatinib is a potent and irreversible dual EGFR/HER-2 TKI. There are no reports of afatinib-related AKI.

**VEGFR TKIs:** Apatinib is a small-molecule VEGFR inhibitor that mainly acts on VEGF2. There is no report regarding AKI.

Regorafenib is a new oral multitarget phosphokinase inhibitor that has a strong inhibitory effect on VEGFR-2, platelet-derived growth factor receptor (PDGFR)-β, fibroblast growth factor receptor-1 and c-kit and thus exerts multiple antitumor effects. There are no reports about the relationship between regorafenib and AKI.

Sunitinib belongs to a class of selective multitarget TKIs that play an antitumor role by interacting with VEGF, PDGFR-β, c-kit, Flt-3 and ret. Sunitinib has been recommended for use in gastrointestinal stromal tumors (GISTs)[59]. It has been reported that sunitinib can cause acute and chronic interstitial nephropathy[60,61].

Imatinib is effective for GISTs and can reduce recurrence and improve overall survival[62]. The FAERS report found that 25 events of imatinib-related renal toxicity were AKI[55]. The US prescribing information on sunitinib concludes that there is no need to adjust the starting dose for patients with mild, moderate and severe kidney injury[63]. There are no reports of imatinib-related AKI.

**Anti-VEGF and anti-VEGFR monoclonal antibodies:** Anti-VEGF and anti-VEGFR monoclonal antibodies mainly include bevacizumab and ramucirumab, which prolong the survival time of patients with gastrointestinal tumors and delay recurrence[64,65]. The most common symptom of both drugs is asymptomatic proteinuria, and there are...
no reports of drug-related AKI.

**B-Raf inhibitors**: Vemurafenib and dabrafenib are orally available small-molecule kinase inhibitors targeting mutations that activate B-Raf. B-Raf is a member of the Raf family of growth-signal transduction protein kinases. Mutations in B-Raf result in the constitutive activation of this signaling pathway, leading to uncontrolled cell growth [66]. B-Raf mutation is also present in CRC and is used in the treatment of metastatic CRC, although the therapeutic effect is not as good as in malignant melanoma[67]. In the phase II study of the vemurafenib trial, one of the 132 participants died from vemurafenib-induced AKI[68]. Hence, regular monitoring of kidney function is recommended during treatment.

**Immune checkpoint inhibitors**

Immune checkpoint inhibitors (ICIs) are a novel and promising anticancer therapy. This novel class of drugs includes humanized antibodies that inhibit downstream immunity pathways [including cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed cell death 1 (PD-1) or its ligand (PD-L1)] with the objective of enhancing the antitumor immune response. PD-1 inhibitors such as nivolumab and pembrolizumab and PD-L1 inhibitors such as atezolizumab, avelumab and vedolizumab (durvalumab) have been approved for multiple indications. However, by increasing the immune system’s activity, ICIs can cause inflammatory side effects; these are called immune-related adverse events (irAEs). Renal toxicities have been increasingly recognized as complications of ICIs.

In a pooled analysis of > 3000 patients treated with ICIs, the overall incidence of AKI was 2.2%. In contrast, the incidence of severe AKI was 0.6%, and the incidence of renal irAEs was 1.9% with nivolumab and 2.0% with ipilimumab monotherapy. AKI occurred more frequently in patients who received combination therapy with ipilimumab and nivolumab (4.9%) than in patients who received monotherapy with ipilimumab (2.0%), nivolumab (1.9%) or pembrolizumab (1.4%)[69]. A review study of a PD-1 inhibitor with > 10000 patients found a total incidence of AKI of 2.2%. The pooled incidence of AKI with nivolumab treatment was 2.3%, and that with pembrolizumab was 2.0%[70]. However, there are few reported cases of kidney damage caused by PD1 in gastrointestinal tumors. One case of nivolumab-induced acute granulomatous tubulo-interstitial nephritis (TIN) in a patient with gastric cancer has been reported[71].

ICIs can fight cancer tolerance through the physiological downregulation of immune responses[72,73]. The principal mechanism of ICIs is the blockade of immune checkpoints, including CTLA-4 on the surface of T cells and PD-1 and its receptor PD-L1, which reactivates quiescent T cells in the tumor microenvironment and enables them to resume their antitumor activity and ability to mediate tumor cell death. Treatment with ICIs produces many cytokines, and inflammatory factors can cause kidney tissue damage[74,75].

Studies have also shown that DNA mismatch repair-deficient (dMMR)/microsatellite instability-high (MSI-H) (dMMR/MSI-H) CRCs are associated with a higher mutational burden and that these patients benefit less from conventional chemotherapy and have shorter overall survival and dense immune cell infiltration[76]. PD1-blocking antibodies, pembrolizumab and nivolumab have shown efficacy in patients with dMMR-MSI-H metastatic CRC, which highlights the enormous therapeutic prospects [77].

**Tumor lysis syndrome**

Tumor lysis syndrome (TLS) is a tumor emergency caused when many tumor cells lyse, releasing large amounts of potassium, phosphorus and nucleic acid into the systemic circulation. TLS occurs mainly during chemotherapy in hematological tumors. TLS can also occur in gastrointestinal tumors[78-81]. The primary mechanism is nucleic acid catabolism to uric acid, which leads to hyperuricemia and significant uric acid excretion. The increase can lead to uric acid deposition in the renal tubules, which can also cause renal vasoconstriction, renal autoregulation damage, renal blood flow reduction, and inflammation, resulting in AKI[82]. Hyperphosphatemia and calcium phosphate deposition in the renal tubules can also cause AKI. This release many intracellular substances (potassium, phosphorus and nucleic acid, which can be metabolized to produce uric acid) into the systemic circulation. The metabolic consequences include hyperkalemia, hyperphosphatemia, secondary hypocalcemia, hyperuricemia, and AKI[83].
**SURGERY-RELATED AKI**

Surgery is the most essential treatment for gastrointestinal tumors. Gastrectomy with lymph node dissection constitutes an essential component of multimodal treatment for resectable gastric cancer[84]. Surgical resection is the only treatment that can cure localized colon cancer. The goal of surgical resection of primary colon cancer is to remove the tumor, large vessel pedicles, and lymphatic drainage area of the affected colon[85]. Nevertheless, surgery is also obviously related to AKI. Studies report a prevalence of 3%–35% for postoperative AKI and 0.5%–25% for all-cause postoperative mortality within the first year in patients who have undergone major abdominal surgery[86]. Postoperative AKI occurred in 17.4%–20.3% of patients who underwent laparoscopic CRC resection[27,87]. Of 4718 patients who underwent gastric cancer surgery, 14.4% developed postoperative AKI[13]. Compared with patients without AKI, patients with AKI were associated with increased 8–30-d mortality and 31–90-d mortality[87]. In a Danish population-based study of mortality after emergency surgery for colon cancer, mortality during the first 30 d after surgery was increased in patients with decreased kidney function who were receiving RRT[88]. A small cohort study that included 288 medical records from elective rectal cancer surgeries found an in-hospital mortality rate of 18.2% in patients with AKI, whereas the in-hospital mortality rate of patients without AKI was 0.7%[89].

AKI is a multifactorial condition. For example, anesthetics have an impact on the occurrence of postoperative AKI. First, stable intraoperative hemodynamics (especially a mean arterial pressure > 55 mmHg)[90,91] and average blood volume can help maintain renal perfusion and reduce postoperative AKI. Second, inhaled anesthetics can temporarily and reversibly inhibit renal function, decreasing renal blood flow, GFR, urinary sodium excretion, and urine output. Possible mechanisms include the loss of renal self-regulation, decreased renal blood flow, neuroendocrine response and neurohumoral factors[92]. A preoperative nil-by-mouth regimen, perioperative blood and intravascular fluid loss, extravasation of fluid from the vascular compartment (third-space effect), insensible fluid losses may also contribute to the occurrence of AKI. AKI can also develop from complications such as sepsis or electrolyte derangement associated with ileus[87]. Major surgery introduces the risk of fluid depletion at several stages. Furthermore, hypotension can lead to dysfunctional intrarenal microcirculation due to patchy hypoperfusion areas in the kidney and potentially add to the risk of developing AKI[92-95].

The perioperative fluid management is also notably related to AKI. The association of perioperative fluid overload with worsening postoperative morbidity is well established[96,97]. In recent studies, oliguria was significantly associated with AKI. Several recent studies demonstrated that intraoperative oliguria was associated with postoperative AKI in patients undergoing major abdominal surgery. Studies have also reported that intraoperative oliguria is significantly associated with increased postoperative AKI[98-100]. The possible mechanism of oliguria is as follows: Many factors, including the overall hemodynamic status, sympathetic activity, and the effects of hormones such as aldosterone and antidiuretic hormone influence urine output. Renal hypoperfusion in perioperative settings can be caused by hypovolemia, systemic vasodilatation (due to anesthesia or inflammation), positive pressure ventilation, or low cardiac output[101]. However, some studies showed that additional intravenous fluids or diuretics did not protect against AKI in oliguric patients[102,103]. Additionally, there have been several studies regarding intraoperative oliguria with AKI in patients undergoing abdominal surgery. This unresolved problem needs further research.

The choice of surgical method can also affect the occurrence of AKI. The use of the laparoscopic approach in treating CRC has been shown to promote recovery and reduce postoperative pain, the length of hospital stay, blood loss volumes, and complication rates[104,105]. Pneumoperitoneum, considered essential for adequate exposure in laparoscopic surgery, is associated with increased intraabdominal pressure (IAP) and its associated hormonal modifications[106]. Demyttenaere et al[107] reported decreased renal function and renal blood flow during pneumoperitoneum, which could be linked to AKI.

High IAP can be observed after abdominal surgery due to reduced abdominal compliance, fluid overload or capillary leakage[108]. When IAP remains elevated (> 12 mmHg) for a prolonged time, it can progress to intra-abdominal hypertension (IAH) [74], which is characterized by decreased renal arterial inflow and venous outflow and leads to AKI[108,109].
Systemic inflammation can be triggered by many factors, both intraoperatively and postoperatively. Sepsis, ischemic injury, trauma, and the surgery itself can all lead to inflammation. These triggers cause the release of proinflammatory cytokines and damage-associated molecular patterns that exert pleiotropic effects, leading to alterations in the renin-angiotensin-aldosterone system, microcirculation, and endothelial cell integrity. They also cause oxidative stress, initiate the apoptosis cascade, and alter coagulation pathways with the formation of microvascular thrombi. All of these effects lead to organ stress and, ultimately, organ injury[110,111]. All of these factors may be present in gastrointestinal tumor surgery.

Increasing evidence has demonstrated that intraoperative blood transfusions may contribute to organ injury in susceptible patients by promoting a proinflammatory state, exacerbating oxidative tissue stress, and activating leukocytes and the coagulation cascade, thus paradoxically impairing oxygen delivery[112,113]. The use of hydroxyethyl starch (HES) has been associated with AKI[114]. However, this association has not been demonstrated in the surgical setting, particularly after gastroenterological surgery[115].

CONTRAST-INDUCED AKI

There are few studies of postoperative AKI caused by contrast agents in gastrointestinal tumors, and only one study of gastric surgery patients revealed that the use of contrast agents was an independent predictor of postoperative AKI[13]. Nevertheless, a prospective study concluded that there was no association between preoperative intravenous contrast administered for computed tomography (CT) up to 7 d before surgery and postoperative AKI. The authors claimed that the risk of contrast-induced nephropathy should not be a reason for avoiding contrast-enhanced CT[19].

CANCER-RELATED REASONS

Gastrointestinal tumors, especially CRC, can also directly invade the kidneys or ureter, resulting in ureteral obstruction, and affected patients experience hydronephrosis, especially when the tumor is in the ascending colon or descending colon (that is, near the kidneys). When the tumor enlarges, it may directly invade the kidney. The tumor may cause lymph node metastasis, lymph node enlargement, fusion into a mass, ureteral invasion or kidney invasion.

PREVENTIVE MEASURES AND TREATMENTS FOR AKI IN GASTROINTESTINAL TUMOR PATIENTS

As mentioned earlier, there are many factors in the diagnosis and treatment of gastrointestinal tumors that can affect the occurrence and development of AKI alone or in combination and can even increase the risk of death. When treating AKI in gastrointestinal tumor patients, it is necessary to comprehensively evaluate the patient’s general condition and identify all factors that may affect renal function, including cancer- and non-cancer-related factors. Compared with the general population, oncology patients require increased attention during AKI treatment. In a study of solid tumor patients admitted to intensive care units, AKI was chiefly related to sepsis (80%), hypovolemia (40%) and outflow tract obstruction (17%)[116]. When AKI is caused by postrenal factors, the obstruction should be relieved first, and a J-tube should be placed in a timely manner to ensure smooth drainage. Timely imaging examinations and disease management in patients with gastrointestinal tumors are important because these patients constitute a high-risk group for postrenal AKI[117]. If AKI is not due to a postrenal factor, maintaining adequate hydration is the most important intervention for prerenal AKI and ATN and is easily administered. As previously discussed, AKI can be caused by a variety of factors, such as insufficient volume (due to chemotherapy-related nausea, vomiting, and diarrhea) and/or drugs (such as diuretics). Hypercalcemia or the use of drugs that affect autoregulation of the kidneys (such as ACEIs/ARBs or NSAIDs) can further increase the risk and severity of prerenal AKI. Insufficient fluid management during the perioperative period, blood loss, and water loss caused by the surgical process can lead to insufficient renal...
perfusion and induce the occurrence of AKI. Therefore, the key is to ensure hemodynamic stability.

**Liquid management**

Hypovolemia is a common cause of AKI during the perioperative period\([20-22]\); the body fluids are redistributed, the amount of extracellular fluid decreases, and the amount of fluid in the third space increases. Limiting the amount of fluid replacement and ensuring an appropriate amount of hydration can prevent the increase in cavity pressure and organ edema caused by fluid entering the interstitial space, thereby improving the patient’s prognosis. Goal-directed fluid therapy (GDFT) has been implemented in the clinic. GDFT is defined as the use of timely monitoring during the perioperative period, the development of an individualized rehydration plan, and the management of patient hemodynamic parameters through volume adjustment and vasoactive drugs. To approach a normal physiological state, it is important to ensure sufficient cardiac output, meet the oxygen demands of the kidneys and other organs, and prevent organ failure. Brienza *et al*\([118]\) conducted a meta-analysis that included 4220 perioperative patients, and the results showed that maintaining optimal hemodynamics during the perioperative period could reduce the risk of renal damage. Compared with traditional fluid rehydration methods, GDFT reduces the incidence of AKI during the perioperative period. Water overload, myocardial ischemia and excessive use of catecholamines can increase the risk of perioperative AKI, and avoiding excessive infusion and reducing catecholamine dosages can reduce this risk \([118]\). In addition, it should be noted that urine output is not an ideal target parameter for GDFT. A study of noncardiac surgery patients with normal essential renal function revealed no significant correlation between oliguria and AKI, but vasopressin and diuretics were related to ARF.

When a patient in a hypovolemic state develops oliguria without fluid therapy, long-lasting renal hypoperfusion may eventually develop into ARF\([109]\). Conversely, inappropriate diuretics may cause prerenal AKI; therefore, unless there is clear evidence of fluid overload, diuretics are not recommended during the perioperative period\([119,120]\).

Compared with traditional fluid therapy, the intraoperative application of GDFT can reduce fluid usage and postoperative complications, including wound infection, intestinal obstruction, AKI, pulmonary edema and heart failure\([121-123]\); shorten the hospital stay\([121,124]\); maintain perioperative hemodynamic stability\([125,126]\); and reduce the level of circulating lactic acid\([127]\). Meta-analyses by Brienza *et al*\([118]\) and Egil *et al*\([128]\) also showed that compared with the traditional fluid group, the GDFT group had a decreased risk of postoperative AKI. There are no reliable kidney-targeted drugs that can prevent and reduce the occurrence of AKI\([129]\). Hence, maintaining renal perfusion is still the most important preventive measure for protecting renal function\([100]\).

Jhanji *et al*\([130]\) concluded that GDFT can optimize stroke volume, maintain the microcirculation blood flow rate and improve tissue oxygenation, which may be one of the mechanisms of improved prognosis\([130]\). GDFT can maintain the expected cardiac output so that the kidneys have sufficient blood supply and can reduce renal vasoconstriction\([118]\). It is generally believed that GDFT is a fluid management strategy that can be used to improve systemic blood perfusion, maintain normal renal perfusion and improve tissue oxygenation. Sufficient cardiac output also reduces the contraction of renal blood vessels, thereby reducing AKI. Liquid selection in goal-oriented fluid therapy that restricts the intake of chlorine-containing fluids can reduce the risk of AKI and improve mortality\([131]\). Therefore, a large amount of normal saline is not recommended during the perioperative period. As mentioned above, HES is related to AKI, and 6% HES should be used reasonably according to the indications. However, for patients at a high risk of AKI and those with preexisting renal insufficiency, the use of HES should be avoided\([132]\). In terms of the intraoperative GDFT strategy, crystalloid or colloidal fluid should be selected as the background fluid. A randomized controlled study of patients undergoing colon surgery showed that the use of crystalloid versus colloidal fluid in GDF had little effect on postoperative complications\([133]\).

Although there was no association between preoperative intravenous contrast administered for CT before surgery and postoperative AKI\([19]\), because patients with hypovolemia are more likely to develop contrast-induced AKI (CI-AKI) than patients with euvolemia, guidelines recommend adequate hydration, especially for patients with risk factors\([134]\). The author also believes that for patients with CKD, it is necessary to pay close attention to renal function during follow-up to prevent AKI.
Infections increase morbidity in AKI patients; therefore, it is also vital to identify related symptoms early so that therapy can be started appropriately. It is necessary to consider that treatment can lead to further kidney complications, including AKI, under certain circumstances. This change in kidney function can necessitate adjusting a patient’s cancer care, including chemotherapy options, diagnostic evaluation options, and other types of supportive care[117].

In cases of sepsis-associated AKI, it is essential to optimize fluid therapy and withdraw nephrotoxic drugs. Additionally, the early initiation of RRT before the development of fluid overload may improve treatment outcomes[71].

**Treatment and prevention with ICIs**

For irAEs caused by PD-1/PD-L1, the use of glucocorticoids, TNF-α antagonists, mycophenolate mofetil, or other drugs for temporary immunosuppression can effectively address most of these issues. The most common irAE is ATN. Although the incidence of irAEs is very low, it is still worthy of attention. A study described 13 patients with ICI-induced AKI who underwent kidney biopsy. Among them, 12 patients had ATIN, 11 received glucocorticoid therapy and nine of them had improvement in renal function[69]. Although patients with thrombotic microangiopathies received glucocorticoid therapy, their condition did not improve. The American Society of Clinical Oncology guidelines summarize the management of nephrotoxicity[135].

Different treatments are given according to the increase in the blood creatinine level. Generally, the blood creatinine level is 2-3 times higher than the baseline value, and hormone therapy should be administered. Patients can be treated with renal replacement when necessary. The expression of PD-L1 on cancer cells is the premise of establishing therapy; if PD-L1 is not highly expressed on malignant cells, the use of PD-L1 should be avoided to prevent the occurrence of AKI[136].

**Treatment and prevention with chemotherapy**

Regardless of whether neoadjuvant chemotherapy, postoperative adjuvant chemotherapy, or late palliative chemotherapy is used, we should fully assess the risk factors for AKI before chemotherapy is initiated. The establishment of a diagnosis of drug nephrotoxicity may be challenging in oncology patients treated with numerous agents. In addition to their immediate toxic effects on the renal parenchyma, these agents can decrease renal functional reserve[137]. The medications most often associated with AIN are calcineurin inhibitors, antibiotics, proton pump inhibitors and herbal medications[138]. Steroid therapy is effective for the treatment of AIN caused by different types of medications[139].

For example, the simultaneous use of NSAIDs and nephrotoxic antibiotics should be avoided, and contrast-induced nephropathy should be considered and prevented during the assessment of tumor-related disease. At the same time, renal function should be fully evaluated before chemotherapy. If patients are diagnosed with CKD, an evaluation should be made to determine when the dose of chemotherapy drugs should be reduced or a different type of drug should be used. Additionally, the blood volume of tumor patients should be evaluated in a timely manner before medication to prevent the excessive use of diuretics; avoid insufficient blood volume, prevent infection and avoid sepsis. Once AKI occurs, suspicious drugs should be stopped, the etiology and mechanism of AKI should be analyzed and determined, and interventions for prerenal factors, such as supplementing capacity, correcting hypercalcemia, resolving hypercoagulability, and discontinuing ACEIs/ARBs, should be taken.

**Treatment and prevention of TLS-related AKI:** TLS-related AKI usually occurs approximately 24 h after chemotherapy. Prevention is critical, especially for tumor patients with a high tumor burden, a low introductory GFR, and sensitivity to chemotherapy drugs. Correcting electrolyte disturbances, reducing blood uric acid, and ensuring adequate hydration can reduce the risk of AKI, and high-risk patients can also be given intravenous fluids before chemotherapy[140]. Hydration can reduce blood uric acid, blood phosphorus, and blood potassium concentrations, increase renal blood flow, and keep electrolyte balance.

**Treatment and prevention with chemotherapeutic drugs**

Cisplatin is one of the most commonly used antitumor and nephrotoxic drugs. In patients with pre-existing renal impairment, the best method for cisplatin therapy is unknown. The US FDA has not approved any kidney-related dose adjustment guidelines. Studies suggest that patients with renal impairment should receive a reduced dose of cisplatin, but there is still a lack of data[141]. Clinical trial protocols usually require serum creatinine < 177
μmol/L or CrCl ≥ 60 mL/min for patients to receive a full dose of cisplatin. The manufacturer recommends that unless or until serum creatinine is < 1.5 mg/100 mL and/or blood urea nitrogen is < 25 mg/100 mL, multiple courses of cisplatin should be given.

Carboplatin and oxaliplatin are safe for the kidneys. Studies included renal biopsies have shown that both carboplatin and oxaliplatin can cause not only ATN but also AIN[53,142]. Steroid treatment for AIN is controversial. In cases in which renal failure progresses even after drug discontinuation, steroid administration is recommended if the interstitial fibrosis area is 75% or less[143]. In cases in which it is unclear whether AIN is drug-induced, it is essential to discontinue the suspected drugs as soon as possible.

5-FU, capecitabine and irinotecan delivered via a nonrenal pathway rarely cause AKI. Therefore, patients with renal dysfunction do not need to receive an adjusted dose, but oral fluoropyrimidine capacity is contraindicated in patients with severe renal impairment (CrCl < 30 mL/min). Once AKI is diagnosed, the dose should be reduced by 25%.

Gemcitabine-associated thrombotic microangiopathy (TMA) is believed to be rare, with an estimated incidence rate of 0.015%. TMA treatment includes the withdrawal of gemcitabine, antihypertensive therapy, plasma exchange and dialysis[144]. Related studies were unable to determine the role of hormones in TMA, and there is still no suitable preventive method[145].

VEGF pathway inhibitors (bevacizumab and aflibercept) are a class of antiangiogenic small-molecule TKIs (sunitinib, sorafenib, pazopanib, etc.), and although proteinuria is a common effect of all VEGF pathway-targeted drugs, the factors related to the occurrence and severity of proteinuria remain unclear. At present, there is no research finding indicating that VEGF pathway inhibitors induce AKI[48]. In summary, renal biopsy is always the gold standard for the diagnosis of drug-related AKI[146].

**Prevention-related factors in perioperative AKI**

IAH can cause a decrease in renal blood flow. However, for gastrointestinal tumor patients undergoing laparoscopic surgery, the duration of pneumoperitoneum during surgery should be kept as short as possible. Blood transfusions also play an essential role in AKI because they also cause hyperkalemia; therefore, unnecessary blood transfusions should be avoided in patients undergoing gastric surgery. In addition to regularly checking kidney function during the perioperative period, checking urine output every six hours is an excellent way to evaluate the occurrence of AKI.

**Enhanced recovery pathways**

The hallmark of enhanced recovery pathways (ERPs) is the bundled application of evidence-based perioperative interventions. While no two programs are identical, core components include establishing a patient safety climate, creating multidisciplinary teams, and providing comprehensive patient education, multimodal analgesia, minimally invasive surgical techniques, goal-directed fluid administration and optimized nutrition[147,148]. ERPs have gained widespread popularity across gastrointestinal surgical subspecialties as a means to hasten postoperative recovery[149,150]. ERPs resemble an overall plan; standardized ERP measures for colorectal surgery hospital patients include: (1) Patient education; (2) Avoidance of routine bowel preparation; (3) Precise fluid intake up to 2 h before surgery; (4) Administration of a preoperative oral carbohydrate solution (i.e., PreOP, Nutricia; Numico, Zoetermeer); (5) Avoidance of preoperative sedatives; (6) Epidural analgesia for open surgery; (7) Protocolized fluid administration with intraoperative GDFT via noninvasive hemodynamic monitoring using Vigileo/FloTrac or esophageal Doppler (EDM Dexter Medical, Inc., Irvine, TX); (8) Avoidance of hypothermia; and (9) Avoidance of routine surgical drains[151]. During the treatment process, a multidisciplinary team proposed optimizing fluid therapy, avoiding fasting, using minimally invasive surgical methods and early feeding, and using specifically proposed interventions to solve preoperative hypoproteinemia, the most prominent of which is preoperative nutritional optimization. Nutritional optimization is the core component of an ERP with potential intervention points. Successful nutritional intervention before and after surgery is related to improved bowel recovery. Further studies are necessary to evaluate the feasibility and effectiveness of risk factor mitigation or the individualization of bundled therapies to reduce AKI in ERPs for colorectal surgery[151].
Continuous RRT

Despite these temporary measures, patients with gastrointestinal tumors may still develop AKI during treatment and require RRT. They may also develop other initial indications for continuous RRT (CRRT), such as metabolic acidosis, persistent oliguria or anuria, and hyperkalemia, which are difficult to correct.

The decision to discontinue RRT in patients with AKI is based on the following clinical scenarios: Intrinsic kidney function has adequately improved to meet demands, the disorder that prompted the need for renal support has improved, or CRRT is no longer consistent with the goals of care. There is no definitive prospective evidence to guide clinicians, but urine output appears to be predictive of successful RRT discontinuation. In one study of patients on CRRT, 24-h urine output > 400 mL/d in those not taking diuretics or > 2300 mL/d in those taking diuretics was associated with a > 80% chance of successful RRT discontinuation. Other studies have suggested that the quantitation of timed urinary creatinine and urea excretion may be helpful [152,153].

CONCLUSION

Tumor treatment has developed rapidly in the past two decades, and the survival durations of patients with gastrointestinal tumors have been prolonged. However, the prevalence of factors that cause AKI has also increased significantly. Therefore, nephrologists and oncologists need to pay attention to patients’ renal function during each treatment. However, the author is pleased to see that research on goal-oriented therapy and ERPs has been published in recent years that may reduce the occurrence of AKI. Future research should focus on more on ERPs and on GDFT.

REFERENCES

Su YQ et al. AKI in gastrointestinal tumor


WJCC | https://www.wjgnet.com

Su YQ et al. AKI in gastrointestinal tumor

10.1371/journal.pone.0140197


102 Ho KM, Sheridan DJ. Meta-analysis of frusemide to prevent or treat acute renal failure. BMJ 2006; 333: 420 [PMID: 16861256 DOI: 10.1136/bmj.38902.605347.7C]


119 Brienza N, Giglio MT, Marucci M, Fiore T. Does perioperative hemodynamic optimization protect


Application of vascular endothelial cells in stem cell medicine

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Abstract

Stem cell medicine is gaining momentum in the development of therapy for various end-stage diseases. The search for new seed cells and exploration of their application prospects are topics of interest in stem cell medicine. In recent years, vascular endothelial cells (VECs) have attracted wide attention from scholars. VECs, which form the inner lining of blood vessels, are critically involved in many physiological functions, including permeability, angiogenesis, blood pressure regulation, immunity, and pathological development, such as atherosclerosis and malignant tumors. VECs have significant therapeutic effects and broad application prospects in stem cell medicine for the treatment of various refractory diseases, including atherosclerosis, myocardial infarction, diabetic complications, hypertension, coronavirus disease 2019, and malignant tumors. On the one hand, VECs and their extracellular vesicles can be directly used for the treatment of these diseases. On the other hand, VECs can be used as therapeutic targets for some diseases. However, there are still some obstacles to the use of VECs in stem cell medicine. In this review, advances in the applications and challenges that come with the use of these cells are discussed.

Key Words: Vascular endothelial cells; Stem cell medicine; Angiogenesis; Atherosclerosis; Tissue defects; Refractory diseases

Core Tip: Vascular endothelial cells (VECs) are involved in several physiological and pathological processes, including angiogenesis, control of blood pressure, and treatment-resistant diseases. Therefore, researchers have applied VECs in stem cell medicine and achieved beneficial results, demonstrating that these cells have a broad potential for application in many fields. This review discusses the functions, applic-
Liang QQ et al. Application of vascular endothelial cells

INTRODUCTION

With the rapid development of medical science and technology[1,2], methods for the treatment of many diseases have been improved. However, there is still a lack of effective treatments for some refractory diseases, such as atherosclerosis[3], myocardial infarction (MI)[4], hypertension[5], malignant tumors[6], and diabetes[7]. Some of the current treatment methods are capable of exerting an effect, but most of them can only function to inhibit the disease without the ability to cure it. In recent years, with the understanding of stem cell biology deepening[8], researchers have found that stem cells, which are capable of self-renewal and differentiation, may provide new solutions for promoting recovery of body defects[9] and treating many intractable diseases[10,11]. The use of stem cells in the field of medicine has been an emerging topic in the past two decades. The main methods of stem cell medicine include using stem cells alone, coculturing stem cells with another type of cells, and the combination of stem cells with a variety of materials and cytokines. Therefore, the exploration of suitable seed cells attracts attention constantly in stem cell medicine. Vascular endothelial cells (VECs), a single layer of cells that lines the inner surface of blood vessels[12], have been widely studied in recent years. A large number of studies have shown the function of VECs in angiogenesis[13,14], the regulation of blood pressure, and the promotion of various pathological processes[15]. VECs have promising potential in stem cell medicine. VECs promote angiogenesis in tissue regeneration and transplanted, improve neural recovery, and act as therapeutic targets for a variety of diseases[16], including atherosclerosis, hypertension, diabetes, and malignant tumors. These recent studies have shown promise for the use of VECs in stem cell medicine. The research progress of VECs is remarkable and has attracted worldwide attention. Although there have been some reviews of VECs[15], the application of VECs in the field of stem cell medicine has been rarely reviewed. Therefore, a systematic description of the application scope and mode of VECs in stem cell medicine is urgently needed. This review aims to discuss the application of VECs in stem cell medicine and focuses on some existing problems, solutions, and aspects that need to be further studied.

SEPARATION, CULTURE AND IDENTIFICATION OF VECs

Sources of VECs

VECs come from a wide range of sources, including various organs from humans and animals. VECs derived from the human umbilical vein are most commonly used[17-21], because human umbilical vein endothelial cells (HUVECs) offer the advantages of sufficient sources, favorable cell activity, ability to obtain a large number of cells at one time, and importantly, availability without any major ethical controversy. In addition, the coronary artery and omentum are also donors for VECs. Shishkova et al[22] cocultured primary human coronary artery and internal thoracic artery endothelial cells and identified their mutually beneficial paracrine interactions. Wang et al[23] extracted mouse aortic endothelial cells, while Schwartz[24] cultured bovine aortic endothelial cells and Reckless et al[25] cultured rabbit aortic endothelial cells. Winiarski et al[26] explored strategies to extract microvascular endothelial cells from the omentum. These studies enriched sources of VECs.

To expand the source of VECs, scholars induced human pluripotent stem cells, including human embryonic stem cells and induced pluripotent stem cells, to differentiate into VECs[27]. Although it has been shown that VECs derived from pluripotent stem cells exhibit some characteristics of endothelial cells, the expression of some key
VEC genes is decreased in stem cell-derived VECs, and some epithelial genes are detected[28]. As a result, most researchers prefer tissue-derived VECs to pluripotent stem cell-derived VECs.

**Separation of VECs**

There are three classic methods for the isolation of VECs: (1) Mechanical scraping method[29]; (2) Tissue block adherent method[30]; and (3) Enzyme digestion method [31]. Because of its high efficiency, enzyme digestion is the most commonly used method. However, the cells obtained by enzyme digestion are of low purity and often contaminated by other cells. Therefore, many researchers have pursued purification methods of VECs. Abbot et al[32] first purified human synovial microvascular endothelial cells by magnetic bead sorting, which is still frequently used in recent years for its high purity. However, magnetic bead sorting could affect the activity of the cells. Density gradient centrifugation is another purification method that is based on the physical properties of endothelial cells[33]. It is an effective method for cell purification, but if the cells are mixed with other components of similar densities in the tissue, it is difficult to separate them. In addition, repeated centrifugation may impact the state of cells and increase the risk of cell damage. Fluorescence-activated cell sorting is another commonly used method[34] that is equipped with good reproducibility, high efficiency, and no effect on cell activity.

**Culture of VECs**

VECs are cultured adherently in most cases. However, there are still major differences between adherent culture methods and the *in vivo* microenvironment, and there is the disadvantage of low culture efficiency. Scholars have explored various methods for the culture of VECs in the pursuit of better culture conditions. Locatelli et al[35] cultured the HUVECs in microgravity and observed that the HUVECs made a series of adaptive changes in order to achieve a new equilibrium in this environment. Wang et al[27] applied VECs to three-dimensional (3D) culture in alginate saline gel and found that this method could provide a better environment for cells compared with 2D culture in terms of cell quantity and quality. Bartaula-Brevik et al[36] cultured HUVECs in a bioreactor system and found HUVECs in the bioreactor performed good abilities in angiogenesis. These studies provided the potential for some new culture methods to be applied in VECs culture.

**Identification of VECs**

Identification of VECs is not difficult and microscopic observation is the most common method. Although VECs from different sources differ microscopically, they all show a paving stone-like morphology. Mitotic, dikaryotic, and polykaryotic nuclei can be observed in the process of cultivation over time. To further identify VECs, scholars focused on exploring their specificity, including the expression of specific surface markers and biological factors. Flow cytometry and immunofluorescence are universal methods for identification and CD31 is the most commonly detected surface marker for VECs. Evaluation of certain biological factors is also helpful for identification of VECs, including VIII factor and von Willebrand factor[37].

**ROLE AND MECHANISM OF VECs IN PHYSIOLOGICAL AND PATHOLOGICAL PROCESSES**

VECs function as a single layer of cells lining the inner surface of the cardiovascular system and play important roles in both physiological and pathological processes. First, VECs act as a barrier between blood and the surrounding tissues, which is especially important for penetration[38]. Second, VECs also serve as an endocrine organ in the body, capable of synthesizing and releasing various endothelial-derived vasoactive factors to regulate vascular tone and coagulation. Third, VECs have receptors that interact with various biological factors and are involved in the regulation of angiogenesis and immune responses[15]. Finally, VECs participate in some diseases[39], such as atherosclerosis and malignant tumors.

**Barrier and regulation of permeability**

VECs are closely arranged on the inner surface of blood vessels and not only provide a smooth surface for healthy blood circulation, but also serve as a selective barrier that is conducive to the exchange of nutrients, wastes, and various signaling molecules to
maintain the dynamic balance of tissues, organs, and the circulatory system throughout the body[40]. Therefore, VECs regulate the permeability of vessels. In different physiological and pathological states, a variety of factors interact with VECs and change the morphology of VECs and the intercellular spaces, leading to changes in the vascular endothelial permeability. In addition to inflammatory mediators such as histamine, bradykinin, thrombin, and platelet-activating factor, vascular endothelial growth factor (VEGF) is also involved in the regulation of endothelial permeability [41]. VEGF is an important signaling molecule synthesized and secreted by VECs and other cells, including smooth muscle cells, fibroblasts, and immune cells. VEGF can interact with VECs to regulate vascular permeability. VEGF binds to VEGF receptor 2 (VEGFR2), activates an intracellular tyrosine kinase activity, regulates downstream signals, and increases vascular penetration[40].

Blood pressure
The regulation of blood pressure is a complex process, and VECs function greatly in it. VECs regulate blood pressure via the synthesis and secretion of paracrine signaling molecules and act on smooth muscle cells, whose contraction and relaxation control vascular tension and thus regulate blood pressure[15]. Molecular regulatory networks are one of the research hotspots at home and abroad. Endothelin and NO have attracted wide attention due to their important roles in blood pressure regulation among various molecules.

Endothelin, which is produced by VECs, is an important factor for the promotion of vasoconstriction. Three isoforms of endothelin have been reported, among which, endothelin-1 is the most effective and long-lasting for vasoconstriction. When blood pressure needs to rise, VECs secrete endothelin for vasoconstriction. Endothelin couples with endothelin receptor A, which is located in vascular smooth muscle cells. Endothelin receptor A mainly induces smooth muscle contraction and constricts blood vessels, thus raising blood pressure[42].

Vasodilation is mainly regulated by NO that is synthesized by endothelial NO synthase in VECs. NO functions as a vasodilative factor partly in two ways. First, NO counteracts the contractile effect of acetylcholine on vascular smooth muscle[13]. Second, NO is able to stimulate increased concentration of cyclic guanosine monophosphate and relax vascular smooth muscle[44].

Together, all of these signaling molecules regulate the dynamic stability of blood pressure. They provide the possibility for VECs to be targeted in blood pressure regulation.

Angiogenesis
VECs have significant influence on angiogenesis. New vessels stem from the established vessels with VECs protruding into filopodia[13]. During new blood vessel formation, VECs differentiate into different phenotypes, including so-called tip cells and stalk cells. Tip cells explore signaling molecules and sense the environment, while stalk cells grow to ensure that new blood vessels continue to elongate. When new vessels meet, a vascular anastomosis occurs[45]. VECs have binding sites for a variety of cytokines and are regulated by these cytokines to promote angiogenesis. VEGF is a key proangiogenic factor. It binds to three receptors: VEGFR1, VEGFR2, and VEGFR3. The former two receptors have a great influence on angiogenesis, especially VEGFR2, which promotes the migration and proliferation of VECs by activating phospholipase C-α and phosphatidylinositol-3 kinase and binding to TYR951[46]. In the angiogenic environment, the formation and secretion of the powerful proangiogenic molecule VEGF are increased. VEGF can regulate the proliferation and migration of VECs. Pulkkinen et al[47] found that as a specific endothelial target of VEGF, bone morphogenetic proteins (BMPs) 2/4/6 have a significant impact on the regulation of angiogenesis. The Hippo signaling effector TAZ is the key for BMPs to control VEGF signaling via the regulation of VEGFR2 expression. In this way, TAZ can regulate VEC survival and proliferation. In addition, other signaling molecules such as heat shock protein A12b, store-operated calcium entry-associated regulatory factor, and orai1 have also been found to be involved in the regulation of VECs and contribute to the progression of angiogenesis.

Hypoxia is an important promoter of angiogenesis especially in a tumor microenvironment. Hypoxia can upregulates hypoxia-inducible factor-1, a factor that activates the transcription of proangiogenic factors including VEGF[48], fibroblast growth factors (FGFs), and placental growth factor (PLGF). PLGF binds to the tyrosine kinase receptor of VECs to regulate VECs, and FGFs regulate the migration of VECs, both of which can promote the angiogenic process of VECs[13]. It is reported that hypoxia also activates hypoxia-inducible-factor-α-independent proangiogenic pathways including...
the mechanistic target of rapamycin and unfolded protein response[49]. Tumoral angiogenesis induces an unharmonious angiogenic profile.

**Endothelial-mesenchymal transition**

Endothelial-mesenchymal transition (EMT) describes a state in which VECs have lost the characteristic phenotype and functions of endothelial cells and gained the morphological and functional characteristics of mesenchymal stem cells[50]. This transition is important for the maturation of blood vessels and heart valves[51], which may be considered a part of angiogenesis. Many factors, including oxidative stress, fatty acid oxidation, hyperglycemia, and shear stress forces, can be initiators for EMT. However, sometimes EMT might lead to pathological changes and the onset of many diseases, such as MI, atherosclerosis, and hypertension. Therefore, it is important to understand the change and regulation mechanism of EMT of VECs. In the past decade or so, scholars have pursued in-depth exploration of the EMT mechanism and its influence on the body’s condition. The transforming growth factor (TGF)-α signaling pathway has been generally regarded as the main regulatory factors for EMT[52]. The TGF-α signaling pathway promotes inhibition of the endothelial gene that encodes connectin and activation of Smad-independent pathways. Then cell adhesion is loosened and EMT occurs.

Activation of some other pathways such as the BMP signaling pathway, Notch signaling pathway, Wnt signaling pathway, and the inflammatory process can also regulate EMT[51].

**Atherosclerosis development**

As a chronic inflammatory vascular disease, atherosclerosis in the early stage is characterized by the deposition of lipids and complex polysaccharides in the vascular endothelium[46]. Dysfunction and inflammation of VECs have an impact on the early progression of atherosclerosis[53]. NO signaling and reactive oxygen species (ROS) signaling are responsible for regulating VEC activation. NO mainly inhibits the secretion of proinflammatory factors and the migration of immune cells to maintain VECs in a quiescent state. In contrast, ROS is critical to the regulation of inflammation, resulting in VEC activation. Under inflammatory conditions, the nuclear factor kappa-light-chain enhancer of activated B cells signaling pathway (NF-κB) is induced by ROS. NF-κB acts as a promoter for monocyte recruitment and alteration of permeability[34]. This process contributes to atherosclerosis. VEC dysfunction promotes the occurrence of atherosclerosis by damaging the integrity of VECs, changing the role of VECs in the control of blood pressure, blood flow, and coagulation, and promoting the deposition of lipids and thrombi on the surface of VECs. The molecular mechanism of VECs in the mediation of atherosclerosis has been explored. Huang et al[55] found that the scavenger receptor B-1 in VECs serves as a mediator to promote atherosclerosis by mediating and accumulating low-density lipoprotein. This study demonstrates the mediating role of VECs in atherosclerosis.

Atherosclerotic plaques are a feature of atherosclerosis and contain many mesenchymal cells. Some of these mesenchymal cells originate from EMT of VECs[56]. The accumulation of mesenchymal cells is crucial in atherosclerosis. Mesenchymal cells can secrete proinflammatory molecules and synthesize extracellular matrix proteins and metalloproteases to promote plaque formation. However, the specific role of VEC-derived mesenchymal cells in atherosclerotic plaques has not yet been elucidated.

**Immunoregulation**

VECs are not only an integral part of the cardiovascular system, but also act as an immune organ throughout the body that is involved in immunoregulation. VECs function in both innate and adaptive immune responses. When carrying out innate immune functions, VECs are involved in many immune functions that macrophages perform[57]. VECs possess danger-associated molecular patterns that recognize harmful endogenous and exogenous components. They are also equipped with some immune receptors, including Toll-like receptors, that induce a series of proinflammatory cellular responses. VECs exert their immune effects in several ways[58-62]. First, VECs act as a barrier against invasive damage and maintain a balance of hemostasis or coagulation. Second, VECs deliver and recruit migrated immune cells[63]. Finally, equipped with the function of primary paracrine secretion, VECs can secrete chemokines, interleukins, interferons, and growth factors. Although VECs are not classical immune cells, they have an important effect on the immune process via the mechanisms described above[64,65].
Endothelial glycocalyx is also of importance in the immunomodulatory function of VECs. The endothelial glycocalyx tends to be damaged by sepsis\cite{66}. Endothelial permeability changes as the endothelial glycocalyx is destroyed. Without the protective layer, VECs are directly exposed to the blood and come into contact with various inflammatory cells and cytokines that promote VEC damage. Fluid extravasation and edema coincide with VEC dysfunction. Therefore, the integrity of endothelial glycocalyx is essential for the immune function and other physiological functions of VECs.

**Tumor development**

Angiogenesis is vital in tumor formation and development. Tumor blood vessels transport oxygen, nutrients, and signaling molecules, and assist in the removal of waste for tumor growth, invasion, and metastasis. The formation of tumor blood vessels mainly occurs through two methods: Sprouting angiogenesis and intussusceptive angiogenesis\cite{45}. Sprouting angiogenesis\cite{13} is the synergism of tip cells and stalk cells regulated by VEGF and Notch signaling, which leads to the formation and continuous elongation of blood vessel buds and promotes the formation of blood vessels. This is a common form of tumor angiogenesis. In intussusceptive angiogenesis, VECs first form an endodermal tube\cite{67}. Then, a base-degraded collagen bundle is attached to the lateral side of the VEC tube and surrounds the lumen. Finally, myofibroblasts promote the maturation of the connective tissue of the blood vessel. The newly formed blood vessel then gives off branches.

It has been reported that VEGF receptors modulate the formation of blood vessels in tumors and are involved in the progression of tumor development. Krebs et al\cite{68} investigated the relationship between VEGFR2 and prostate cancer. VEGFR2, as one of the main therapeutic targets of tyrosine kinase inhibitors (TKIs), was upregulated in high-risk prostate cancer. Although TKI-based regimens do not achieve promising result for unselected prostate cancer patients at first sight, they can be beneficial for different patient subgroups. This study uncovered the roles of VEGF receptors in angiogenesis and indicated that VEGF receptors can be taken into consideration in tumor treatment.

**CLINICAL PROSPECTS**

The role of VECs in blood pressure regulation, angiogenesis, inflammatory processes, tumor development, and atherosclerosis has provided new insights into many medical issues, including tissue engineering and refractory diseases. The application of VECs in these contexts has been widely studied.

**Tissue engineering**

Tissue engineering has been a topic of interest in recent years. It aims to solve problems involving tissue repair and reconstruction. However, there are still many obstacles for vascularization in traditional stem cell medicine, especially in large tissues, which often die due to insufficient blood supply\cite{69}. Because of their excellent angiogenic ability, VECs have attractive prospects in stem cell medicine. This research direction is mainly focused on coculture with other cells and endothelial-cell-derived extracellular vesicles.

Coculture with stem cells is the most commonly used method for VECs in tissue engineering and researchers have made lasting advances in this realm. Niemistö et al were the first to coculture VECs and fibroblasts to promote angiogenesis in vitro\cite{70}. Recently, Piard et al\cite{71} cocultured HUVECs and human mesenchymal stem cells to promote vascularization and bone regeneration. The level of angiogenesis positively correlated with the total number of HUVECs. These two studies highlight the potential of VECs in angiogenesis. Coculturing VECs with other cells not only promotes vascular regeneration, but also exerts an important effect on tissue regeneration through the interactions caused by contact with other cells. Mutschall et al\cite{72} cocultured HUVECs and adipose-derived stem cells for bone regeneration. They found that mineralized substrates and alkaline phosphatase activity were increased, as was the expression of angiogenic marker genes. This study demonstrates that VECs not only promote angiogenesis through coculture but also promote tissue regeneration via cell contact. It provides a new direction that VECs can be cocultured with other cells to function via cell contact, and more should be explored about this contact.
VECs have also been used to build disease models in vitro, which provide a foundation for the development of treatments for various diseases. Campisi et al. [73] used human induced pluripotent stem cell-derived VECs, brain pericytes, and astrocytes to construct a microvascular network in vitro in order to simulate the complex microenvironment of the blood-brain barrier. The establishment of this model represents a new avenue for the study of complex physiological states, which is beneficial for the development of new drugs and therapeutic methods. More study can be conducted for distinct models.

Extensive study of extracellular vesicles has occurred in recent years, and VEC-derived extracellular vesicles have been an area of particular interest. Venkat et al. [74] found that the use of VEC-derived extracellular vesicles in mice with cerebral ischemia could promote angiogenesis in the brain and increase the density of axons and myelin sheath and polarization of M2 macrophages. The use of VEC-derived extracellular vesicles can effectively avoid many immune problems compared with using VECs directly. This research opens up a new door for the application of VECs.

**Refractory diseases**

**Cardiovascular diseases:** VECs are found on the inner surface of cardiovascular vessels, and affect both physiological functions and pathological processes of the cardiovascular system. Therefore, VECs have the potential to serve as seed cells or therapeutic targets. VEC-derived exosomes may have additional potential in the treatment of many cardiovascular diseases, including MI, atherosclerosis, and hypertension.

MI is a serious cardiovascular disease, which is caused by continuous ischemia and hypoxia of the coronary artery. In those experiencing MI, it is difficult to restore the blood supply to the pathological myocardium. After continuous exploration for MI treatments, researchers have focused on regeneration of the coronary vessels. Some have applied tissue engineering methods to implant cells and scaffolds into damaged areas. VECs are considered to be suitable as seed cells because of their critical role in angiogenesis. Ye et al. [75] used VECs for the treatment of MI in pigs. Their results showed that this strategy could effectively control the development of the disease and improve myocardial function. Rabbani et al. [76] extracted autogenous VECs from sheep saphenous veins and then injected the cells into the area of MI. They found that autogenous VECs promoted angiogenesis and functional recovery in MI areas. These studies demonstrate the potential of VEC transplantation in the reconstruction of blood supply and functional recovery in MI. However, the transplantation of VECs still coincides with issues such as potentially low cell survival rate and strong immunogenicity of allogeneic VECs. Therefore, some researchers have turned their attention to exosomes derived from VECs. Ong et al. [77] used VEC-derived exosomes as a vehicle to deliver miRNA-210 and miRNA-126 to cardiac progenitor cells. The results showed that the treatment increased the ejection fraction and improved heart function. This study demonstrates that VEC-derived exosomes can act as a delivery agent in the treatment of MI. This suggests that VEC-derived exosomes can also play a role of transmission in other diseases, which has great clinical value and needs to be confirmed by more studies.

Aside from cell and exosome transplantation, VECs could also be a potential target for the treatment of MI. Myocardial fibrosis is a consequence of heart attack and eventually leads to heart failure. EMT is essential for myocardial fibrosis. Therefore, the process of myocardial fibrosis can be controlled by the regulation of EMT. Chen et al. [78] found that NUR77, an orphan nuclear receptor, inhibits EMT and thus regulates myocardial fibrosis. Yin et al. [79] found that Tongxinluo, a common drug used to treat cardiovascular disease, enhanced the expression of endothelial markers in VECs and inhibited EMT. As a result, it inhibits myocardial fibrosis and facilitates the recovery of the blood supply. These studies have demonstrated that the control of EMT can reduce the occurrence of myocardial fibrosis and thus improve recovery of the myocardial blood supply. Researchers have attempted to identify the target molecules of VECs. Li et al. [16] observed the changes in VECs in mouse models of MI and studied the effect of plasmalemma vesicle-associated protein on the proliferation of VECs in vitro. They demonstrated that plasmalemma vesicle-associated protein, a VEC-specific marker, directly regulates the proliferation of VECs. This protein may be an emerging potential therapeutic target. Although it is believed that VECs can be used as a target in the treatment of MI, the precise mechanism and methods of treatment require further exploration, and more work should be done in different animal models.

Apoptosis, dysfunction, and coagulation of VECs are all triggers for atherosclerosis, and represent the early manifestations of the disease. VECs have potential to function in the treatment of atherosclerosis. Studies have also shown that exosomes derived
from VECs can be effective in the development of atherosclerosis. Inflammatory hyperplasia of the arterial wall is a hallmark of atherosclerosis. Control of arterial wall hyperplasia is a promising direction for the treatment of atherosclerosis. Li et al[80] modulated the molecular expression of VEC-derived exosomes and used these exosomes for in vivo studies. The results showed that the formation of new intima was reduced and the phenotype of vascular smooth muscle cells was altered when VEC-derived exosomes mediated by CD137 signaling were injected. This study showed that VEC-derived exosomes are promising targets for the treatment of atherosclerosis.

Owing to the important role that VECs plays in the progression of atherosclerosis, the control of VECs via various mechanisms has been considered a promising direction for atherosclerosis treatment. Therefore, VECs can be used as a target for atherosclerosis therapy. Some researchers have developed enhanced external counterpulsation, which is a form of noninvasive treatment[81,82]. Enhanced external counterpulsation treats atherosclerosis by increasing the shear stress acting on VECs to inhibit VEC apoptosis. This method is able to reduce the causes of atherosclerosis and is effective for atherosclerosis control. This study demonstrated that enhanced external counterpulsation can be effective as a treatment for atherosclerosis. It also illustrates that more new methods for atherosclerosis treatment may be developed with VECs as the target.

Covered on the surface of VECs, extracellular glycocalyx lesions make contributions to VEC dysfunction and the early development of atherosclerosis. On the contrary, restoring the integrity of the extracellular glycocalyx is beneficial to reverse the dysfunction of VECs and facilitate early treatment of atherosclerosis. Mitra et al[83] published a detailed review on this possibility and the corresponding methods for targeting the extracellular glycocalyx in atherosclerosis treatment.

Hypertension is an important and harmful cardiovascular disease, and its development leads to organic changes in blood vessels. VECs are important managers of vascular tension and the occurrence of hypertension is closely related to VEC dysfunction. Although there are currently some treatment methods for hypertension, they hardly address the recovery of dysfunctional VECs. Some researchers have explored VECs as a target for the treatment of hypertension and found that targeted regulation of VECs can be a potential approach. Guo et al[84] found that endothelial sirtuin 6 (SIRT6), a highly conserved nicotinamide adenine dinucleotide-dependent histone deacetylase[85], can enhance the function of VECs, inhibit their aging and apoptosis, and facilitate vasodilation of NO. As a result, VEC target regulation via modulating SIRT6 has potential in the treatment of hypertension. BMP receptor (BMPR)-2, which is specifically expressed in VECs, regulates angiogenesis by controlling the expression of VECs. It has been reported that the absence of BMPR-2 in VECs can lead to pulmonary hypertension[86]. Therefore, modulation of BMPR-2 has also been considered as a method to treat pulmonary hypertension. Spiekeroetter et al[87] treated pulmonary hypertension with FK506, a drug that alleviates pulmonary artery endothelial cells by inducing BMPR-2. They found that low-dose FK506 is capable of promoting recovery of dysfunctional VECs, which finally reverses pulmonary hypertension. These studies suggest that rescuing VEC dysfunction can be a potential therapeutic method for the treatment of pulmonary hypertension.

The EMT of VECs also contributes to the development of hypertension. Wang et al[12] found that promotion of EMT facilitated the development of pulmonary hypertension. Therefore, some researchers have considered treating hypertension by targeting EMT. Yu et al[88] downregulated EMT via application of paeoniflorin to alleviate pulmonary hypertension. Tsutsumi et al[89] also identified that pulmonary hypertension could be treated by inhibiting EMT with TKI nintedanib. Zhang et al[90] found that hydrogen solubility inhibited EMT in pulmonary artery hypertension. These studies all highlight the therapeutic potential of EMT in hypertension, although the specific drugs and the methods by which they are administered require further study.

Neurological diseases: In addition to their application in cardiovascular disease, VECs have also been used in the treatment of neurological disease. Zhou et al[91] discovered that in the process of nerve injury, brain microvessels function as phagocytes to engulf myelin debris. During this process, VECs are also involved in angiogenesis associated with demyelinating lesions. This study suggested that the role of VECs in demyelinating lesions may lead to new therapeutic approaches for neurological diseases via control of the phagocytic process.

Extracellular vesicles from VECs are also helpful in nervous system impairment. Yue et al[92] cocultured HUVECs with neurons and found that HUVEC-derived exosomes prevented neuronal injury. Venkat et al[74] found that exosomes derived
from brain VECs can promote neurological recovery in diabetic stroke mice. These studies demonstrated that VEC-derived extracellular vesicles may be used as a drug directly or as a carrier of other drugs. However, the method and effectiveness of the treatment need to be further studied.

**Diabetes:** Diabetes mellitus is a chronic metabolic disease that is difficult to cure and is accompanied by a variety of complications. Beta cell dysfunction in the pancreas is the main cause of insulin-dependent diabetes mellitus, and the main approach for treatment involves increasing the source of insulin. Pancreatic transplantation may be a promising treatment for the promotion of insulin production. Yue et al. cocultured HUVECs and beta cells and constructed a bioartificial pancreas encapsulation device [92]. They found that coculture with HUVECs enhanced secretion of islet beta cells. Barba-Gutierrez et al.[93] covered isolated islets with VECs and found that VECs could enhance the vascularization of pancreatic islets, promote insulin secretion, and improve the success rate of transplantation. Lazzari et al.[20] cultured human skin fibroblasts and HUVECs in pancreatic acellular scaffolds and found that HUVECs significantly increased the vasculature of the scaffolds. These studies confirmed the role of VECs in promoting vascularization and enhancing islet function in pancreas and islet transplantation.

When exposed to high blood glucose concentration for an extended period of time, VECs may experience pathological changes, including the overexpression of ROS, which is an essential promoter of VEC dysfunction. VEC dysfunction further brings about vascular disease in multiple organs of the body and is the basis of various complications. Therefore, treatment of VEC dysfunction has become one of the methods to prevent and treat diabetic complications. Studies have found that metformin, the first-line antidiabetic agent, is a good regulator for the control of VEC dysfunction in diabetic patients, in addition to its main target for the control of blood glucose by respiratory chain complex 1. Ouslimani et al.[94] found that metformin can reduce ROS and inhibit the occurrence of VEC dysfunction. Targosz-Korecka et al.[95] found that metformin can promote recovery of endothelial glycocalyx dysfunction, which is conducive to the recovery of VEC dysfunction. In addition, other approaches to treat diabetic VEC dysfunction are being explored. Wang et al.[96] found that 12(S)-hydroxyeicosatetraenoic acid [12(S)-HETE], an arachidonic acid metabolite, is able to damage VECs and alter VEC permeability by changing the phosphorylation levels of adherens junctions. Otto et al.[97] conducted a study in a mouse model of diabetes to identify the function of 12(S)-HETE. They found that 12(S)-HETE is capable of activating intracellular cation channel transient receptor potential vanilloid 1. VEC dysfunction is promoted through the process above. Conversely, inhibition of VEC dysfunction prevents the progression of diabetes. These findings suggest that the regulation of 12(S)-HETE to rescue VEC dysfunction could be a new therapeutic approach for diabetes. These studies validate the importance and mechanisms of VECs in the development of diabetes and, more importantly, shed new light on the potential of targeting VECs for the treatment of diabetes. The mechanism of treatment and additional drugs and treatment methods need to be further investigated.

**Malignant tumors:** Malignant tumors are life-threatening and remain difficult to cure. Excessive angiogenesis is a characteristic of many malignant tumors. Therefore, many researchers have begun to explore whether VECs can be used for malignant tumor therapy. The therapeutic application of VECs in malignant tumors mainly occurs in two ways: (1) Serving as a target for clinical treatment; and (2) Participating in the construction of in vitro malignant tumor models. Early antiangiogenic drugs failed to identify malignant tumor VECs from normal VECs, leading to damage of healthy VECs during treatment. Recently, it was found that under the influence of the tumor microenvironment, tumor VECs are heterogeneous and express different phenotypes from normal VECs[98,99], which provides opportunities for successful VEC-targeted treatment of malignant tumors. However, anticancer mechanisms and new drugs targeting VECs should be developed more widely.

To explore clinical treatment methods, malignant tumor models have been comprehensively studied. Lazzari et al.[20] cocultured pancreatic malignant tumor cells, fibroblasts, and HUVECs to construct a pancreatic malignant tumor model in vitro and this model is helpful in advance of preclinical drug trials. Swaminathan et al.[100] established a model of breast cancer in vitro by coculturing mammary epithelial cells and VECs on alginate scaffolds. Furlan et al.[101] established several different coculture models of VECs and cancer cells to study the related mechanisms of angiogenesis in breast cancer. These models can be used for the development of new anticancer drugs and treatments.
**Inflammation:** VECs also have potential in the treatment of inflammation, especially in coronavirus disease 2019 (COVID-19), which is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[102], a virus that has had significant impact on the world since 2019. Pathogenic mechanisms and treatment methods of COVID-19 have attracted worldwide attention and extensive research on SARS-CoV-2 has been carried out. It has been widely reported that SARS-CoV-2 binds to angiotensin-converting enzyme 2 in VECs[103], affecting the balance between angiotensin-converting enzyme 2, angiotensin-converting enzyme 1, and angiotensin II, which leads to inflammation and damage of VECs and organs. Therefore, promotion of VEC recovery represents a new way to enhance therapeutic effects and improve the prognosis of COVID-19. In addition, the endothelial glycocalyx is also damaged by COVID-19[104]. Studies have found that there is an increase in endothelial glycocalyx fragments in patients with COVID-19. This finding not only indicates that endothelial glycocalyx fragments can be used to evaluate the extent of endothelial injury, but also reflects the extent of damage to the body by COVID-19. It demonstrates that the recovery of endothelial glycocalyx injury to reactivate the function of VECs may be another method to treat COVID-19.

In addition, thrombus formation is a serious complication in COVID-19 patients and VECs are also targeted by SARS-CoV-2. Khan et al[105] found that large thrombi in COVID-19 patients entered the heart and were life-threatening. Other studies have found that the occurrence of thromboembolism is related to the severity of disease progression and mortality[106,107]. Anticoagulation is also regulated by VECs to some extent. Therefore, anticoagulation and restoration of normal functions of VECs are crucial in the treatment of patients with COVID-19. However, much effort still needs to be made toward finding effective treatments.

**Problems and solutions of VECs application**

In the application of VECs, there are still some problems that should be addressed. First, cell sources and culture methods need to be carefully considered. Tissue-derived VECs are more reliable than human-induced VECs. For example, the aorta and the human umbilical vein are common sources[23,35,36]. Second, how to obtain a large number of VECs for medical applications and how to make VECs function in the most efficient way are still worth further exploration. HUVECs are the most frequent choice due to their excellent proliferation and amplification ability[72,92]. In terms of culture methods, emerging research in recent years has broken out of the limitation of 2D culture and developed new culture methods, including 3D culture and microgravity culture for VECs[35,71]. These new culture methods also improved the quality and amplification efficiency of VECs. Third, in the process of cultivating VECs, it is necessary to prevent not only the contamination of microorganisms, but also the contamination of other cells. Crouch et al[34] have described in detail the steps taken to isolate and purify VECs in adult mouse brain microregions via fluorescent-activated cell sorting with anti-CD31 antibodies. This recent study has provided a good method for the purification of VECs. The application of VECs will inevitably encounter immunogenic obstacles, and the application of autologous cells[76] and extracellular vesicles[74,80] is a good solution. However, this is usually limited in the clinic (Table 1).

**CONCLUSION**

VECs have been widely used in stem cell medicine because of their important roles in angiogenesis and tissue regeneration. However, the application of VECs is subject to many restrictions, including limited sources of VECs, invasive acquisition processes, and immune-rejection due to the immunogenicity of heterogeneous and allogeneic VECs. Although induced pluripotent stem cells represent a new source of VECs, their phenotypes are different from those of tissue-derived VECs and there is some uncertainty about their application. If VEC transplantation is to be used in clinical treatment, there are still ethical concerns as well as a lack of relevant application norms at present. The application of VECs in stem cell medicine is mostly allotransplantation, and the problem of immunogenicity arising from it remains to be solved. Many studies have shown that VECs have potential to function as therapeutic targets for a variety of diseases such as atherosclerosis, MI, hypertension, malignant tumors, and COVID-19. However, many treatment methods and mechanisms are still in the verification stage and lack sufficient clinical evidence, especially the role of VEGFRs in development and treatment of malignant tumors.
Table 1 Summary of roles of vascular endothelial cells as checkpoint for immunological patrolling

<table>
<thead>
<tr>
<th>Role of VECs</th>
<th>Molecule type</th>
<th>Suggested mechanisms</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Express pattern recognition receptors</td>
<td>TLRs (TLR1-TLR10)</td>
<td>Contribute to early stages of the immune response against various microbial agents</td>
<td>Sturtzel et al[15]</td>
</tr>
<tr>
<td></td>
<td>NLRs</td>
<td>Sense intracellular microbial invaders and danger molecules produced under stress</td>
<td>Fleissner et al[58]</td>
</tr>
<tr>
<td></td>
<td>RLRs</td>
<td>Involved in antiviral immune response and contribute to chronic inflammatory disease</td>
<td>Asdonk et al[59]</td>
</tr>
<tr>
<td></td>
<td>AIM2-like receptors</td>
<td>Form an inflammasome with the ligand and ASC to activate caspase-1</td>
<td>Hornung et al[60]</td>
</tr>
<tr>
<td></td>
<td>C-type lectin receptors</td>
<td>Regulate signal cascades in response to distinct pathogen- or self-derived components</td>
<td>Kim et al[61]</td>
</tr>
<tr>
<td>Express proangiogenic molecules</td>
<td>FGFs</td>
<td>Anneal adherens junctions and promote VEC migration</td>
<td>Potente et al[13]</td>
</tr>
<tr>
<td></td>
<td>NEU1</td>
<td>Restrain VEC migration</td>
<td>Cross et al[62]</td>
</tr>
<tr>
<td></td>
<td>VEGF</td>
<td>Induces VEC phenotype changes and regulates proliferation and migration of VECs</td>
<td>Potente et al[13]</td>
</tr>
<tr>
<td></td>
<td>IL-8</td>
<td>Induces VEC proliferation</td>
<td>Sturtzel et al[15]</td>
</tr>
<tr>
<td>Express adhesion molecules</td>
<td>P-selectin</td>
<td>Recruits leukocytes</td>
<td>Sturtzel et al[15]</td>
</tr>
<tr>
<td></td>
<td>E-selectin</td>
<td>Attaches monocytes</td>
<td>Sturtzel et al[15]</td>
</tr>
<tr>
<td></td>
<td>ICAM-1; VCAM-1</td>
<td>Function as VEC activation markers</td>
<td>Sturtzel et al[15]</td>
</tr>
<tr>
<td>Express MHC</td>
<td>MHC I</td>
<td>Leads to recruitment of antigen-specific; naïve CD8+ T cells</td>
<td>Mai et al[63]</td>
</tr>
<tr>
<td></td>
<td>MHC II</td>
<td>Presents endothelial antigens to immune cells</td>
<td>Mai et al[63]</td>
</tr>
<tr>
<td>Express immune checkpoints</td>
<td>PD-L1/2</td>
<td>Inhibits T cell activation</td>
<td>Rodig et al[64]</td>
</tr>
<tr>
<td></td>
<td>ENO-1</td>
<td>A major glycolytic enzyme, over-expressed in various cancer tissues</td>
<td>Zheng et al[65]</td>
</tr>
<tr>
<td>Express pro-inflammatory cytokines</td>
<td>IL-10, IL-6, and IL-8</td>
<td>Function as a complementary mechanism for the detrimental effects of viruses on atherosclerosis</td>
<td>Asdonk et al[59]</td>
</tr>
</tbody>
</table>

TLRs: Toll-like receptors; NLRs: Nucleotide-binding oligomerization-domain (NOD)-like receptors; RLRs: Retinoic acid inducible gene-1 (RIG-I) like receptors; AIM2: Absent in melanoma 2; NEU1: Epidermal growth factor like domain 7; IL: Interleukin; ICAM: Intercellular adhesion molecule; VCAM: Vascular cell-adhesion molecule; MHC: Major histocompatibility complex; PD-L1/2: Programmed death-ligand 1/2; ENO-1: Enolase 1; FGFs: Fibroblast growth factors; VEC: Vascular endothelial cell; VEGF: Vascular endothelial growth factor.

Despite the numerous challenges, the important role played by VECs and their exosomes in many physiological and pathological processes has prompted a new direction for the treatment of many diseases and represents a broad prospect in the development of stem cell medicine.

REFERENCES

Liang QQ et al. Application of vascular endothelial cells


43 Furchgott RF, Zawadzki JV. The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. *Nature* 1980; 288: 373-376 [PMID: 6253831 DOI: 10.1038/309837a0]


Campisi M, Shin Y, Osaki T, Hajal C, Chiono V, Kamm RD. 3D self-organized microvascular
model of the human blood-brain barrier with endothelial cells, pericytes and astrocytes. *Biomaterials* 2018; 180: 117-129 [PMID: 30852046 DOI: 10.1016/j.biomaterials.2018.07.014]


77 Ong SG, Lee WH, Huang M, Dey D, Kodo K, Sanchez-Freire V, Gold JD, Wu JC. Cross talk of combined gene and cell therapy in ischemic heart disease: role of exosomal microRNA transfer. *Circulation* 2014; 130: S60-S69 [PMID: 25260057 DOI: 10.1161/CIRCULATIONAHA.113.007917]


86 Hong KH, Lee YJ, Lee E, Park SO, Han C, Beppu H, Li E, Raiizada MK, Bloch KD, Oh SP. Genetic ablation of the BMPR2 gene in pulmonary endothelium is sufficient to predispose to pulmonary arterial hypertension. *Circulation* 2008; 118: 722-730 [PMID: 18663089 DOI: 10.1161/CIRCULATIONAHA.107.736001]


Reference text.
Application of traditional Chinese medicine in treatment of Helicobacter pylori infection

Ru-Jia Li, Yuan-Yuan Dai, Chun Qin, Gan-Rong Huang, Yan-Chun Qin, Yong-Yi Huang, Zan-Song Huang, Xian-Ke Luo, Yan-Qiang Huang

Abstract

Helicobacter pylori (H. pylori) has a high rate of infection and antibiotic resistance and poses a serious threat to human life. One of the main strategies to overcome drug resistance is to develop new treatment plans. Traditional Chinese medicine (TCM) that is commonly used to treat many diseases in China can reduce drug resistance and increase the eradication rate of H. pylori. In this paper, we review the research progress on TCM in the treatment of H. pylori infection. The mechanism of action of TCM is reviewed and research and applications of TCM in the treatment of H. pylori are demonstrated. Finally, we discuss problems confronting the use of TCM for the treatment of H. pylori infection and propose possible solutions. In addition, the plans of TCM in H. pylori treatment were also screened: Dampness-heat syndrome in the spleen and stomach, deficiency of spleen and stomach, and cold-heat complicated syndrome, and the effective components therein are studied. The antibacterial effect of TCM is relatively slow; for rapid improvement of the treatment effect of refractory H. pylori gastritis, we provide an appropriate treatment regime combining TCM and Western medicine with immune-regulatory and synergistic antibacterial effects.

Key Words: Helicobacter pylori; Traditional Chinese medicine; Treatment; Antibacterial effect; Antibiotic resistance

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**Core Tip:** With the widespread use of antibiotics, *Helicobacter pylori* (*H. pylori*) has a high rate of infection and antibiotic resistance, posing a serious threat to human life. The development of new drugs is difficult. One of the main strategies to overcome drug resistance is to develop new treatment plans. Traditional Chinese medicine (TCM) is commonly used to treat many diseases in China, and it can reduce drug resistance and increase eradication rates of *H. pylori*, which is recognized by most patients. In this paper, the treatment plans of TCM in *H. pylori* treatment are screened out: Dampness-heat syndrome in the spleen and stomach, deficiency spleen and stomach, cold-heat complicated syndrome, and the effective components are analyzed. It is recommended that doctors choose appropriate integrated traditional Chinese and western medicine treatments based on the dialectical type of TCM etiology and the characteristics of *H. pylori* resistance. The program provides new methods and new ideas for the radical cure of *H. pylori* infection.

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**INTRODUCTION**

*Helicobacter pylori* (*H. pylori*) infection is an important cause of diseases such as chronic gastritis, peptic ulcer, gastric cancer, and other diseases[1-3]. In addition, *H. pylori* infection is also associated with a variety of parenteral diseases such as periodontitis and secondary immune thrombocytopenic purpura[4]. Currently, *H. pylori* infects more than half of the world’s population with the rates of infection higher in developing countries and in some undeveloped areas (> 80%)[5-7]. The prevention and treatment of *H. pylori* infection remain a critical unmet need of major public health significance. Currently, *H. pylori* eradication programs in Western medicine mainly include standard triple, and non-bismuth or bismuth quadruple therapies. However, the drug resistance rate of *H. pylori* is increasing whilst the eradication rate continues to decrease due to the long-term use and abuse of antibiotics[8-10]. Traditional Chinese medicine (TCM) demonstrates a number of potential advantages in the treatment of *H. pylori* infection such as high eradication rates and low levels of toxicity[11]. According to epidemiological statistics, the total effective rate of TCM treatment for *H. pylori* infection can reach 95.45%[12]. This paper reviews the application of TCM in the treatment of *H. pylori* infection and provides a reference for scientists and clinicians regarding the use of TCM in *H. pylori* infection.

**IMPACT OF TCM ON ETIOLOGY AND PATHOGENESIS OF *H. PYLORI* INFECTION**

TCM treats diseases mainly according to the theory of human body balance (Yin and Yang). *H. pylori* infection belongs to the category of "damp-heat pathogenic Qi" or "toxins from pathogenic bacteria". People who have deficiency of spleen and stomach are exposed to external moisture and cool and are more susceptible to pathogenic toxins which in this case refer to *H. pylori*[13]. According to TCM syndrome differentiation and types, *H. pylori* infection can be divided into five types: Deficiency of spleen and stomach, dampness-heat syndrome in spleen and stomach, stomach-Yin deficiency, liver-stomach disharmony, and blood stasis in the stomach collaterals. Deficiency of spleen and stomach, and stomach-Yin deficiency were classified into the group with spleen Qi and stomach-Yin deficiency (SQSYD), and the group of other three types have no SQSYD[14].

Although *H. pylori* infection occurs in the stomach, disease occurs in the spleen. The external invasion of pathogenic Qi, deficiency of vital Qi, and dysfunction of the Qi machinery are the causes of onset. Dampness-heat syndrome in spleen and stomach is an important inducing factor as the humid and hot environment in the stomach...
provides favorable conditions for the growth of bacteria. In addition, the damaged gastric mucosa and the damaged normal physiological structure in the stomach increase susceptibility to *H. pylori* infection[15]. Deficiency of spleen and stomach is often the root cause of related stomach diseases induced by *H. pylori* infection. These stomach diseases are commonly characterized by damp-heat and blood stasis[16]. *H. pylori* infection-related gastritis belongs to "root deficiency and branch excess". The deficiency of spleen and stomach often causes humans being susceptible to *H. pylori* infection due to a series of pathological changes such as damp-heat and blood stasis. These changes result in diseases such as chronic atrophic gastritis and intestinal metaplasia[17,18]. In recent years, most TCMs for treating *H. pylori* infection are spleen-invigorating and Qi-invigorating, which can also support spleen Qi deficiency and stomach weakness as a basic mechanism of pathogenesis in *H. pylori* infection[19].

**RESEARCH AND APPLICATION OF TCM IN TREATMENT OF H. PYLORI INFECTION**

TCM treatment involves the use of medicines with Chinese characteristics. Some monomer compositions containing mucosal protective agents have high eradication rates of *H. pylori* and show low drug resistance, reduced adverse reactions, and low toxicity, and even kill drug-resistant *H. pylori*[20]. The treatment of *H. pylori* infection with TCM emphasizes overall regulation of adult health[21]. In addition to the principle of drug selection to enhance the resistance to infection and eliminate pathogenic factors, TCM aims to replenish Qi, invigorate Qi, promote blood circulation, and remove blood stasis as well as detoxify and dissipate heat[22].

According to TCM syndrome differentiation and types of *H. pylori* infection, an appropriate treatment plan should be selected specifically based on the principle of considering syndrome differentiation and combination of diseases and syndromes. This should enable the development of individualized treatments according to the specific conditions of each patient and allows different TCM formulae to be given according to different symptoms. Cold-natured herbs supplemented with a moderate amount of hot-natured drugs are often used as the main TCM treatment for *H. pylori* infection. Drugs that impact circulation and blood stasis can be added according to specific syndromes to eliminate *H. pylori* and prevent recurrence[23]. TCM treatment for *H. pylori* infection also considers the ingredient addition and reduction method which means that, based on the use of several kinds of TCMs for invigorating the spleen and Qi replenishing, reasonable addition and decrease of ingredients in TCM can be made aiming at different symptoms. For example, more medicines for warming kidney and invigorating spleen can be prescribed for those with Yang deficiency, and more medicines for strengthening the spleen and Qi for those with Qi (a vital energy that circulates through the body at all time) deficiency may be used. Medicines that tonify Qi with a sweet taste and gentle smell should be selected for damp-heat constitution[24]. Based on the "National Consensus for the Treatment of *H. pylori* and related Symptoms based on Integrative Traditional Chinese and Western Medicine" [25], and research of different syndrome types and TCM at home and abroad[26-34], the recommended treatment scheme of TCM is displayed in Table 1.

There are many examples of remarkable therapeutic effects achieved with TCM, which are also supported by some experimental evidence. Yang used Coptis and Officinal Magnolia Bark Beverage and Banxia Xiexin Decoction to treat 20 *H. pylori*-infected patients as the observation group. The total effective rate after treatment reached 95.0%, which was much higher than that of the control group that was treated with Western medicine alone (60.0%). Also, TCM symptom complex score improved significantly with a low recurrence rate[35]. Lin et al[36] randomly divided 60 *H. pylori*-infected rats into control group, model group, and groups of medium-concentration and high-concentration of Liujuanzi decoction according to their curative effect. The study showed decreased levels of inducible nitric oxide synthase activity and nitric oxide in the gastric mucosa of the high concentration Liujuanzi decoction group (1.195 ± 0.026 mmol/g). In addition, serum tumor necrosis factors-α and interleukin (IL)-6 levels were also significantly down-regulated, effectively improving the pathological changes in the gastric mucosa and demonstrating the effectiveness and safety of this decoction[36]. Liang[37] used Xiaoyou Fuwei decoction to treat patients with *H. pylori* infection, with a total effective rate of 94.7% achieved. This decoction could inhibit the activity of arylamine acetyltransferase and multidrug-resistant strains *in vitro* to remove *H. pylori*. Also, the study showed improvements in the clinical symptoms of patients who had protected gastric mucosa by promoting the expression of villi
Table 1 Recommended scheme for traditional Chinese medicine syndrome differentiation and typing

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Treatment</th>
<th>Main prescription</th>
<th>Medicament</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dampness-heat syndrome in spleen and</td>
<td>Clearing heat and dampness, and regulating</td>
<td>Magnolia officinalis, Coptis</td>
<td>H. pylori-infected patients and showed an eradication rate of 94.23%, which</td>
</tr>
<tr>
<td>stomach (heat)</td>
<td>and neutralizing Qi</td>
<td>chinesis, Acorus tatarinowii,</td>
<td>was significantly higher than that of the control group (78.85%). The TCM</td>
</tr>
<tr>
<td>Dampness-heat syndrome in spleen and</td>
<td></td>
<td>Rhizoma Pinelliae, Sojae</td>
<td>syndrome complex score decreased significantly ($P &lt; 0.01$) in the treated</td>
</tr>
</tbody>
</table>
| stomach (cold)                       |                                               | Semen Praeparatum, Gardenia| group which also indicated a significant decrease in adverse reactions ($P < 0.01$)[38]. Taken together, these studies showed the potential importance of TCM in $H. pylori$ treatment, but the question remains as to which TCM ingredients are active therein.
| Deficiency spleen and stomach (cold) | Strengthening spleen and replenishing qi, and  | Costusroot, Amomi fructus,  | $H. pylori$ infection is mediated by bacterial urease, which is the main virulence factor. Bacterial urease hydrolyzes urea to produce carbon dioxide and ammonia, which increases pH in the stomach. As a result, $H. pylori$ can effectively colonize acidic environments.
| and stomach (cold)                   | easing stomach                                 | Citrus, Rhizoma Pinelliae Preparatu, Radix codonopsis, Rhizoma Atractylodes, Portia cocos, Glycyrrhizae |
| Cold-heat complicated syndrome        | Opening with acidity and decreasing bitter, and | Radix Atractylas, Semen Coicis, Codonopsis pilosula, Paeonia lactiflora Pall, | For example, Chinese medicine Angelica can protect the gastric mucosa of patients infected with $H. pylori$ by decreasing the inflammatory response through the nuclear factor kappa B-mediated inflammatory response signaling pathway, decreasing the production of peroxide, and enhancing peroxidase activity to effectively prevent $H. pylori$-induced gastritis and other diseases[45]. The pathogenicity of a series of diseases (such as peptic ulcers) after $H. pylori$ infection is mediated by bacterial urease, which is the main virulence factor. Bacterial urease hydrolyzes urea to produce carbon dioxide and ammonia, which increases pH in the stomach. As a result, $H. pylori$ can effectively colonize acidic environments. The active ingredient of honey can inhibit $H. pylori$ urease with an inhibition rate of about 45%[42]. These ingredients of TCM have been widely applied in Chinese medicine preparations for eradicating $H. pylori$[46].
|                                      | regulating stomach Qi and removing painful     | Codonopsis pilosula, Atractylodes macrocephala, Atractylodes Lancea, Magnolia officinalis, Coptis chinesis, Costusroot, Rhizoma corydalys, Sepia esculenta |
TCMs for treating *H. pylori* infection are mainly cold-natured herbs supplemented by warm and hot herbs which aim to treat heat, Qi stagnation and blood stasis, and Qi deficiency. Heat-clearing drugs include Scutellaria, Coptis chinensis, and rhubarb; dehumidifying drugs include Wrinkled Glanthysso, atractyloides, and Magnolia officinalis; tonifying medicines are glycyrrhiza, ginseng, and white peony root; drugs for relieving exterior disorders include ginger, mint, and chrysanthemum; and mild medicines are Evodia rutaecarpa and clove. The aforementioned drugs have all been widely used in Chinese medicine decoctions and preparations for *H. pylori* eradication. The most bitter drugs can effectively relieve fever, remove dampness, promote blood circulation, and replenish Qi. These act to greatly improve the *H. pylori* eradication rate and reduce adverse reactions. Of the medicines mentioned above, Coptis chinensis is a single Chinese herb which has the highest efficacy for eradicating *H. pylori*. The main component of Coptis chinensis that inhibits *H. pylori* is berberine. The bactericidal mechanism of berberine may be elucidated through inhibition of oxidation of bacterial glucose and metabolic intermediates of glucose which act to kill *H. pylori*.[47] Some of the quinolone alkaloid components in the Chinese medicine Evodia can inhibit the growth of *H. pylori* without eradicating other intestinal flora[48]. Based on the prescriptions mentioned in Table 1, the effective ingredients of the main anti-*H. pylori* monomers of TCM in these prescriptions are summarized by combining with current research results[49-63]. As shown in Table 2, the effective ingredients of these drugs may provide a basis for understanding the mechanism of action of Chinese medicines and provide ideas for novel research directions.

**PROBLEMS AND SOLUTIONS ENCOUNTERED BY TCM IN TREATMENT OF H. PYLORI INFECTION**

Although the treatment of *H. pylori* with TCM can achieve a high eradication rate with low drug resistance and toxicity, problems towards its widespread clinical use remain. Specifically, these include: (1) The extraction of active ingredients of TCM has not yet been performed; (2) pharmacological research on single Chinese herbs and compound preparations remains to be performed; (3) the mechanism of *H. pylori* eradication has not been fully revealed; (4) studies relating to TCM are largely based on small sample sizes which fail to establish a complete *H. pylori* eradication treatment plan; (5) some medicines do not meet the requirements of finished medicines; and (6) diverse lifestyles and diets from different regions may affect responses. The corresponding solutions to these problems are illustrated in Figure 1[62-67], yet there remain many obstacles towards completely resolving these problems.

**COMBINATION OF TCM AND WESTERN MEDICINE IS IDEAL SOLUTION FOR TREATMENT OF H. PYLORI INFECTION**

Compared to simple Western medicine and TCM treatments, the combination of these approaches may provide the ideal solution for the treatment of *H. pylori* infection. Antibiotics have advantages and disadvantages characterized by fast onset, broad antibacterial spectrum, being prone to drug resistance, adverse reactions, severe side effects, and difficulty in completely eradicating *H. pylori*. TCM also exhibits advantages and disadvantages including slow immune-regulation and onset, reduced drug resistance, low toxicity, complex mechanisms of action, and few side effects[68]. Therefore, the combination of the two treatment strategies may be used to effectively cure *H. pylori* infection. Recently, the combination of Chinese and Western medicine has been shown to effectively alleviate *H. pylori* drug resistance, shorten the course of antibiotics, reduce the use of antibiotics, and also improve clinical adverse reactions and toxic side effects[69].

Currently, the theory of combination of TCM and Western medicine for *H. pylori* treatment should be used to select a reasonable treatment plan according to the different stages of diseases and different syndromes. TCM is used for *H. pylori* prevention when patients are not infected. During infection treatment, combined treatments of TCM and Western medicine, such as TCM combined with triple or quadruple treatment for 14 d, can improve the eradication rate. After failure to eradicate infection when the strain has developed drug resistance[70], TCM can be used for conditioning of organism. Refractory gastritis is classified as a type of warm and cold complex regional pain syndrome during treatment of a long course of
### Table 2 Anti-*Helicobacter pylori* active ingredients in the recommended classification scheme

<table>
<thead>
<tr>
<th>Main anti-<em>H. pylori</em> drugs</th>
<th>Active ingredients in anti-<em>H. pylori</em> drugs</th>
<th>Drug-resistant inhibitors</th>
<th>Drug-resistant Sensitizer</th>
<th>Synergies agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magnolia officinalis</td>
<td>Magnolol, honokiol</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Coptis chinensis</td>
<td>Berberine, rhizome, epiberberine, palmatine, coptisine</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Gardenia</td>
<td>geniposide</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Radix scutellariae</td>
<td>Baicalin, baicalein, neobaicalein, norwogonin, skullcap flavone, acaecin, wogonin</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Radix Astragalus</td>
<td>astragalus saponin</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Rheubarb</td>
<td>Rhein, emodin</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Evodia</td>
<td>Limonin, rutecarpine</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Bupleurum</td>
<td>saikosaponin-d</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Rhizoma corydalisis</td>
<td>Quinolone alkaloids</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pogostemon cablin</td>
<td>Patchouli alcohol</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Curcuma longa</td>
<td>Diterpenoid C extracted from radix curcumae, curcumin</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ginseng</td>
<td>Panaxotriol, ginsenoside</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pseudo-ginseng</td>
<td>Sanchinoside</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*: Existing literature has shown this effect; -: No previous research reporting this effect; *H. pylori*: *Helicobacter pylori*.

![Bottleneck problems and solutions](image)

**Figure 1 Bottleneck problems encountered by traditional Chinese medicine in treatment of *Helicobacter pylori* and their solutions.**

Many trials have been conducted in combination with antibiotics or proton pump inhibitors based on the recommended scheme of TCM syndrome differentiation. The total effective rate of *H. pylori* eradication, adverse reactions, *H. pylori*-induced treatment rate of related diseases, and disease in patients with spleen Qi deficiency and stomach weakness, and warm and cold complex regional pain syndrome[71].
Table 3 Anti-Helicobacter pylori program of combination of traditional Chinese and Western medicines

<table>
<thead>
<tr>
<th>TCM syndrome-type</th>
<th>Treatment</th>
<th>Course of treatment and dose</th>
<th>Efficient rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dampness-heat syndrome in the spleen and stomach (heat)</td>
<td>Jiawei Pingwei powder combined with triple therapy (Rabeprazole + Clarithromycin + Amoxicillin)</td>
<td>Jiawei Pingwei powder (2 times/d) + Rabeprazole (10 mg, 2 times/d) + Clarithromycin (0.25 g, 2 times/d) + Amoxicillin (0.25 g, 2 times/d). Course of treatment: 14 d</td>
<td>The combined treatment: 93.48%; Western medicine alone: 77.55%</td>
</tr>
<tr>
<td>Deficiency spleen and stomach (cold)</td>
<td>Xiangsha Liujunzi decoction combined with antibiotic (Rabeprazole)</td>
<td>Xiangsha Liujunzi decoction (1 time /d) + Rabeprazole (10 mg, 2 times/d). Course: 14-28 d</td>
<td>The combined treatment: 96.67%; Western medicine alone: 80.00%</td>
</tr>
<tr>
<td>Cold-heat complicated syndrome</td>
<td>Banxia Xiexin secction combined with antibiotics (Omeprazole + aluminum magnesium carbonate)</td>
<td>Banxia Xiexin decoction (2 times/d) + Omeprazole (10 mg, 2 times/d) + aluminum magnesium carbonate (0.5 g, 3 times/d). Course: 14-28 d</td>
<td>The combined treatment: 96.00%; Western medicine alone: 76.00%</td>
</tr>
</tbody>
</table>

TCM: Traditional Chinese medicine.

the amount of antibiotics used were compared and investigated for a variety of programs. The combinations of Chinese and Western medicines are summarized in Table 3[[72-74]. However, due to the small sample size of individual experiments, the efficiency remains uncertain.

Due to the individual differences of the patients, a reasonable adjustment to treatment can be made based on local drug resistance situation and the medication history of each patient. For example, other antibiotics can be used when the patient is resistant to clarithromycin. In addition, ingredients in the TCM can be added or subtracted according to the actual situation of the patient. For example, in the curative effect of Sijunzi Decoction, if the patient is afflicted with stomach pain, extra Rhizoma corydalis and salvia can be added, or if a patient has stomach Yin deficiency, extra charles abraham and liriope can be added to improve the patient compliance and tolerance.

It has been hypothesized that TCM is complex in its decoction and ingredients, with an unclear mechanism with persistent safety concerns about the medication. The effective ingredients of TCM with clear efficacy can be used to replace TCM decoction when combined with Western medicine. For example, Liu et al[[75] combined pantoprazole with berberine to treat 40 H. pylori-infected patients as the observation group, achieving a total effective rate of 92.5%, which was much higher than that of the control group that was treated with triple therapy (75.0%). In addition, the levels of inflammatory cytokines such as IL-2 and IL-6 were significantly lower in the observation group after treatment than in the control group[[75]. The discovery of the active ingredients in anti-H. pylori TCM, and transformation of its derivatives may not only improve the efficiency of treatment, but also facilitate the exploration of the underlying mechanism of action to promote the development of TMC and Western medicine combinations.

CONCLUSION

There is an urgent need for the development of novel H. pylori treatment and prevention strategies due to high rates of infection and drug resistance. As the development of new drugs remains challenging, the formulation of new treatment programs is currently the main measure to cure or alleviate drug resistance. TCM has achieved some promising results in the treatment of H. pylori infection. Some natural Chinese medicine monomers such as Chinese herbal compounds and TCM preparations have been shown to exert inhibitory effects in the treatment of H. pylori infection. These agents provide an important reference for curing H. pylori infection or intractable gastritis. In the long-term exploration, TCM has been proven to be beneficial as it is reliable, safe, and effective for the treatment of H. pylori infection. It has significant potential for popularization and wider application.

REFERENCES

1 Sonnenberg A, Lash RH, Genta RM. A national study of Helicobacter pylori infection in gastric biopsy specimens. Gastroenterology 2010; 139: 1894-1901.e2; quiz e12 [PMID: 20727889 DOI: 10.1053/j.gastro.2010.08.018]
Li RJ et al. TCM in treatment of H. pylori infection

2 Hu ZH, Niu XP. [Analysis of risk factors related to failure of Helicobacter pylori eradication in the southern part of Anhui province]. Youjiang Minzu Yixueyuan Xuebao 2019; 41: 629-632, 641


6 Chi ZC, Qi YQ, Dong QJ, Si JL. [Diagnosis and treatment of Helicobacter pylori infection and related diseases]. Beijing: Military Medical Science Press, 2008


19 Wu WZ, Zhou XB. [Experience of Zhou Xiaobo on Treating Helicobacter Pylori Associated Chronic Gastritis]. Sichuan Zhongyi 2017; 35: 1-4


25 Hu FL, Zhang SS. [National consensus for the treatment of Helicobacter pylori and related symptoms}
based on Integrative Traditional Chinese and Western Medicine]. Beijing Yiye 2018; 40: 792-798 [DOI: 10.15932/j.2053-9713.2018.08.021]


33 Feng HK [Zuojin Decoction combined with Quadruple Therapy for Gastric Ulcer (Ganwei Buhe) Randomized Parallel Controlled Study]. Shiyouyong Zhongyi Neike Zazhi 2018; 32: 22-24 [DOI: 10.13729/j.issn.1671-7813.x.2018.1050]


Li RJ et al. TCM in treatment of H. pylori infection


Zhang SF, Lei ZR. [Lei Zhengrong’s Experience in Treating Refractory Chronic Gastritis]. *Guiyang Zhongyi Xueyuan Xuebao* 2010; 32: 12-14


CASE CONTROL STUDY

Impact of cytomegalovirus infection on biliary disease after liver transplantation - maybe an essential factor

Jing-Yi Liu, Jian-Rui Zhang, Li-Ying Sun, Zhi-Jun Zhu, Lin Wei, Wei Qu, Zhi-Gui Zeng, Ying Liu, Xin-Yan Zhao

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

Conflict-of-interest statement: The

Abstract

BACKGROUND
Cytomegalovirus (CMV) infection is common in liver transplant (LT) recipients, and biliary complications occur in a large number of patients. It has been reported that CMV-DNA is more detectable in bile than in blood.

AIM
To investigate the effects of CMV infection on biliary complications by comparing the levels of CMV-DNA in the bile and blood of patients after LT.

METHODS
We conducted a retrospective analysis of 57 patients who underwent LT, 10 of these patients had no biliary complications and 47 patients had biliary complications. We also compared the levels of CMV-DNA in patients’ bile and blood, which were sampled concurrently. We used RNAscope technology to identify CMV in paraffin-embedded liver sections.

RESULTS
CMV-DNA was not detected in bile samples and was detected in 2 blood samples
INTRODUCTION

Biliary complications occur in up to 40% of patients after liver transplantation (LT) and cause significant mortality[1-3]. Post-LT biliary complications include strictures (anastomotic and non-anastomotic), leaks, stones, sphincter of Oddi dysfunction, and recurrence of primary biliary diseases. Cytomegalovirus (CMV) infection is a common opportunistic infection in LT recipients[4-5] and can occur in the liver, lungs, and gut and as a systemic infection[6-7]. CMV infection in LT recipients has been associated with many complications in addition to an increased risk of graft loss and death. CMV disease in LT patients most frequently presents as CMV syndrome, with the constellation of fever, neutropenia, and/or thrombocytopenia or as CMV hepatitis, as evidenced by elevated levels in liver function tests.

In our clinical work, we have found that in some patients with biliary complications after LT, CMV-DNA in the bile was positive but was negative in blood[8]. Rauber et al[9] reported that CMV was more frequent in bile than in liver biopsy or serum. Bile is obtained from patients without biliary complications. In the 47 patients with biliary complications, CMV-DNA was detected in 22 bile samples and 8 blood samples, both bile and blood samples were positive for CMV-DNA in 6 patients. The identification rate of CMV-DNA in blood was 17.0%, and was 46.8% in bile. Moreover, tissue samples from 4 patients with biliary complications tested positive using RNAscope technology but were negative with hematoxylin and eosin staining. During the follow-up period, graft failure occurred in 13 patients with biliary complications, 8 of whom underwent retransplantation, and 3 died. CMV-DNA in bile was detected in 9 of 13 patients with graft failure.

CONCLUSION

In patients with biliary complications, the identification rate of CMV-DNA in bile was higher than that in blood. Blood CMV-DNA negative patients with biliary complications should still be monitored for CMV-related biliary tract diseases. Potential occult CMV infection may also be a contributing etiological factor in the development of graft failure.

Key Words: Liver transplantation; Cytomegalovirus infection; Graft failure; Biliary complications; RNAscope in situ hybridization; Retrospective study

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This finding suggests that serum CMV-DNA may be negative in patients with CMV biliary tract disease after LT. Testing for CMV in the biliary tract may be a novel approach for diagnosing occult CMV biliary disease. The present study aimed to determine the role of CMV infection in biliary complications after LT.

**MATERIALS AND METHODS**

**Patients**
From December 2012 to January 2020, 57 patients who underwent LT in Beijing Friendship Hospital were retrospectively analyzed; 10 patients did not have biliary complications and 47 patients did have biliary complications.

Patients had routine blood CMV-DNA tested every 1-2 mo according to different risk levels during the first year and had blood CMV-DNA tested every 3-6 mo according to previous CMV infection in the late postoperative period. Patients had not routinely tested CMV-DNA in body fluid such as urine and bile.

All patients received universal prophylaxis or pre-emptive therapy for CMV infection. For high-risk patients (CMV IgG D+/R-), universal prophylaxis with intravenous ganciclovir or oral valganciclovir therapy was applied immediately after surgery. Pre-emptive treatment was be used to prevent CMV infection from progressing to CMV disease when patients were positive for CMV-DNA in blood or body fluid.

**Methods**
When patients presented to the hospital with nonspecific symptoms, such as jaundice, abdominal pain, and fever, the diagnosis of biliary complications was confirmed by laboratory tests, like abnormal liver function and increased bilirubin, and imaging examination. Some of the biliary complications were proven by pathologic biopsy.

We routinely collected the bile samples weekly for patients with biliary complications by endoscopic nasobiliary drainage, percutaneous transhepatic cholangial drainage, or indwelling T-tube. For patients without complications, we obtained the bile samples by indwelling T-tube when it was removed. We analyzed the bile and blood samples for the presence of CMV-DNA.

We conducted a retrospective analysis of all patients and compared the levels of CMV-DNA in bile and blood, which were sampled concurrently. We also used RNAscope technology to identify CMV in paraffin-embedded liver sections from patients with biliary complications.

**Ethics**
The study was conducted following the Declaration of Helsinki and was approved by local ethics committees. All patients gave informed consent.

**Bile CMV-DNA analysis**
Bile samples were analyzed for the presence of CMV by polymerase chain reaction (PCR) after DNA extraction. Nucleic acid was isolated from bile samples with a Diagnostic Kit for the Quantification of Human Cytomegalovirus DNA (PCR-fluorescence method) (Zhongshan University, Daan Gene, China). At the beginning of the experiment, 1 mL of each bile sample was transferred to a 1.5 mL centrifuge tube. The tubes were centrifuged at 12000 rpm for 5 min, and the supernatants were removed. Fifty microliters of DNA extraction buffer were added, and the samples were incubated at 100 °C for 10 min and centrifuged at 12000 rpm for 5 min. Then, two of each resulting filtrate was used for PCR amplification. Amplification and detection were performed on a LightCycler instrument (Roche, Shanghai, China) with a thermocycling profile of 93 °C for 2 min followed by 40 cycles at 93 °C for 5 s and 57 °C for 45 s.

**Blood CMV-DNA analysis**
Blood samples were analyzed for the presence of CMV by PCR after DNA extraction. Nucleic acid was isolated from blood samples with a Diagnostic Kit for the Quantification of Cytomegalovirus DNA (PCR-fluorescence method). At the beginning of the experiment, 1 mL of each blood sample was transferred to a 1.5 mL Eppendorf tube. The samples were incubated at 4 °C overnight, and the filtrate (serum) was transferred into a fresh 1.5 mL Eppendorf tube. Fifty microliters of serum were transferred to a 1.5 mL Eppendorf tube, and 50 mL of DNA extraction buffer was added. The samples
were incubated at 100 °C for 10 min and centrifuged at 12000 rpm for 5 min. Then, 2 mL of each resulting filtrate was used for PCR amplification. The amplification and detection procedures were the same as those for the bile samples.

RNAscope in situ hybridization
The RNAscope assay uses a novel and proprietary method of in situ hybridization to detect single RNA molecules from virtually any gene in various tissue samples, including formalin-fixed paraffin-embedded (FFPE) tissues. The sensitivity and specificity of RNAscope in situ hybridization (RISH) have been determined with a variety of viral entities, including high-risk human papillomaviruses, hepatitis E virus, and hepatitis C virus.

Analysis of FFPE tissues was conducted following the RNAscope® 2.5 HD Detection Kit (BROWN) Quick Guide for FFPE Tissues (Advanced Cell Diagnostics, Newark, CA, United States). These samples underwent deparaffinization, proteolytic digestion with enzyme denaturation, and hybridization with probes. RNAscope target RNA was retrieved by initial incubation at 98 °C for 15 min followed by incubation with the RNAscope enzyme at 40 °C for 30 min. V-CMV, peptidylpropyl isomerase B (positive control), and DapB (negative control) probes were added and allowed to hybridize for 2 h at 40 °C. Then, AMP1, 3,3’-diaminobenzidine (DAB) (40 °C for 30 min), AMP2 DAB (40 °C for 15 min), AMP3 DAB (40 °C for 30 min), AMP4 DAB (40 °C for 15 min), AMP5 DAB (room temperature for 30 min), and AMP6 DAB (room temperature for 15 min) were incubated for the noted amount of time, and the slides were washed with the BOND reagent. The slides were incubated with DAB for 15 min and then counterstained with hematoxylin for 2 min. Finally, the samples were rinsed with water, and coverslips were affixed.

Statistical analysis
All analyses were performed with SPSS 23.0 (Armonk, NY, United States). Parametric variables are expressed as the mean ± SD, whereas nonparametric variables are given as the median (interquartile range). Continuous data were compared with the nonparametric Mann-Whitney U test. Differences between actuarial estimates were analyzed with the log-rank test. Frequency differences were compared with the chi-square test. For expected frequencies less than 5, Fisher’s exact test was used. P < 0.05 was considered statistically significant.

RESULTS

Patient characteristics
The demographics and clinical characteristics of the 57 patients are described in Table 1, and Table 2 describes the clinical data of adult patients. The median interval between LT and the procedure for obtaining bile was 14.35 mo (range = 1.0-134.3 mo) and 0.5 mo (range = 0.2-27.5 mo) in patients with and without biliary complications, respectively. The Pediatric End-Stage Liver Disease score of children was 16.7 ± 13.5, and the Model for End-Stage Liver Disease score of adults was 14.6 ± 6.8, which had no statistically significant difference with patients without complications. The biliary reconstructions and drainage technique were not statistically different, neither was the incidence of graft rejection and hepatic artery thrombosis. The P value of biliary CMV status and cold/warm ischemia time was less than 0.05 in Table 1, which included the children and adults. However, the P value of cold/warm ischemia time was more than 0.05 in Table 2 with adults only.

All the patients without biliary complications had negative CMV-DNA in bile, and only 2 patients had positive blood CMV-DNA.

Of the 47 patients with biliary complications, the median age was 33.0 years (3.3-51.8 years), including 30 male patients and 17 female patients. Ten patients received living donor liver transplantation (LDLT), 34 patients received deceased donor liver transplantation (DDLT), and 3 patients received cross-assisted liver transplantation. The mean follow-up period was 57.2 mo (range = 1.3-159.7 mo). During the follow-up period, graft failure occurred in 13 patients with biliary complications, 5 patients died due to graft failure, 8 patients underwent retransplantation, and 3 patients died. Ten patients without biliary complications and 39 patients with biliary complications were alive at the end of the follow-up period.
Table 1 Demographics and clinical characteristics comparisons by biliary complications

<table>
<thead>
<tr>
<th>Patients with biliary complications (n = 47)</th>
<th>Patients without biliary complications (n = 10)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr) 33.0 (3.3-51.8)</td>
<td>51.6 (40.6-54.5)</td>
<td>0.021</td>
</tr>
<tr>
<td>Sex (M/F) 30/17</td>
<td>10/0</td>
<td>0.059</td>
</tr>
<tr>
<td>Primary disease (child)</td>
<td></td>
<td>/</td>
</tr>
<tr>
<td>Biliary atresia 11</td>
<td>0</td>
<td>/</td>
</tr>
<tr>
<td>Metabolic disease 6</td>
<td>0</td>
<td>/</td>
</tr>
<tr>
<td>Other 2</td>
<td>0</td>
<td>/</td>
</tr>
<tr>
<td>PELD 16.7 ± 13.5</td>
<td></td>
<td>/</td>
</tr>
<tr>
<td>Primary disease (adult)</td>
<td></td>
<td>/</td>
</tr>
<tr>
<td>Liver failure 3</td>
<td>0</td>
<td>/</td>
</tr>
<tr>
<td>Decompensated liver cirrhosis 14</td>
<td>10</td>
<td>/</td>
</tr>
<tr>
<td>HCC 9</td>
<td>0</td>
<td>/</td>
</tr>
<tr>
<td>Other 2</td>
<td>0</td>
<td>/</td>
</tr>
<tr>
<td>MELD 14.4 ± 6.3</td>
<td>15 ± 5.5</td>
<td>0.533</td>
</tr>
<tr>
<td>Liver transplantation 0.056</td>
<td></td>
<td>/</td>
</tr>
<tr>
<td>LDLT 10</td>
<td>0</td>
<td>/</td>
</tr>
<tr>
<td>DDLT 34</td>
<td>10</td>
<td>/</td>
</tr>
<tr>
<td>Cross-assisted liver transplantation 3</td>
<td>0</td>
<td>/</td>
</tr>
<tr>
<td>Cold ischemia time (min) 361.9 ± 244.4</td>
<td>582.1 ± 150.9</td>
<td>/</td>
</tr>
<tr>
<td>Warm ischemia time (min) 5 (3-5)</td>
<td>5 (5-7)</td>
<td>0.025</td>
</tr>
<tr>
<td>Biliary reconstruction (Duct-to-duct / Roux-en-Y) 23/9</td>
<td>1/9</td>
<td>0.404</td>
</tr>
<tr>
<td>Blood CMV status (P/N) 8/39</td>
<td>8/2</td>
<td>0.822</td>
</tr>
<tr>
<td>Biliary CMV status (P/N) 22/25</td>
<td>0/10</td>
<td>0.016</td>
</tr>
<tr>
<td>Rejection (Yes/No) 29/4</td>
<td>9/1</td>
<td>0.855</td>
</tr>
<tr>
<td>HAT (Yes/No) 1/32</td>
<td>0/10</td>
<td>0.578</td>
</tr>
<tr>
<td>Biliary drainage 1</td>
<td></td>
<td>/</td>
</tr>
<tr>
<td>PTCD 30</td>
<td>0</td>
<td>/</td>
</tr>
<tr>
<td>ENBD 12</td>
<td>0</td>
<td>/</td>
</tr>
<tr>
<td>T-tube 5</td>
<td>10</td>
<td>/</td>
</tr>
<tr>
<td>Outcome (alive/died) 39/8</td>
<td>10/0</td>
<td>0.365</td>
</tr>
</tbody>
</table>

HCC: Hepatocellular carcinoma; LDLT: Living donor liver transplantation; DDLT: Deceased donor liver transplantation; CMV: Cytomegalovirus; HAT: Hepatic artery thrombosis; PTCD: Percutaneous transhepatic cholangial drainage; ENBD: endoscopic nasobiliary drainage; PELD: Pediatric end-stage liver disease; MELD: Model for end-stage liver disease; M: Male; F: Female; P: Positive; N: Negative.

Biliary CMV-DNA detection

Biliary CMV-DNA was detected in 22 of 47 patients. Table 3 shows the patients’ baseline demographics with biliary complications and compares demographic and clinical parameters based on the biliary CMV-DNA status of the patients. The detected biliary CMV-DNA levels were between 100 copies/mL and 1.5 × 106 copies/mL. The median interval between surgery and biliary CMV-DNA detection was 9.7 mo (range = 1.6-91.7 mo).

Among the 47 patients with biliary complications after LT, 21 had biliary anastomotic strictures (Figure 1), of whom 14 patients were positive for CMV-DNA. Only 8 patients with other biliary complications had positive bile CMV-DNA (Table 4). This difference was statistically significant (P = 0.020).
Table 2 Demographics and clinical characteristics comparisons by biliary complications in adults

<table>
<thead>
<tr>
<th>Patients with biliary complications (n = 28)</th>
<th>Patients without biliary complications (n = 10)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>49.3 (37.8-57.5)</td>
<td>51.6 (40.6-54.5)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>19/9</td>
<td>10/0</td>
</tr>
<tr>
<td>Primary disease (adult)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver failure</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Decompensated liver cirrhosis</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>HCC</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>MELD</td>
<td>14.6 ± 6.8</td>
<td>15 ± 5.5</td>
</tr>
<tr>
<td>Liver transplantation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDLT</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>DDLT</td>
<td>25</td>
<td>10</td>
</tr>
<tr>
<td>Cross-assisted liver transplantation</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Cold ischemia time (min)</td>
<td>477.9 ± 193.7</td>
<td>582.1 ± 150.9</td>
</tr>
<tr>
<td>Warm ischemia time (min)</td>
<td>5 (3.25-5)</td>
<td>5 (5-7)</td>
</tr>
<tr>
<td>Biliary reconstruction (Duct-to-duct/Roux-en-Y)</td>
<td>16/2</td>
<td>9/1</td>
</tr>
<tr>
<td>Blood CMV status (P/N)</td>
<td>6/22</td>
<td>2/8</td>
</tr>
<tr>
<td>Biliary CMV status (P/N)</td>
<td>10/18</td>
<td>0/10</td>
</tr>
<tr>
<td>Rejection (Yes/No)</td>
<td>3/16</td>
<td>1/9</td>
</tr>
<tr>
<td>HAT (Yes/No)</td>
<td>1/18</td>
<td>0/10</td>
</tr>
<tr>
<td>Outcome (alive/died)</td>
<td>25/3</td>
<td>10/0</td>
</tr>
</tbody>
</table>

HCC: Hepatocellular carcinoma; LDLT: Living donor liver transplantation; DDLT: Deceased donor liver transplantation; CMV: Cytomegalovirus; HAT: Hepatic artery thrombosis; MELD: Model for end-stage liver disease; M: Male; F: Female; P: Positive; N: Negative.

Among the 13 patients with graft failure, 9 patients had positive bile CMV-DNA. Of the 8 patients who died, 5 patients had positive bile CMV-DNA.

**Blood CMV-DNA detection**

Of the 47 patients with biliary complications, CMV-DNA in blood was detected in 8 patients. Six patients tested positive for CMV-DNA in both blood and bile simultaneously. CMV-DNA was positive only in blood in 2 patients. Furthermore, both bile and blood were negative for CMV-DNA in 23 of 47 patients (Table 5). The positive identification rate of CMV-DNA in blood was 17.0% (8/47), and the positive identification rate in bile was 46.8% (22/47); the P value was 0.123. The difference was not statistically significant.

**RNAscope**

We performed hematoxylin eosin staining of liver tissue in patients after LT. Although the results were negative, pathological manifestations were identified in patients who tested positive for bile CMV-DNA. These pathological manifestations included infiltration of inflammatory cells in the portal tract area, vacuolar degeneration in the portal tract area, deletion in the portal tract area, dilatation of the lumen, and epithelial disorder or degeneration in the small bile duct. However, the patients who tested negative for CMV-DNA did not exhibit these manifestations; thus, we believe these manifestations were related to CMV infection. In recent years, some studies have reported that RISH is more sensitive than immunohistochemistry (IHC) in detecting CMV. Therefore, we used RISH to test for the presence of CMV in paraffin-embedded liver sections from 8 patients who tested positive for biliary CMV-DNA. Four patients tested positive using RNAscope technology (Figure 2).
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Table 3 Demographics and clinical parameter comparisons by biliary cytomegalovirus status in patients with biliary complications

<table>
<thead>
<tr>
<th>Biliary cytomegalovirus status</th>
<th>Children with biliary complications</th>
<th>Adults with biliary complications</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Positive (n = 12)</strong></td>
<td><strong>Negative (n = 7)</strong></td>
<td><strong>Positive (n = 10)</strong></td>
</tr>
<tr>
<td>Age</td>
<td>25.8 (7.9-126.3) mo</td>
<td>9.0 (6.0-94.1) mo</td>
<td>51.6 ± 8.3 yr</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>6/6</td>
<td>5/2</td>
<td>7/3</td>
</tr>
<tr>
<td>Primary disease (child)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biliary atresia</td>
<td>7</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Metabolic disease</td>
<td>4</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Primary disease (adult)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver failure</td>
<td>/</td>
<td>/</td>
<td>1</td>
</tr>
<tr>
<td>Decompensated liver cirrhosis</td>
<td>/</td>
<td>/</td>
<td>4</td>
</tr>
<tr>
<td>HCC</td>
<td>/</td>
<td>/</td>
<td>5</td>
</tr>
<tr>
<td>Other</td>
<td>/</td>
<td>/</td>
<td>0</td>
</tr>
<tr>
<td>Liver transplantation</td>
<td></td>
<td></td>
<td>0.351</td>
</tr>
<tr>
<td>LDLT</td>
<td>6</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>DDLT</td>
<td>6</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Cross-assisted liver transplantation</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Cold ischemia time (min)</td>
<td>169 (57.5-547.5)</td>
<td>94 (55.5-296)</td>
<td>445.5 (195.5-583.8)</td>
</tr>
<tr>
<td>Warm ischemia time (min)</td>
<td>3 (3-6)</td>
<td>3.5 (1.5-5.5)</td>
<td>5</td>
</tr>
<tr>
<td>Biliary reconstruction (Duct-to-duct/Roux-en-Y)</td>
<td>4/3</td>
<td>3/4</td>
<td>0.710</td>
</tr>
<tr>
<td>Laboratory parameters before bile drainage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin (mol/L)</td>
<td>100.4 (35.2-390.8)</td>
<td>14.9 (9.5-36.9)</td>
<td>91.0 (35.9-203.0)</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>287.1 (58.2-635.0)</td>
<td>66.1 (54.3-123.0)</td>
<td>115.2 (69.2-189.8)</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>106.0 (71.8-445.8)</td>
<td>79.0 (44.0-98.0)</td>
<td>117.0 (71.5-151.5)</td>
</tr>
<tr>
<td>ALP (U/L)</td>
<td>702.0 (177.0-1096.8)</td>
<td>256.0 (183.0-968.0)</td>
<td>368.0 (168.8-908.0)</td>
</tr>
<tr>
<td>GGT (U/L)</td>
<td>469.5 (388.25-847.25)</td>
<td>478.0 (206.0-1206.0)</td>
<td>334.5 (160.5-731.5)</td>
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<tr>
<td>Bac Inf. (biliary tract) (P/N)</td>
<td>9/3</td>
<td>5/2</td>
<td>4/4</td>
</tr>
<tr>
<td>Biliary stricture (P/N)</td>
<td>12/0</td>
<td>5/2</td>
<td>9/1</td>
</tr>
<tr>
<td>Rejection (Yes/No)</td>
<td>1/7</td>
<td>0/6</td>
<td>2/5</td>
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<tr>
<td>HAT (Yes/No)</td>
<td>0/8</td>
<td>0/6</td>
<td>0/7</td>
</tr>
<tr>
<td>Outcome (Alive/Died)</td>
<td>9/3</td>
<td>5/2</td>
<td>0.865</td>
</tr>
</tbody>
</table>

DISCUSSION

CMV infections are the primary cause of illness and death in immunocompromised patients, and CMV infection usually has no clinical symptoms[10-11]. Although pp65 antigen and CMV-DNA in serum are useful and early markers of CMV infection, it was reported that CMV detection in body fluids and tissues was more sensitive than in blood[12-14].

ERCP: Endoscopic retrograde cholangiopancreatography; PTCD: Percutaneous transhepatic cholangial drainage; AST: Aspartate aminotransferase; ALT: Alanine transaminase; ALP: Alkaline phosphatase; GGT: Gamma glutamyl transferase; CRP: C-reactive protein; HCC: Hepatocellular carcinoma; LDLT: Living donor liver transplantation; DDLT: Deceased donor liver transplantation; Bac Inf.: Bacterial infection; HAT: Hepatic artery thrombosis; M: Male; F: Female; P: Positive; N: Negative.
Table 4 Comparison of biliary complications and bile cytomegalovirus-DNA

<table>
<thead>
<tr>
<th>Biliary complications</th>
<th>Anastomotic stricture</th>
<th>Non-anastomotic stricture</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bile cytomegalovirus-DNA</td>
<td>Positive</td>
<td>14</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>7</td>
<td>18</td>
</tr>
<tr>
<td>Total</td>
<td>21</td>
<td>26</td>
<td>47</td>
</tr>
</tbody>
</table>

Table 5 Comparison of biliary and blood cytomegalovirus-DNA in patients with biliary complications

<table>
<thead>
<tr>
<th>Biliary CMV-DNA</th>
<th>Positive</th>
<th>Negative</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood cytomegalovirus-DNA</td>
<td>6</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>23</td>
<td>39</td>
</tr>
<tr>
<td>Total</td>
<td>22</td>
<td>25</td>
<td>47</td>
</tr>
</tbody>
</table>

Figure 1 Endoscopic cholangiogram showing anastomotic strictures after liver transplantation.

It is worth noting that only 10 adult patients without biliary complications were included in this study. Only the patients who presented to the hospital with biliary complications would receive endoscopic nasobiliary drainage, percutaneous transhepatic cholangial drainage, or biliary surgery to resolve their problem. In 10 patients without biliary complications, T-tube was used to get the bile. The T-tube was placed during LT following the surgeon’s judgment of the biliary system. We obtained the bile specimens at the time when the T-tubes were removed. A T-tube is not routinely inserted in children. This is the reason why the group of patients without biliary complications did not include children.

To reduce statistical error, we compared baseline data not only between patients with and without biliary complications but also between groups of adults. The demographics and clinical characteristics of the 57 patients are described in Table 1, and Table 2 describes the clinical data of adult patients. It is understandable that the P value related to age and cold/warm ischemia time in Table 1 was less than 0.05, but in Table 2 it was more than 0.05. LDLT is more commonly used in pediatric LT, resulting in a significant difference in cold/warm ischemia time compared with adult LT. The P value of biliary CMV status was less than 0.05, which also confirmed the relationship between biliary CMV status and biliary complications. There were no statistically significant differences in other baseline data in patients with or without biliary complications.

Table 3 shows the demographics and clinical parameters of patients with biliary complications and different biliary CMV status. In children with biliary complications, the P value of bilirubin showed that a higher bilirubin level might indicate positive biliary CMV status.
Figure 2 RNAscope in situ hybridization tests for the presence of cytomegalovirus in paraffin-embedded liver tissue samples. A: Positive control; B-D: Patient 3, Patient 6, Patient 10; E and F: Patient 13. We used RNAscope in situ hybridization to test for the presence of cytomegalovirus in paraffin-embedded liver sections from 8 patients who tested positive for biliary cytomegalovirus-DNA. Four patients tested positive using RNAscope technology.

The biliary complications observed were primarily biliary strictures and obstructions. Biliary strictures complicate approximately 2%-14% of LT cases and are classified as anastomotic and non-anastomotic[15]. Gotthardt et al[16] reported that biliary CMV was associated with non-anastomotic stenosis after LT. This study showed that biliary anastomotic strictures were related to biliary CMV infection (Figure 3). The positive rate of bile CMV-DNA was higher in patients with biliary anastomotic strictures than in patients with non-anastomotic strictures (See Table 4). The P value also showed this difference was statistically significant. Positive biliary CMV DNA led to biliary strictures that caused an elevation of bilirubin. As children have a smaller biliary tract, when they develop biliary complications they are more likely to show high hyperbilirubinemia.

Murine models suggest that CMV latency occurs in epithelial and endothelial cells. Latent CMV in hepatic sinusoidal endothelial cells leads to its reactivation in the liver[17]. CMV infection promotes fibroblast proliferation during the bile duct’s healing process, resulting in anastomotic scarring, which leads to biliary anastomotic stenosis. In scar tissue, myofibroblasts are active. The relevant literature confirms that myofibroblasts play an important role in forming a benign biliary stricture, which is an important cause of anastomotic contracture and postoperative anastomotic biliary strictures[18]. In addition, CMV infection reduces the expression of monocyte chemoattractant protein-1 in fibroblasts and promotes inflammation by binding to macrophage inflammatory protein (MIP)-1 MIP-1α, and MIP-1β[19]. Given the small sample size in this study, future studies should expand the sample size.
Figure 3 Comparison of biliary complications and bile cytomegalovirus-DNA. In 21 patients with anastomotic stricture, 66.7% (14/21) of patients had positive bile cytomegalovirus (CMV)-DNA. In 26 patients with other biliary complications, 30.8% (8/26) of patients had positive bile CMV-DNA. These results showed that biliary anastomotic stricture was more relevant to biliary CMV infection in this study.

Our research demonstrated that in 10 patients without biliary complications, none had positive CMV-DNA in bile, and 2 patients had positive CMV-DNA in blood. In patients with biliary complications, the positive rate of CMV-DNA in bile was much higher than that in blood. However, the difference between the positive rate in bile and blood of patients with biliary complications was not statistically significant ($P = 0.123$, See Table 5).

CMV infection may present only as viremia without clinical symptoms. In patients with biliary complications after LT, the phenomenon that CMV DNA in bile is positive, but CMV-DNA in blood is negative, may be highly suggestive of CMV biliary disease. According to a summary of these results, serum pp65 antigen and CMV-DNA negative patients with biliary complications should still be monitored for CMV-related biliary diseases. Testing for CMV in the biliary tract may be a novel approach for diagnosing occult CMV biliary diseases.

Routine detection of CMV in liver tissue is not sensitive. We used RISH to test paraffin-embedded liver sections from 8 patients with positive biliary CMV-DNA. All the tissues tested negative with CMV IHC, but the tissues of 4 patients tested positive using RISH. The results of our study suggest that RISH is more sensitive than IHC, which is consistent with previous studies[20-21]. Moreover, it also demonstrated that the identification rate of CMV-DNA in bile was higher in patients with CMV diseases. In this study, graft dysfunction occurred in 13 patients with biliary complications, 5 patients died, 8 patients underwent secondary transplantation, and 3 patients died after retransplantation. CMV-DNA in the biliary tract was detected in 9 of 13 patients with graft failure. The 1-year cumulative survival rate was 96.0%, the 3-year cumulative survival rate was 91.6%, and the 5-year cumulative survival rate was 86.2% in patients with CMV-DNA negative bile. The 1-year cumulative survival rate was 90.9% in patients with CMV-DNA positive bile, and the cumulative 3- and 5-year survival rates were 75.7% (Figure 4). Occult CMV infection is a risk factor for chronic graft failure and mortality after kidney transplantation[22-25]. Our study suggested that occult CMV infection might be related to chronic graft dysfunction and death in patients after LT. CMV infection in the biliary tract leads to increased biliary obstruction, which in turn increased bilirubin level, and the likelihood of graft dysfunction increased. Verdonk et al[26] showed that CMV-DNA positive recipients were more likely to be CMV-DNA positive in bile after surgery, which may be related to CMV reactivation in vivo after LT following treatment with immunosuppressive agents. Therefore, it is important to detect CMV-DNA regularly after transplantation[12]. For patients with these risk factors, close monitoring, adjustment of the immunosuppressive regimen, and targeted prevention may reduce the risk of chronic graft failure[24]. Graft dysfunction after LT has been reported to occur in 50% of
patients with biliary tract non-anastomotic strictures[26]. Among the 13 patients with graft failure, 6 had an anastomotic stricture and 7 had no anastomotic stricture. These results are consistent with previous studies.

Currently, prophylactic or preemptive treatment with ganciclovir or valganciclovir has partly reduced the incidence of CMV disease[27-28]. Patients in this study were given antiviral drug therapy, such as ganciclovir or valganciclovir, after CMV infection, and CMV-DNA gradually turned negative in bile and blood.

**CONCLUSION**

In this study, the positive rate of CMV-DNA in bile was higher than that in the blood of patients with biliary complications after LT. Therefore, CMV-DNA negative patients with biliary tract complications should be monitored for CMV-related biliary tract diseases and tested for CMV-DNA in bile. RISH is more sensitive than traditional immunohistochemical methods to detect CMV infection in liver tissue. Furthermore, occult CMV infection may be associated with biliary anastomotic stenosis and a contributing factor in graft failure, leading to high mortality after surgery. Improving CMV prevention strategies and treatment options is a priority.

**ARTICLE HIGHLIGHTS**

**Research background**

The association of cytomegalovirus (CMV) with biliary complications after liver transplant (LT) is an essential topic in clinical practice.

**Research motivation**

In clinical work, we have found that CMV-DNA in the bile and blood was inconsistent in patients with biliary complications after LT, and the positive rate of CMV-DNA in bile was higher than that in the blood.

**Research objectives**

To investigate the impact of CMV infection on biliary disease.

**Research methods**

We conducted a retrospective analysis of the clinical data from 57 patients with or without biliary complications.

**Research results**

CMV detection in bile is more sensitive than in blood. RNAscope in situ hybridization is more sensitive than traditional methods to detect CMV infection in liver tissue. Biliary CMV infection is definitively associated with biliary complications and poor
prognosis after LT, especially anastomotic stenosis.

**Research conclusions**

Patients with negative CMV-DNA in blood should still be monitored for bile CMV-DNA. Bile CMV infection maybe a contributing etiological factor in the development of graft failure.

**Research perspectives**

Current prevention strategies for CMV infection are inadequate and clinical doctors should be more vigilant of biliary CMV infection.

**REFERENCES**


Case Control Study

Blood tests for prediction of deep endometriosis: A case-control study

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Author contributions: Chen ZY participated in the design of this study, drafted the manuscript, and performed the statistical analysis; Zhang LF, Zhang YQ, Zhou Y, and Li XY carried out the study and collected data; Huang XF participated in the design of this study and made critical revision related to the important intellectual content of the manuscript; All authors read and approved the final manuscript.

Institutional review board statement: The study was reviewed and approved by the Institutional Ethics Committee at Women’s Hospital School of Medicine, Zhejiang University, No. IRB-20200049-R.

Informed consent statement: The data are anonymous, and the requirement for informed consent was therefore waived.

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

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Abstract

BACKGROUND
Deep endometriosis (DE) is the most aggressive subtype of endometriosis. The diagnosis may be challenging, and no biomarkers that can discriminate women with DE from those without DE have been developed.

AIM
To evaluate the role of blood hemostatic parameters and inflammatory indices in the prediction of DE.

METHODS
This case-control study was performed at the Women’s Hospital, Zhejiang University School of Medicine between January 2015 and December 2016. Women with DE and women with benign gynecologic disease (control group) eligible for gynecological surgery were enrolled. Routine plasma hemostatic parameters and inflammatory indices were obtained before surgery. Univariate and multivariate analysis were performed. Receiver operating characteristic (ROC) curves were generated, and areas under the curve (AUC) were calculated to assess the predictive values of the selected parameters.

RESULTS
A total of 126 women were enrolled, including 31 with DE and 95 controls. Plasma fibrinogen (Fg, $P < 0.01$), international normalized ratio ($P < 0.05$), and C-reactive protein levels ($P < 0.01$) were significantly higher in women with DE compared with controls. Plasma hemoglobin (HB) levels ($P < 0.05$) and shortened thrombin time ($P < 0.05$) were significantly lower in women with DE than in controls. Plasma Fg levels [adjusted OR (aOR) 2.12, 95% confidence interval (CI): 1.31-3.75] and plasma HB levels (aOR 0.48, 95%CI: 0.29-0.78) were significantly associated with DE (both $P < 0.05$). ROC analysis showed that the diagnostic value of Fg or HB alone for DE was limited. The AUC of the combination of both
INTRODUCTION

Endometriosis, which is characterized by the presence of endometrial glands and stroma at ectopic sites, affects approximately 10% of women of reproductive age. Up to 80% of women with endometriosis suffer from chronic pain, and up to 50% of women suffer from infertility. Endometriosis-related productivity loss and decreased quality of life lead to a heavy economic burden[1]. Endometriosis can be classified as superficial endometriosis (SUP), ovarian endometrioma (OMA), and deep endometriosis (DE)[2]. DE is the most aggressive of the three subtypes that constitute endometriosis. It is defined as an endometriotic lesion penetrating a depth of > 5 mm and showing aggressive behavior[3]. It can affect the uterosacral ligaments, parametrium, bladder, and bowel. Patients with DE usually present with severe pelvic pain and low fertility. The heterogeneity of the disease makes the diagnosis of DE a clinical challenge[4-6] that may be delayed for more than 8 years[7]. Accidental intraoperative diagnosis of DE is also common. DE often requires surgical therapy, and a high incidence of surgical morbidity of DE has been reported[8]. Therefore, developing new approaches for predicting DE before surgery is of crucial importance.

In previous years, symptoms and clinical history, pelvic examination, blood tests, transvaginal ultrasound, and magnetic resonance imaging (MRI) have been proposed for the preoperative prediction of endometriosis[9-13]. However, the clinical presentation of DE tends to vary. Some women experience severe pain, while others remain asymptomatic[10-11]. Pelvic examination results and the accuracy of ultrasound or MRI diagnosis can significantly vary in relation to the location of DE[13], and assessment by vaginal examination or image diagnosis depends on the level of expertise. The benefit of blood test prediction of deep endometriosis would have the advantages of being noninvasive, no exposure to harmful radiation, rapid reporting, and low cost. Several studies have explored the predictive value of blood biomarkers such as serum CA-125 in DE[11-12]. Low sensitivity and specificity reduce the value of serum CA-125 as a single test in the diagnosis of DE. In fact, a reliable noninvasive marker for preoperative diagnosis of this disease has not yet been introduced.

The most widely accepted etiologic mechanism of endometriosis is retrograde menstruation resulting in ectopic implantation of endometrium in the pelvic cavity. The ectopic implanted endometrium can lead to recurrent bleeding, subsequent repeated tissue injury, and inflammation[14]. Endometriosis has also been associated with increased activation of the coagulation system and fibrinolysis system, and markers as a dual marker index was 0.773 with improved sensitivity (67.7%) and specificity (78.9%) at cutoffs of 3.09 g/L and 126 g/L, respectively.

CONCLUSION

The combination of Fg and HB was a reliable predictor of DE. A larger study is needed to confirm the findings.

Key Words: Deep endometriosis; Diagnosis; Fibrinogen; Hemoglobin; Inflammation

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Data sharing statement: Statistical code, and data set available from the corresponding author at (email: huangxiufeng@zju.edu.cn). Participants gave informed consent for data sharing but the presented data are anonymized and risk of identification is low.

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

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Specialty type: Obstetrics and gynecology

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Peer-review report’s scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

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Blood hemostatic profiles and deep endometriosis

Chen ZY et al.

Elevated plasma fibrinogen (Fg) levels, shortened thrombin time (TT), shortened activated partial thromboplastin time (APTT), shortened prothrombin time (PT), and increased expression of urokinase-type plasminogen activator and plasminogen activator inhibitors[15-19]. The data indicate that women with endometriosis might have a potential hypercoagulable state. Additionally, a high concentration of proinflammatory cytokines was reported in women with endometriosis[20-21]. Nevertheless, whether these routine hemostatic parameters and inflammatory indices have any predictive value in terms of preoperative diagnosis of DE has not yet been determined. This study was conducted to assess whether DE could be identified by routine hematological parameters before surgery. The study objectives were to estimate the predictive values of routine hemostatic parameters and inflammatory indices for DE.

**MATERIALS AND METHODS**

**Study subjects**

A case-control study was performed at the Women’s Hospital, Zhejiang University School of Medicine between January 2015 and December 2016. Approval for this study was obtained from the Institutional Ethics Committee at Women’s Hospital School of Medicine, Zhejiang University (IRB-20200049-R). Data were retrospectively retrieved from an electronic database. Inclusion criteria for the DE group were: (1) 18 to 40 years of age[13]; and (2) DE defined as endometriotic lesions that infiltrated the uterosacral ligaments by > 5 mm and muscularis propria (bladder, intestine, ureters). Lesions were confirmed by pathology. Patients with DE who simultaneously had SUP or OMA were also included[2,14]. Exclusion criteria for the DE group were: (1) A history of abnormal uterine bleeding in the previous 3 mo; (2) A history of acute inflammation, suspected infectious disease, malignancy, metabolic diseases, and autoimmune disease in the previous 3 mo; (3) Pregnancy; (4) Hormonal therapy, including oral contraceptives, gonadotropin-releasing hormone analogs, or any other hormonal treatment, antithrombotic and hemostatic agents, and herbal compounds during the previous 3 mo; (5) Medical emergencies; and (6) With non-fasting lipid profiles.

Women between 18 and 40 years of age with surgical treatment at the same time for benign gynecologic diseases, including benign ovarian tumors, tubal infertility, cervical intraepithelial neoplasia, and intrauterine adhesion, but without any evidence of endometriosis, were recruited as controls. Detailed histories, thorough physical examinations of the abdominal-pelvic cavity, and sonography screening were performed by designated experts. The exclusion criteria were the same as for the DE group. Women to be enrolled in the controls with suspected endometriosis presenting dysmenorrhea or tenderness in the pelvic cavity or were also excluded.

During the study period, 698 patients with endometriosis were scheduled for surgery in the general gynecology department. However, 667 women were excluded because they did not meet the selection criteria, 154 who were > 40 years of age, 251 with non-fasted blood collection, 138 with no surgical treatment, with hormonal treatment, or complicated by other diseases, 124 with pathologically proven endometriosis but not DE phenotype. The remaining 170 eligible women without endometriosis were enrolled; 75 cases were excluded, 30 because of suspected endometriosis, 21 with no surgical treatment, and 24 complicated by inflammatory, or metabolic, or autoimmune diseases.

**Blood collection and laboratory methods**

All participants had routine peripheral blood tests before surgery. Blood samples with ethylenediaminetetraacetic acid (EDTA) as the anticoagulant were used to obtain a complete blood count, platelet count, HB level, neutrophil count, and lymphocyte count with a, autoanalyzer (Beckman, Coulter LH750). Coagulative parameters, including PT, TT, APTT, and Fg were determined with an automatic blood coagulation analyzer (STAGO, Evolution ISTA-R-IV, Germany). The neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), international normalized ratio (INR), platelet distribution width, neutrophil number, lymphocyte number, and mean platelet volume were also calculated. Considering crosstalk between lipid metabolism and coagulation function, serum lipid profiles including total cholesterol, total triglycerides, high-density lipoprotein, and low-density lipoprotein were tested and measured by enzymatic colorimetric assay after an overnight fast of 12 h. C-reactive protein (CRP) levels were simultaneously determined. The blood samples without EDTA were centrifuged at 3500 g, and serum supernatants were collected. CRP levels
were assayed in fresh serum using an immunoturbidimetric assay (Abbott, Architect CI6000). Intra- and interassay coefficients of variation for all measurements were 5% and 10%, respectively.

**Statistical analysis**
Continuous data were reported as means ± SD for normally distributed variables, and variables that were not normally distributed were reported as medians and range. Between-group differences of variables with a normal distribution were tested by analysis of variance and Student’s t-test. For variables with a non-normal distribution, differences were compared with Kruskal-Wallis and Wilcoxon tests. Categorical variables were reported as n (%), and the χ²-square test was used to compare the distribution across different groups. Stepwise logistic regression was used to assess the association of hemostatic profiles with the presence of DE. All indices of interest such as age, body mass index (BMI), history of delivery and abortion, inflammatory indices, and serum lipid profiles that could cause a confounding bias were entered into the initial model as potential risk factors with SLE = 0.05 and SLS = 0.10. The final model was built using all significant variables in the multivariate analysis. Receiver operating characteristic (ROC) curves were constructed, and the area under curves was calculated to determine the predictive power of the independent risk factors. The statistical analysis were conducted with SAS, version 9.4 (SAS Institute, Cary, NC, United States). P values < 0.05 were considered statistically significant.

**RESULTS**

**Subject characteristics**
A total of 126 women were enrolled in this study, 31 with DE and 95 without DE (Figure 1). The indications for surgery in the DE patients were a pelvic mass, history of infertility, pelvic pain with failed analgesics. DE involved the uterosacral ligament in 26 (83.9%) patients, the colorectal septum in two (6.5%), the ureter in one (3.2%), and the sigmoid in two (6.5%). Adenomyosis was suspected in 13 women with no uterine fibroids on transvaginal ultrasound. The indications for surgery in controls were benign ovarian tumors and tubal infertility (54 cases), cervical intraepithelial neoplasia (28 cases), and intrauterine adhesion (13 cases). Baseline clinical characteristics are shown in Table 1. There were no differences in age, BMI, parity, abortion, and lipid profiles between the study and the control groups.

**Differences in hemostatic profiles and inflammatory indices between patients with and without DE**
Plasma Fg (P < 0.01), INR (P < 0.05), and CRP levels (P < 0.01) of women with DE were significantly higher than those in controls. Plasma HB levels (P < 0.05) and TT (P < 0.05) of women with DE were significantly lower than those in controls. Differences between the other hematological parameters in the two groups were not significant (Table 2).

**Multivariate analysis of hemostatic parameters and inflammatory indices**
Multivariate analysis (Table 3) showed that plasma Fg levels [odds ratio (OR) 1.67, 95%CI: 1.13-2.46], PT (OR 1.63, 95%CI: 1.12-2.38), plasma HB levels (OR 0.63, 95%CI: 0.42-0.92), and TT (OR 0.69, 95%CI: 0.48-0.99) were significantly associated with the presence of DE (all P < 0.05). No relationships between the other hematological parameters and the presence of DE were found. APTT, INR, NLR, and PLR were not included in the multivariable logistic models, considering that they overlapped with other parameters.

After adjusting for potentially confounding factors including age, BMI, history of delivery and abortion, and serum lipid profiles, plasma Fg levels [adjusted OR (aOR) 2.12, 95%CI: 1.31-3.75] and plasma HB levels (aOR 0.48, 95%CI: 0.29-0.78) remained significantly associated with the presence of DE (both P < 0.05, Table 4). The relationship between PT/TT and DE was no longer significant.

**Predictive performance of Fg and HB for DE detection**
The predictive performance of Fg and HB for DE was investigated using ROC analysis. The area under the curve (AUC) of Fg was 0.639 (95%CI: 0.524-0.755, sensitivity = 58.1%, specificity = 70.5%), and that of HB was 0.664 (95%CI: 0.552-0.776, sensitivity = 64.3%, specificity = 62.1%) for the diagnosis of DE. The AUC of the combination of
Table 1 Baseline clinical characteristics and serum lipid profiles of participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control group (n = 95)</th>
<th>DE (n = 31)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr), mean ± SD</td>
<td>31.57 ± 5.03</td>
<td>32.10 ± 5.13</td>
<td>0.61</td>
</tr>
<tr>
<td>BMI (kg/m(^2)), mean ± SD</td>
<td>21.37 ± 2.67</td>
<td>20.36 ± 2.17</td>
<td>0.06</td>
</tr>
<tr>
<td>Parity, n (%)</td>
<td></td>
<td></td>
<td>0.41</td>
</tr>
<tr>
<td>0</td>
<td>35 (71.43)</td>
<td>14 (28.57)</td>
<td></td>
</tr>
<tr>
<td>≥ 1</td>
<td>60 (77.92)</td>
<td>17 (22.08)</td>
<td></td>
</tr>
<tr>
<td>Abortion, n (%)</td>
<td></td>
<td></td>
<td>0.90</td>
</tr>
<tr>
<td>0</td>
<td>50 (75.76)</td>
<td>16 (24.24)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>18 (72.00)</td>
<td>7 (28.00)</td>
<td></td>
</tr>
<tr>
<td>≥ 2</td>
<td>27 (77.14)</td>
<td>8 (22.86)</td>
<td></td>
</tr>
<tr>
<td>TG (mmol/L), median (Q1-Q3)</td>
<td>0.80 (0.64-1.12)</td>
<td>0.81 (0.57-0.99)</td>
<td>0.33</td>
</tr>
<tr>
<td>TC (mmol/L), median (Q1-Q3)</td>
<td>4.27 (3.80-4.82)</td>
<td>4.09 (3.80-4.77)</td>
<td>0.80</td>
</tr>
<tr>
<td>HDL (mmol/L), median (Q1-Q3)</td>
<td>1.32 (1.14-1.59)</td>
<td>1.39 (1.19-1.55)</td>
<td>0.70</td>
</tr>
<tr>
<td>LDL (mmol/L), median (Q1-Q3)</td>
<td>2.16 (1.83-2.60)</td>
<td>2.16 (1.81-2.69)</td>
<td>0.98</td>
</tr>
</tbody>
</table>

Data are mean ± SD for normally distributed variables, medians (Q1-Q3) for variables without a normal distribution, and n (%) for categories variables. BMI: Body mass index, DE: Deep endometriosis; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; TC: Total cholesterol; TG: Total triglycerides.

Table 2 Hemostatic parameters and inflammation indices of participants with or without deep endometriosis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Controls (n = 95)</th>
<th>DE (n = 31)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT (s)</td>
<td>12.91 ± 0.61</td>
<td>13.11 ± 0.59</td>
<td>0.11</td>
</tr>
<tr>
<td>INR</td>
<td>1.01 (0.98-1.04)</td>
<td>1.05 (1.00-1.07)</td>
<td>0.03</td>
</tr>
<tr>
<td>APTT (s)</td>
<td>36.11 ± 3.16</td>
<td>36.84 ± 3.18</td>
<td>0.27</td>
</tr>
<tr>
<td>TT (s)</td>
<td>15.56 ± 0.61</td>
<td>15.29 ± 0.56</td>
<td>0.03</td>
</tr>
<tr>
<td>Fg (g/L)</td>
<td>2.83 (2.53-3.14)</td>
<td>3.09 (2.73-3.97)</td>
<td>0.01</td>
</tr>
<tr>
<td>PLT (10(^9)/L)</td>
<td>228.00 (185.00-258.00)</td>
<td>235.00 (212.00-262.00)</td>
<td>0.32</td>
</tr>
<tr>
<td>HB (g/L)</td>
<td>130.00 (124.00-136.00)</td>
<td>126.00 (115.00-130.00)</td>
<td>0.02</td>
</tr>
<tr>
<td>WN (10(^9)/L)</td>
<td>3.90 (3.00-4.80)</td>
<td>3.30 (2.80-4.10)</td>
<td>0.27</td>
</tr>
<tr>
<td>WL (10(^9)/L)</td>
<td>1.65 (1.30-2.00)</td>
<td>1.60 (1.30-1.80)</td>
<td>0.34</td>
</tr>
<tr>
<td>MPV (fL)</td>
<td>8.60 (7.90-9.70)</td>
<td>8.40 (7.80-8.90)</td>
<td>0.23</td>
</tr>
<tr>
<td>PCT (%)</td>
<td>0.19 (0.17-0.22)</td>
<td>0.20 (0.18-0.23)</td>
<td>0.21</td>
</tr>
<tr>
<td>NLR</td>
<td>2.16 (1.59-3.20)</td>
<td>2.31 (1.58-2.78)</td>
<td>0.86</td>
</tr>
<tr>
<td>PLR</td>
<td>130.00 (108.82-180.00)</td>
<td>154.71 (128.95-179.09)</td>
<td>0.08</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>12.91 ± 0.61</td>
<td>13.11 ± 0.59</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Data are mean ± SD for normally distributed variables and medians (Q1-Q3) for abnormal variables without a normal distribution. APTT: Activated partial thromboplastin time; CRP: C-reactive protein; Fg: Fibrinogen; HB: Hemoglobin; INR: International standardized ratio; MPV: Mean platelet volume; NLR: Neutrophil-to-lymphocyte ratio; PCT: Platelet distribution width; PLR: Platelet-to-lymphocyte ratio; PLT: Platelet count; PT: Prothrombin time; TT: Thrombin time; WL: Lymphocyte number; WN: Neutrophil number.

Both markers was 0.773 with improved sensitivity (67.7%) and specificity (78.9%) at a cutoff of 3.09 (g/L) and 126 (g/L), respectively (Table 4, Figure 2). The combination of both markers as a dual marker index significantly improved the diagnostic accuracy.
Table 3 Unadjusted association of hemostatic parameters and inflammation indices with deep endometriosis by logistical regression

<table>
<thead>
<tr>
<th>Variables</th>
<th>β (SE)</th>
<th>P value</th>
<th>OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT</td>
<td>0.49 (0.19)</td>
<td>0.01</td>
<td>1.63 (1.12, 2.38)</td>
</tr>
<tr>
<td>Fg</td>
<td>0.51 (0.20)</td>
<td>0.01</td>
<td>1.67 (1.13, 2.46)</td>
</tr>
<tr>
<td>TT</td>
<td>−0.38 (0.19)</td>
<td>0.04</td>
<td>0.69 (0.48, 0.99)</td>
</tr>
<tr>
<td>PLT</td>
<td>0.25 (0.19)</td>
<td>0.24</td>
<td>1.26 (0.86, 1.83)</td>
</tr>
<tr>
<td>HB</td>
<td>−0.47 (0.20)</td>
<td>0.02</td>
<td>0.63 (0.42, 0.92)</td>
</tr>
<tr>
<td>WN</td>
<td>−0.22 (0.19)</td>
<td>0.25</td>
<td>0.81 (0.56, 1.16)</td>
</tr>
<tr>
<td>WL</td>
<td>−0.17 (0.19)</td>
<td>0.37</td>
<td>0.85 (0.59, 1.22)</td>
</tr>
<tr>
<td>MPV</td>
<td>−0.22 (0.18)</td>
<td>0.24</td>
<td>0.81 (0.56, 1.15)</td>
</tr>
<tr>
<td>PCT</td>
<td>0.24 (0.18)</td>
<td>0.18</td>
<td>1.27 (0.89, 1.8)</td>
</tr>
<tr>
<td>CRP</td>
<td>−0.19 (0.20)</td>
<td>0.34</td>
<td>0.82 (0.55, 1.22)</td>
</tr>
</tbody>
</table>

CI: Confidence interval; CRP: C-reactive protein; Fg: Fibrinogen; HB: Hemoglobin; MPV: Mean platelet volume; OR: Odds ratio; PCT: Platelet distribution width; PLT: Platelet count; PT: Prothrombin time; SE: Standard error; TT: Thrombin time; WL: Lymphocyte number; WN: Neutrophil number.

Table 4 Stepwise logistical regression analysis and receiver operating characteristic analysis for deep endometriosis, hemostatic parameters, and inflammatory indices

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95%CI)</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>AUC (95%CI)</th>
<th>Cutoff value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fg</td>
<td>2.12 (1.31, 3.75)</td>
<td>0.581</td>
<td>0.705</td>
<td>0.639 (0.524, 0.755)</td>
<td>3.04</td>
</tr>
<tr>
<td>HB</td>
<td>0.48 (0.29, 0.78)</td>
<td>0.645</td>
<td>0.621</td>
<td>0.664 (0.552, 0.776)</td>
<td>128</td>
</tr>
<tr>
<td>Fg + HB</td>
<td>-</td>
<td>0.677</td>
<td>0.789</td>
<td>0.773 (0.677, 0.868)</td>
<td>3.09 + 126</td>
</tr>
</tbody>
</table>

*p < 0.05. Age, BMI, history of delivery and abortion, and serum lipid profiles were entered into the stepwise regression model with SLE = 0.05, SLS = 0.10. AUC: Area under the curve; CI: Confidence interval; Fg: Fibrinogen; HB: Hemoglobin; OR: Odds ratio.

DISCUSSION

This study examined the predictive values of hemostatic parameters and inflammatory indices for DE. Our data suggest that the combination of Fg and HB levels could be used as a reliable predictor of DE. To the best of our knowledge, this is the first report that evaluated hemostatic parameters and inflammatory indices for the prediction of DE. Fg is a known coagulation factor associated with hypercoagulation. As an acute-phase reaction and a hemostatic parameter, Fg has an important role in coagulation, inflammation, and the maintenance of hemostasis [22-23]. Fg is also a marker of inflammation and a major determinant of thrombosis and hemorheology [24]. In this study, we found elevated Fg levels in DE patients, which is consistent with previous findings [15-16].

Increasing evidence shows that pathophysiological changes in endometriosis have features in common with those observed during tissue injury and repair (TIAR) [3,25-26]. TIAR process may contribute to the development of endometriosis. The coagulation and fibrinolytic systems have important roles in TIAR [27]. An increase in plasma Fg is more likely caused by recurrent bleeding in the ectopic implantation of the endometrium and the impairment of the fibrinolytic system in endometriosis. Elevated Fg levels may reflect hemorheological disorders, a potential hypercoagulable status, and subclinical systemic inflammation in endometriosis.

In this study, a shortened TT was found in women with DE, which is in line with previous studies [16-17]. TT reflects anticoagulation, and a shortened TT indicates hypo-fibrinolysis. In this study, an inverse relationship between TT and DE was initially detected by multivariate analysis. After adjusting for confounding factors, the association was no longer significant. Moreover, no differences in APTT and TT were found between the DE and the control groups.
Decreased plasma HB levels were identified in women with DE in this study, which is in line with the findings in women with OMA[28-29]. Moreover, our results revealed an inverse relationship between plasma HB levels and the presence of DE. An inverse association between severity of endometriosis and plasma HB levels was reported in another study[30]. The exact cause of low plasma HB levels in patients with endometriosis is not clear. It may be associated with erythrocyte regulation of iron metabolism disorders or chronic systemic inflammation[31-32]. Low plasma HB levels may be associated with hypoxia, which has been reported to facilitating endometriosis development[33]. Further studies are required to investigate how HB contributes to
the development of DE.

Serum CA-125 antigen is the most frequently used biomarker in the diagnosis of endometriosis in clinic practice\[11,34-35\]. Santulli et al\[36\] reported that serum CA-125 antigen was significantly associated with the severity and the penetration depth of DE; but it is not widely used in the diagnosis of DE. In this study, we found that either plasma Fg levels alone or plasma HB levels were not powerful enough to predict DE. A good predictive value for DE was obtained when plasma Fg levels were combined with HB levels. The AUC of the combination was 0.773, and the specificity was 78.9% at cutoffs of 3.09 g/L and 126 g/L. Ding et al\[37\] investigated the predictive role of Fg for endometriosis and found that the combination of Fg and serum CA-125 had good predictive power for OMA. They showed that Fg had potential predictive value for endometriosis, which is consistent with our results. Our model for predicting DE with the use of plasma Fg and HB may have clinical implications. Using this model, patients suspected of DE should undergo a thorough preoperative assessment through pelvic examination and pelvic imaging to detect DE nodules. Nonetheless, further studies for optimized predictive tools for DE are warranted.

Endometriosis is associated with an inflammatory response. In this study, increased CRP levels were found in the DE group, and there the difference in NLR between women with or without DE was not significant. The results of the value of inflammatory indices such as CRP and NLR in endometriosis in previous studies are not consistent\[29,37-38\]. This inconsistency may be associated with a different course, subtypes, and sample sizes used in those studies. In this study, multivariate analysis did not identify any association between CRP and NLR and the presence of DE.

Low HB levels could be caused by other bleeding disorders such as adenomyosis and uterine fibroids. In this study, 13 patients in the DE group had suspected adenomyosis with no uterine fibroids. Nonetheless, they did not complain of abnormal menstrual bleeding, and the HB levels were still within the normal range. Thus, the decreased HB levels of the DE group could not be attributed to concomitant adenomyosis. In addition, the coexistence of adenomyosis and endometriosis is well known\[39\]. We could not exclude the women with both DE and adenomyosis from the DE group in this study.

Our study has several limitations. First, the size of the DE group was relatively small. The low incidence of DE and strict criteria imposed in this study limited the enrollment. Additionally, this is the first study that evaluated the predictive role of hemostatic parameters for DE, and one of the aims of this study was to inspire future larger investigations. Second, as we did not include cases with only SUP or OMA subtypes, the results may not be applicable for all patients with endometriosis. Finally, there was no ideal control group for studying plasma Fg levels in DE. Our control group consisted of women with surgery for benign gynecological conditions, which permitted a thorough assessment of DE. However, some of the conditions, such as tubal infertility or ovarian cysts, might be associated with altered plasma levels.

In addition to the limitations, the following strengths should also be pointed out. First, the results of Fg/HB and the presence of DE were consistent in both univariate and multivariate analysis. Second, we for adjusted those confounding factors to eliminate possible effects on coagulation function and inflammatory response, which could make the predictive value of Fg and HB more reliable. In addition, these effects were not investigated in the previous relevant studies on endometriosis.

The study findings support the routine combination of Fg and HB as an essential part of the preoperative assessment of patients with suspected DE. The model can be adopted for use in clinical practice. Furthermore, this study suggests that an altered coagulation system may have key involvement in the development of endometriosis. The results also suggested that patients with DE may have a potential hypercoagulable state. Further studies are required to determine the anticoagulant therapy for these patients.

**CONCLUSION**

A combination of Fg and HB could be used in routine clinical practice as a reliable predictor of DE before surgical intervention. Future studies with larger samples are needed to verify the findings and to investigate how Fg and HB contribute to the development of endometriosis, particularly DE.
ARTICLE HIGHLIGHTS

Research background
Deep endometriosis (DE) is the most aggressive subtype of the disease. The diagnosis of DE is challenging. No biomarkers have been identified for discriminating women with DE from those without DE.

Research motivation
Developing new approaches for predicting DE before surgery is of crucial importance. It is unclear whether DE could be identified by routine hematological evaluation before surgery.

Research objectives
To evaluate the role of blood hemostatic parameters and inflammatory indices in the prediction of DE before surgical intervention.

Research methods
A case-control study investigated the value of routine plasma hemostatic parameters and inflammatory indices in women with DE and without endometriosis. Univariate analysis and multivariate analysis following adjustment for potential confounding factors were performed. Receiver operating characteristic curves were generated, and the areas under the curve was calculated to assess the predictive values of the selected parameters.

Research results
Elevated plasma fibrinogen (Fg) and decreased hemoglobin (HB) levels were found in women with DE compared with controls. Plasma Fg and HB levels were significantly associated with DE after adjusting for potential confounding factors. The diagnostic value of Fg or HB alone for DE detection before surgical intervention was limited, but the combination of Fg and HB had good predictive value for DE.

Research conclusions
It suggested that the combination of Fg and HB levels could be used as a reliable predictor of DE. Based on the model, a thorough assessment is recommended for suspected patients with DE.

Research perspectives
Further studies are required to investigate how Fg and HB contribute to the development of endometriosis, particularly DE.

ACKNOWLEDGEMENTS
We thank Li M from Haining Center for Disease Control and Prevention of Zhejiang Province, China for reviewing the statistical methods used in this study.

REFERENCES
Chen ZY et al. Blood hemostatic profiles and deep endometriosis


Association between neutrophil-to-lymphocyte ratio and major postoperative complications after carotid endarterectomy: A retrospective cohort study

Yun Yu, Wei-Hua Cui, Chan Cheng, Yu Lu, Qing Zhang, Ru-Quan Han

BACKGROUND
Carotid artery cross-clamping during carotid endarterectomy (CEA) may damage local cerebral perfusion and induce cerebral ischemia–reperfusion injury to activate local inflammatory responses. Neutrophil-to-lymphocyte ratio (NLR) is an indicator that reflects systemic inflammation. However, the correlation between NLR and complications after CEA remains unclear.

AIM
To investigate the association between NLR and major complications after surgery in patients undergoing CEA.

RESULTS
A total of 224 patients who received CEA were screened for review and 206 were included in the statistical analyses; of whom, 40 (19.42%) developed major postoperative complications. NLR within 24 h after CEA was significantly correlated with major postoperative complications ($P=0.026$). After confounding factors were adjusted, the odds ratio was 1.15 (95% CI: 1.03–1.29, $P=0.014$). The incidence of major postoperative complications in the high NLR group was 8.47...
authors declare no competing interests.

Data sharing statement: The original data is available on request from the corresponding author at ruquan.han@ccmu.edu.cn.

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

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Country/Territory of origin: China

Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review report’s scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

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times that in the low NLR group \( (P = 0.002) \).

CONCLUSION
NLR is associated with major postoperative complications in patients undergoing CEA.

Key Words: Carotid artery stenosis; Carotid endarterectomy; Neutrophil to lymphocyte ratio; Inflammation; Postoperative complication; Major organ dysfunction

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Core tip: We retrospectively evaluated the association between neutrophil-to-lymphocyte ratio (NLR) and major postoperative complications in patients undergoing carotid endarterectomy (CEA). Nearly 20% of patients developed major postoperative complications. NLR within 24 h after CEA was significantly correlated with major postoperative complications. The incidence of major postoperative complications in the high NLR group was 8.47 times that in the low NLR group after confounding factors were adjusted. Since early detection and early treatment help improve outcomes for CEA, inflammatory markers such as NLR may also become potential treatment targets.

Citation: Yu Y, Cui WH, Cheng C, Lu Y, Zhang Q, Han RQ. Association between neutrophil-to-lymphocyte ratio and major postoperative complications after carotid endarterectomy: A retrospective cohort study. World J Clin Cases 2021; 9(35): 10816-10827
URL: https://www.wjgnet.com/2307-8960/full/v9/i35/10816.htm
DOI: https://dx.doi.org/10.12998/wjcc.v9.i35.10816

INTRODUCTION
Carotid endarterectomy (CEA) is a classic surgical method for treating carotid artery stenosis. Occlusion and opening of the carotid artery during CEA may damage local cerebral perfusion and induce cerebral ischemia-reperfusion injury to activate local inflammatory responses[1]. Even after CEA, inflammatory responses in the whole body and carotid plaque tissue may still exist. Serum inflammatory and anti-inflammatory cytokines increase at 6 to 24 h after CEA. Compared with asymptomatic patients, patients with symptomatic carotid artery stenosis have higher concentrations of inflammatory markers in serum and tissues[2]. The elevation of perioperative inflammatory markers suggests an increase in the risk of early carotid artery restenosis after CEA[3]. Inflammatory markers can also become treatment targets[4].

Neutrophil-to-lymphocyte ratio (NLR) is an indicator that reflects systemic inflammation, which has been demonstrated to be an independent and convenient predictor of all-cause death or adverse events in many diseases[5-8]. Endothelial dysfunction is the early stage of atherosclerosis formation[9]. NLR is positively correlated with carotid intima-media thickness, and an increase in NLR may be associated with endothelial dysfunction[10]. NLR > 2.6 is an independent predictor of symptomatic carotid artery disease[11]. In patients receiving CEA for significant carotid artery stenosis, NLR is significantly correlated with the characteristics of vulnerable atherosclerotic carotid plaques on preoperative magnetic resonance angiography[12]. However, the correlation between NLR and complications after CEA remain unclear.

Therefore, we undertook this study to clarify whether NLR was significantly associated with major organ dysfunction after surgery in patients undergoing CEA.

MATERIALS AND METHODS

Study participants
This single-center retrospective cohort study was approved by the Ethics Committee of Beijing Tiantan Hospital (KY2017-024-01). Given the retrospective nature of the study, the Ethics Committee waived the need for written informed consent and no registration was required. Consecutive patients who underwent elective CEA between
January 2016 and July 2018 at Beijing Tiantan Hospital were screened for eligibility. Characteristics of the patients at baseline, neuroimaging data, intraoperative anesthesia management, postoperative complications and length of hospitalization were acquired from the medical record system. Patients were excluded for the following reasons: incomplete data obtained from medical records; severe anemia (hemoglobin < 9 g/dL) before surgery; nongeneral anesthesia; and massive hemorrhage during surgery.

**Anesthesia management**

The method for anesthesia involved intravenous–inhalation anesthesia or total intravenous anesthesia. Intraoperative fluid management involving crystalloids, colloids, blood loss and urine output was collected. Intraoperative blood pressure fluctuations were addressed as follows. The noninvasive blood pressure of the upper limbs was measured and recorded every 5 min during surgery. The mean systolic blood pressure (mean$_{SBP}$), SD of systolic blood pressure (SD$_{SBP}$), mean diastolic blood pressure (mean$_{DBP}$), and SD of diastolic blood pressure (SD$_{DBP}$) from entering to exiting the operating room were calculated to obtain the coefficient of variation in systolic blood pressure (CV$_{SBP}$) and diastolic blood pressure (CV$_{DBP}$). The coefficient of variation = SD/mean value × 100%[13]. Besides, intraoperative vasoactive drugs use including vasopressors and antihypertensive agents was also collected.

**Laboratory and neuroimaging examination measures**

Complete blood count (CBC) was collected at admission and repeated after surgery. Neutrophil and lymphocyte counts in whole blood at admission and within 24 h after CEA were extracted from the medical record system. Preoperative basal NLR values and that within 24 h after CEA were calculated. By using the North American Symptomatic Carotid Endarterectomy Trial criteria, the degree of carotid artery stenosis was independently measured by two trained radiologists blinded to clinical data[14].

**Outcome assessment**

The composite risk of major postoperative complications was adopted as the primary outcome, similar to those used in previous studies[15-17]. Major postoperative complications included neurological, pulmonary and cardiovascular complications and acute kidney injury (AKI). Neurological complications were defined by new focal neurological deficits confirmed by radiology. Pulmonary complications were defined by a new-onset requirement for oxygen or respiratory support[15]. Cardiovascular complications included new-onset myocardial infarction validated by cardiac enzymes, atrial or ventricular arrhythmias and heart failure. According to the Kidney Disease Improving Global Outcomes, AKI was defined as an increase in serum creatinine > 0.3 mg/dL within 48 h after surgery or serum creatinine value 1.5-fold the preoperative baseline value[18]. If the patient had one or more of the above complications, development of major postoperative complications was considered. No assumptions were made to process missing data, and statistical analyses were conducted for patients with complete data.

Secondary outcomes included fever, surgical site infections, urinary infections, deep venous thrombosis (DVT), length of stay in the intensive care unit (ICU), length of hospitalization and cost of hospitalization. A postoperative fever was considered if the axillary temperature was > 38°C. Surgical site infections were determined if wound cultures were positive. Urinary infections were defined as typical symptoms and signs confirmed by routine urine tests. DVT was diagnosed using the color Doppler ultrasound.

**Statistical analysis**

Statistical analyses were performed using EmpowerStats software and R software (R version 3.4.3). Continuous variables were examined using the independent-samples t-test or Kruskal–Wallis test and expressed as mean ± s or median (interquartile range). Analysis of categorical variables was performed using the χ² test and presented as a percentage. After adjusting the confounding factors, smooth curve fitting was used for analyzing the relationship between NLR and post-CEA major complications. By logistic regressions, odds ratios (ORs) and 95% CIs were calculated to assess the association of NLR within 24 h after surgery with postoperative major complications. Model I was adjusted for sex and age. Model II was adjusted for sex, age, body mass index (BMI), American Society of Anesthesiologists (ASA) grade, preoperative combined heart disease, anesthesia method, degree of stenosis on the surgical side,
degree of stenosis on the contralateral side, operating time, intraoperative intake and output, duration of carotid artery occlusion, $CV_{\text{SBP}}$ and $CV_{\text{DBP}}$. $P < 0.05$ indicated that a difference had statistical significance.

**RESULTS**

**Patient characteristics**
This retrospective cohort study screened 224 patients. A total of 17 patients did not have CBC on postoperative day 1 and one patient underwent CEA with cervical plexus block. Therefore, 18 patients were excluded and the data for 206 patients were included in the statistical analyses (Figure 1). Patients were divided into a group with major post-CEA complications (PC group) and a group without major post-CEA complications (WOPC group) according to whether major PC group were present. Baseline characteristics in the two groups are provided in Table 1. The percentage of patients with combined preoperative heart diseases in the PC group (40.0%) was significantly higher than that in the WOPC group (24.10%, $P = 0.042$). The differences in age, sex, BMI, degree of carotid artery stenosis on the surgical side, degree of carotid artery stenosis on the contralateral side, anesthesia method, duration of carotid artery occlusion, intraoperative intake and output volume, intraoperative blood pressure fluctuation, and use of vasoactive drugs between the two groups were all nonsignificant.

**Postoperative outcomes**
Outcome variables stratified by major postoperative complications are shown in Table 2. After CEA, 16 patients (7.77%) developed neurological complications, six (2.91%) developed cardiac complications, 14 (6.80%) developed respiratory complications, and nine (4.37%) developed renal complications. A total of 40 patients (19.42%) developed major postoperative complications. The incidence of fever, surgical site infections, urinary infections and DVT was 4.85%, 1.46%, 1.46% and 2.43%, respectively. The cost of hospitalization in the PC group was significantly higher than that in the WOPC group ($P < 0.001$). More patients in the PC group suffered from fever and DVT ($P < 0.001$). The differences in the length of stay in the ICU, the length of hospitalization, surgical site infections and urinary infections were not significant.

**Association between NLR and major post-CEA complications**
The risk factors associated with post-CEA complications involving vital organs are presented in Table 3. Operating time was significantly correlated with major post-CEA complications ($P = 0.038$). NLR within 24 h after CEA was also significantly correlated with post-CEA complications ($P = 0.026$). Figure 2 showed the correlation between NLR within 24 h after CEA and major postoperative complications. NLR within 24 h after CEA and major postoperative complications showed a curvilinear relationship ($P = 0.025$, degree of freedom = 1.495). With the increase in NLR within 24 h after CEA, the incidence of major postoperative complications gradually increased.

Multiple logistic regression showed that NLR within 24 h after CEA and major postoperative complications were correlated (Table 4). After confounding factors were adjusted, the OR = 1.15 (95%CI: 1.03–1.29, $P = 0.014$). The patients were divided into three groups according to their NLR tertiles within 24 h after CEA; namely, high NLR group (7.66–29.85), middle NLR (4.63–7.65), and low NLR (1.61–4.62). The incidence of post-CEA complications involving vital organs in the high NLR group was 8.47 times that in the low NLR group ($P = 0.002$). The differences in major postoperative complications ($P = 0.015$), fever ($P = 0.040$) and cost of hospitalization ($P = 0.032$) were significant among NLR tertile groups (Table 5).

**DISCUSSION**
This study showed that 19.42% of patients developed major postoperative complications involving the neurological, cardiac and respiratory systems as well as AKI. NLR within 24 h after CEA was significantly correlated with major postoperative complications. The incidence of major postoperative complications in the high NLR group was much higher than that of in the low NLR group after confounding factors were adjusted.
### Table 1 Characteristics of the patients at baseline

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>WOPC group</th>
<th>PC group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>206</td>
<td>166</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>62.0 ± 7.2</td>
<td>61.6 ± 7.3</td>
<td>63.5 ± 6.8</td>
<td>0.151</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
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<td></td>
<td>0.616</td>
</tr>
<tr>
<td>Male</td>
<td>175 (84.95%)</td>
<td>140 (84.34%)</td>
<td>35 (87.50%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>31 (15.05%)</td>
<td>26 (15.66%)</td>
<td>5 (12.50%)</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.33 ± 2.89</td>
<td>25.25 ± 2.85</td>
<td>25.63 ± 3.04</td>
<td>0.461</td>
</tr>
<tr>
<td>Smoking history</td>
<td>118 (57.56%)</td>
<td>97 (58.79%)</td>
<td>21 (52.50%)</td>
<td>0.470</td>
</tr>
<tr>
<td>ASA grade</td>
<td></td>
<td></td>
<td></td>
<td>0.521</td>
</tr>
<tr>
<td>Grade II</td>
<td>157 (81.07%)</td>
<td>136 (81.93%)</td>
<td>31 (77.50%)</td>
<td></td>
</tr>
<tr>
<td>Grade III</td>
<td>39 (18.93%)</td>
<td>30 (18.07%)</td>
<td>9 (22.50%)</td>
<td></td>
</tr>
<tr>
<td>Preoperative combined diseases</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>146 (70.87%)</td>
<td>114 (68.67%)</td>
<td>32 (80.0%)</td>
<td>0.157</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>74 (35.92%)</td>
<td>61 (36.75%)</td>
<td>13 (32.50%)</td>
<td>0.615</td>
</tr>
<tr>
<td>Heart disease</td>
<td>56 (27.18%)</td>
<td>40 (24.10%)</td>
<td>16 (40.0%)</td>
<td>0.042</td>
</tr>
<tr>
<td>Respiratory disease</td>
<td>11 (5.34%)</td>
<td>10 (6.02%)</td>
<td>1 (2.50%)</td>
<td>0.374</td>
</tr>
<tr>
<td>Neurological disease</td>
<td>96 (46.60%)</td>
<td>78 (46.99%)</td>
<td>18 (45.0%)</td>
<td>0.821</td>
</tr>
<tr>
<td>Kidney disease</td>
<td></td>
<td></td>
<td></td>
<td>0.321</td>
</tr>
<tr>
<td>Degree of carotid artery stenosis on the surgical side</td>
<td></td>
<td></td>
<td></td>
<td>0.449</td>
</tr>
<tr>
<td>Mild/moderate stenosis</td>
<td>3 (1.46%)</td>
<td>2 (1.20%)</td>
<td>1 (2.5%)</td>
<td></td>
</tr>
<tr>
<td>Severe stenosis</td>
<td>201 (97.57%)</td>
<td>163 (98.19%)</td>
<td>38 (95.0%)</td>
<td></td>
</tr>
<tr>
<td>Occlusion</td>
<td>2 (0.97%)</td>
<td>1 (0.60%)</td>
<td>1 (2.50%)</td>
<td></td>
</tr>
<tr>
<td>Degree of carotid artery stenosis on the contralateral side</td>
<td></td>
<td></td>
<td></td>
<td>0.146</td>
</tr>
<tr>
<td>Mild/moderate stenosis</td>
<td>169 (85.35%)</td>
<td>132 (83.02%)</td>
<td>37 (94.87%)</td>
<td></td>
</tr>
<tr>
<td>Severe stenosis</td>
<td>21 (10.61%)</td>
<td>19 (11.95%)</td>
<td>2 (5.13%)</td>
<td></td>
</tr>
<tr>
<td>Occlusion</td>
<td>8 (4.04%)</td>
<td>8 (5.03%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Operating time (min)</td>
<td>141.33 ± 40.96</td>
<td>138.39 ± 38.78</td>
<td>153.57 ± 47.62</td>
<td>0.129</td>
</tr>
<tr>
<td>Duration of carotid artery occlusion (min)</td>
<td>22.00 (18.0–44.0)</td>
<td>22.00 (17.0–43.0)</td>
<td>27.0 (18.50–49.50)</td>
<td>0.328</td>
</tr>
<tr>
<td>Anesthesia method</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIVA</td>
<td>163 (79.13%)</td>
<td>129 (77.71%)</td>
<td>34 (85.0%)</td>
<td>0.309</td>
</tr>
<tr>
<td>Combined intravenous–inhalation anesthesia</td>
<td>43 (20.87%)</td>
<td>37 (22.29%)</td>
<td>6 (15.0%)</td>
<td></td>
</tr>
<tr>
<td>Intraoperative intake and output volume (mL)</td>
<td>897.57 ± 333.40</td>
<td>911.85 ± 333.01</td>
<td>839.75 ± 341.01</td>
<td>0.221</td>
</tr>
<tr>
<td>meanSBP</td>
<td>128.82 ± 12.92</td>
<td>128.37 ± 12.77</td>
<td>130.69 ± 13.54</td>
<td>0.309</td>
</tr>
<tr>
<td>SDSBP</td>
<td>20.26 ± 4.91</td>
<td>20.09 ± 5.01</td>
<td>20.93 ± 4.48</td>
<td>0.333</td>
</tr>
<tr>
<td>CVSBP</td>
<td>0.16 ± 0.04</td>
<td>0.16 ± 0.04</td>
<td>0.16 ± 0.03</td>
<td>0.550</td>
</tr>
<tr>
<td>meanDBP</td>
<td>69.61 ± 7.83</td>
<td>69.80 ± 7.77</td>
<td>68.82 ± 8.14</td>
<td>0.480</td>
</tr>
<tr>
<td>SDDBP</td>
<td>10.25 ± 2.70</td>
<td>10.18 ± 2.81</td>
<td>10.42 ± 2.26</td>
<td>0.612</td>
</tr>
<tr>
<td>CVDBP</td>
<td>0.15 ± 0.04</td>
<td>0.15 ± 0.04</td>
<td>0.15 ± 0.04</td>
<td>0.372</td>
</tr>
<tr>
<td>Intraoperative use of vasopressors</td>
<td>84 (40.78%)</td>
<td>65 (39.16%)</td>
<td>19 (47.50%)</td>
<td>0.335</td>
</tr>
</tbody>
</table>
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Table 2 Outcome variables, stratified by major postoperative complications

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>WOPC group</th>
<th>PC group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>206</td>
<td>166</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Major postoperative complications</td>
<td>40 (19.42%)</td>
<td>0</td>
<td>40 (100%)</td>
<td></td>
</tr>
<tr>
<td>Neuronal complications</td>
<td>16 (7.77%)</td>
<td>0</td>
<td>16 (40.0%)</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Cardiac complications</td>
<td>6 (2.91%)</td>
<td>0</td>
<td>6 (15.0%)</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Respiratory complications</td>
<td>14 (6.80%)</td>
<td>0</td>
<td>14 (35.0%)</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>AKI</td>
<td>9 (4.37%)</td>
<td>0</td>
<td>9 (22.50%)</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Fever</td>
<td>10 (4.85%)</td>
<td>4 (2.41%)</td>
<td>6 (15.0%)</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Surgical site infections</td>
<td>3 (1.46%)</td>
<td>1 (0.60%)</td>
<td>2 (5.0%)</td>
<td>0.097</td>
</tr>
<tr>
<td>Urinary infections</td>
<td>3 (1.46%)</td>
<td>1 (0.60%)</td>
<td>2 (5.0%)</td>
<td>0.097</td>
</tr>
<tr>
<td>DVT</td>
<td>5 (2.43%)</td>
<td>1 (0.60%)</td>
<td>4 (10.0%)</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Length of stay in the ICU (d)</td>
<td>1.0 (0–1.0)</td>
<td>1.0 (0–1.0)</td>
<td>1.0 (1.0–1.0)</td>
<td>0.055</td>
</tr>
<tr>
<td>Hospitalization stay (d)</td>
<td>15.56 ± 4.30</td>
<td>15.16 ± 3.63</td>
<td>17.20 ± 6.17</td>
<td>0.105</td>
</tr>
<tr>
<td>Cost of hospitalization (CNY)</td>
<td>24085.15 (21694.72–28395.65)</td>
<td>23786.67 (21568.68–27139.36)</td>
<td>27127.94 (22326.75–31629.55)</td>
<td>&lt; 0.001*</td>
</tr>
</tbody>
</table>

*p < 0.05, statistically significant difference was observed between two groups.

ASA: American society of anesthesiologists; BMI: Body mass index; CEA: Carotid endarterectomy; CV_DBP: Coefficient of variation in diastolic blood pressure; mean_DBP: mean diastolic blood pressure; mean_SBP: mean systolic blood pressure; PC: Post-CEA complications; SD_DBP: Standard deviation of diastolic blood pressure; SD_SBP: Standard deviation of systolic blood pressure; TIVA: Total intravenous anesthesia; WOPC: Without post-CEA complications.

For complications involving the neurological system, NLR can predict and affect clinical outcomes of stroke. Neutrophils are the first cells that invade injured tissues after focal cerebral ischemia. Their proinflammatory feature enhances tissue injury and may cause cerebral ischemia through the induction of thrombosis. Therefore, inflammatory markers may be potential targets for the treatment and prevention of stroke [19]. Within 48–72 h after acute ischemic stroke, patients with NLR ≥ 4.58 were 5.58 times more likely to have a poor outcome than patients with NLR < 4.58 [20]. NLR independently predicted 3-month neurological outcomes and symptomatic intracranial hemorrhage in patients with acute stroke caused by large vessel occlusion of the anterior circulation [21]. Cerebral blood flow (CBF) autoregulation can maintain consistent CBF within a certain blood pressure range, and patients with sepsis usually have damaged CBF autoregulation [22]. Masse et al [23] showed that CBF in sedated septic patients was 62% higher than that in control subjects and did not change with mean arterial pressure. The relationship between inflammation and cerebral hyperperfusion needs to be further studied [23].

A considerable proportion of patients with carotid stenosis also have coronary heart disease. NLR is considered a potential indicator of cardiovascular events. Durmuş et al [24] studied the relationship between NLR and the development of myocardial injury after noncardiac surgery (MINS), which showed that NLR in the MINS group was significantly higher than that in the non-MINS group [24]. For coronary artery disease patients with low high-sensitivity C-reactive protein levels, the elevation of NLR levels could independently predict their long-term outcomes [25]. One post hoc analysis studied patients with coronary heart disease who underwent noncardiac surgery. The results showed that NLR was significantly correlated with major adverse cardiovascular and cerebrovascular events, which were defined as the composite endpoint of death, myocardial ischemia, myocardial infarction, MINS, or embolic or
### Table 3 Risk factors associated with major postoperative complications

<table>
<thead>
<tr>
<th>Statistical value</th>
<th>Post-CEA major complications</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>62.0 ± 7.2</td>
<td>1.04 (0.99, 1.09)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td>0.616</td>
</tr>
<tr>
<td>Male</td>
<td>175 (84.95%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Female</td>
<td>31 (15.05%)</td>
<td>0.77 (0.28, 2.15)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.33 ± 2.89</td>
<td>1.05 (0.93, 1.17)</td>
</tr>
<tr>
<td>ASA grade</td>
<td></td>
<td>1.0</td>
</tr>
<tr>
<td>Grade II</td>
<td>167 (81.07%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Grade III</td>
<td>39 (18.93%)</td>
<td>1.32 (0.57, 3.05)</td>
</tr>
<tr>
<td>Anesthesia methods</td>
<td></td>
<td>0.62 (0.24, 1.58)</td>
</tr>
<tr>
<td>TIVA</td>
<td>163 (79.13%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Combined intravenous–inhalation anesthesia</td>
<td>43 (20.87%)</td>
<td>0.578 (0.24, 1.58)</td>
</tr>
<tr>
<td>Degree of carotid artery stenosis on the surgical side</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild/moderate stenosis</td>
<td>3 (1.46%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Severe stenosis</td>
<td>201 (97.57%)</td>
<td>0.47 (0.04, 5.28)</td>
</tr>
<tr>
<td>Occlusion</td>
<td>2 (0.97%)</td>
<td>2.00 (0.05, 78.25)</td>
</tr>
<tr>
<td>Degree of carotid artery stenosis on the contralateral side</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild/moderate stenosis</td>
<td>169 (85.35%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Severe stenosis</td>
<td>21 (10.61%)</td>
<td>0.38 (0.08, 1.69)</td>
</tr>
<tr>
<td>Occlusion</td>
<td>8 (4.04%)</td>
<td>0 (0, Inf)</td>
</tr>
<tr>
<td>Operating time (min)</td>
<td>141.33 ± 40.96</td>
<td>1.01 (1.0, 1.02)</td>
</tr>
<tr>
<td>Intraoperative intake and output volume (mL)</td>
<td>897.57 ± 333.40</td>
<td>1.00 (1.0, 1.00)</td>
</tr>
<tr>
<td>Duration of carotid artery occlusion</td>
<td>22.0 (18.0-44.0)</td>
<td>1.01 (0.99, 1.03)</td>
</tr>
<tr>
<td>CV_SBP</td>
<td>0.16 ± 0.04</td>
<td>16.36 (0.00, 150500.70)</td>
</tr>
<tr>
<td>CV,DBP</td>
<td>0.15 ± 0.04</td>
<td>40.21 (0.01, 132798.95)</td>
</tr>
<tr>
<td>Preoperative NLR</td>
<td>2.08 ± 0.94</td>
<td>1.21 (0.87, 1.69)</td>
</tr>
<tr>
<td>NLR within 24 h after CEA</td>
<td>5.68 (3.93-8.91)</td>
<td>1.09 (1.01, 1.17)</td>
</tr>
</tbody>
</table>

*P < 0.05.

ASA: American society of anesthesiologists; BMI: Body mass index; CEA: Carotid endarterectomy; CV_SBP: Coefficient of variation in diastolic blood pressure; CV,DBP: Coefficient of variation in systolic blood pressure; NLR: Neutrophil to lymphocyte ratio; TIVA: Total intravenous anesthesia.

Elevated NLR on postoperative day 2 was significantly correlated with higher inhospital mortality, pneumonia, ICU readmission and prolonged ICU stay after cardiac surgery[27]. A study by Lee et al[28] showed that NLR in pneumonia patients in the ICU was significantly higher than that in pneumonia patients in a ward and healthy controls. Compared with the C-reaction protein level, NLR might be a better indicator for evaluating the severity of pneumonia[28]. Another study also proved that NLR was significantly correlated with the pneumonia severity index[29]. Nam et al[30] confirmed that a higher NLR could predict stroke-associated pneumonia in patients with acute ischemic stroke. Moreover, NLR was higher in patients with severe pneumonia[30]. Feng et al[31] studied patients on mechanical ventilation for > 72 h and showed that NLR levels could be used to assess risk factors for mortality caused by ventilator-associated pneumonia[31].
Table 4 Correlation between neutrophil to lymphocyte ratio within 24 h after carotid endarterectomy and major postoperative complications

<table>
<thead>
<tr>
<th>Exposure factors</th>
<th>Unadjusted</th>
<th>P value</th>
<th>Model I</th>
<th>P value</th>
<th>Model II</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>NLR</td>
<td>1.09 (1.01, 1.17)</td>
<td>0.026a</td>
<td>1.08 (1.00, 1.16)</td>
<td>0.041a</td>
<td>1.15 (1.03, 1.29)</td>
<td>0.014a</td>
</tr>
<tr>
<td>NLR tertile groups</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low NLR group</td>
<td>1.0</td>
<td></td>
<td>1.0</td>
<td></td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Middle NLR group</td>
<td>1.60 (0.63, 4.09)</td>
<td>0.322</td>
<td>1.52 (0.59, 3.92)</td>
<td>0.386</td>
<td>3.99 (1.03, 15.49)</td>
<td>0.046a</td>
</tr>
<tr>
<td>High NLR group</td>
<td>2.92 (1.21, 7.02)</td>
<td>0.017a</td>
<td>2.88 (1.17, 7.09)</td>
<td>0.022a</td>
<td>8.47 (2.20, 32.63)</td>
<td>0.002a</td>
</tr>
</tbody>
</table>

aP < 0.05.

Model I-adjusted variables: Sex and age; Model II-adjusted variables: Sex, age, BMI, ASA grade, preoperative combined heart disease, anesthesia method, degree of stenosis on the surgical side, degree of stenosis on the contralateral side, operating time, intraoperative intake and output volume, duration of carotid artery occlusion, CVSBP and CVDBP. ASA: American society of anesthesiologists; BMI: Body mass index; CEA: Carotid endarterectomy; CVSBP: Coefficient of variation in systolic blood pressure; CVDBP: Coefficient of variation in diastolic blood pressure; NLR: Neutrophil to lymphocyte ratio.

Table 5 Outcome variables, stratified by NLR ratio tertile groups

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Low NLR group</th>
<th>Middle NLR group</th>
<th>High NLR group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>206</td>
<td>68</td>
<td>69</td>
<td>69</td>
<td></td>
</tr>
<tr>
<td>Major postoperative complications</td>
<td>40 (19.42%)</td>
<td>8 (11.76%)</td>
<td>11 (15.94%)</td>
<td>21 (30.43%)</td>
<td>0.015a</td>
</tr>
<tr>
<td>Neurological complications</td>
<td>16 (7.77%)</td>
<td>4 (5.88%)</td>
<td>4 (5.80%)</td>
<td>8 (11.59%)</td>
<td>0.346</td>
</tr>
<tr>
<td>Cardiac complications</td>
<td>6 (2.91%)</td>
<td>0 (0.00%)</td>
<td>3 (4.35%)</td>
<td>3 (4.35%)</td>
<td>0.218</td>
</tr>
<tr>
<td>Respiratory complications</td>
<td>14 (6.80%)</td>
<td>2 (2.94%)</td>
<td>5 (7.25%)</td>
<td>7 (10.14%)</td>
<td>0.242</td>
</tr>
<tr>
<td>AKI</td>
<td>9 (4.37%)</td>
<td>2 (2.94%)</td>
<td>1 (1.45%)</td>
<td>6 (8.70%)</td>
<td>0.089</td>
</tr>
<tr>
<td>Fever</td>
<td>10 (4.85%)</td>
<td>1 (1.47%)</td>
<td>2 (2.90%)</td>
<td>7 (10.14%)</td>
<td>0.040a</td>
</tr>
<tr>
<td>Surgical site infections</td>
<td>3 (1.46%)</td>
<td>1 (1.47%)</td>
<td>1 (1.45%)</td>
<td>1 (1.45%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Urinary infections</td>
<td>3 (1.46%)</td>
<td>0 (0.00%)</td>
<td>1 (1.45%)</td>
<td>2 (2.90%)</td>
<td>0.367</td>
</tr>
<tr>
<td>DVT</td>
<td>5 (2.43%)</td>
<td>2 (2.94%)</td>
<td>1 (1.45%)</td>
<td>1 (1.45%)</td>
<td>0.766</td>
</tr>
<tr>
<td>Length of stay in the ICU (d)</td>
<td>1.0 (0–1.0)</td>
<td>1.0 (0–1.0)</td>
<td>1.0 (0–1.0)</td>
<td>1.0 (1.0–1.0)</td>
<td>0.079</td>
</tr>
<tr>
<td>Hospitalization stay (d)</td>
<td>15.56 ± 4.30</td>
<td>15.44 ± 4.40</td>
<td>15.28 ± 4.27</td>
<td>15.96 ± 4.26</td>
<td>0.627</td>
</tr>
<tr>
<td>Cost of hospitalization (CNY)</td>
<td>26886.26 ± 11277.49</td>
<td>24371.70 ± 5233.73</td>
<td>26837.07 ± 12681.34</td>
<td>29413.56 ± 13520.49</td>
<td>0.032a</td>
</tr>
</tbody>
</table>

aStatistically significant difference was observed between the groups.


AKI results from a complex interaction between hemodynamic, toxic and inflammatory factors[32]. Long-term follow-up showed that NLR was an independent predictor of kidney function decline among individuals with diabetes and prediabetes [33,34]. The elevation of NLR immediately after cardiac surgery and on postoperative day 1 was associated with an increased risk of postoperative AKI and 1-year mortality; NLR could assist with the risk stratification of AKI and mortality in high-risk surgical patients[7,35,36]. High NLR levels were associated with increased risks of 30- and 90-day mortality in AKI patients; compared with the lower NLR group (NLR < 5.55), the hazard ratio in the higher NLR group (NLR > 12.14) was 1.37[37]. One recent systematic review and meta-analysis showed that when NLR was used to predict AKI, the sensitivity was 0.736, and the specificity was 0.686, indicating that NLR was a reliable biomarker for the early detection of AKI[38]. One prospective study evaluated the accuracy of a single emergency department measurement of NLR for the early diagnosis of AKI. The results showed that compared with normal controls, patients with AKI had a higher NLR. When the NLR cut-off value was 0.55, the sensitivity was 0.78, the specificity was 0.65, and the OR was 6.423[39].
This study had several limitations. First, the small sample size and the low event rates might have increased the probability of committing a type II error and thus decrease the power of a hypothesis test. Second, this was a retrospective cohort study. The authenticity and completeness of medical records directly affected the reliability of the results.

CONCLUSION

NLR within 24 h after CEA was associated with major postoperative complications. The incidence of major postoperative complications in the high NLR group was 8.47 times that in the low NLR group. Future prospective studies are needed for further evaluation.

ACKNOWLEDGMENTS

We acknowledge Dr. Xing-Lin Chen (Department of Epidemiology and Biostatistics, Empower U, X&Y solutions Inc., Boston, USA) for her excellent technical assistance in
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statistics. We also thank Dr. Kai-Ying Zhang (Department of Anesthesiology, The University of Texas Health Science Center at Houston, USA) for her help with English editing.

ARTICLE HIGHLIGHTS

Research background
Carotid artery cross-clamping during carotid endarterectomy (CEA) may induce cerebral ischemia–reperfusion injury to activate local inflammatory responses.

Research motivation
There is no consensus on the correlation between neutrophil-to-lymphocyte ratio (NLR) and complications after CEA.

Research objectives
This study aimed to evaluate the association between NLR and major complications after surgery in patients undergoing CEA.

Research methods
The demographics, neutrophil and lymphocyte count in whole blood and postoperative outcomes of patients undergoing CEA were retrospectively analyzed.

Research results
NLR within 24 h after CEA was significantly correlated with major postoperative complications. The incidence of major postoperative complications in the high NLR group was 8.47 times of that in the low NLR group.

Research conclusions
NLR is associated with major postoperative complications in patients undergoing CEA.

Research perspectives
Since early detection and early treatment help improve outcomes, inflammatory markers may become potential treatment targets for patients undergoing CEA.

REFERENCES

8 Huang Z, Fu Z, Huang W, Huang K. Prognostic value of neutrophil-to-lymphocyte ratio in sepsis: A


Retrospective Cohort Study

Application of MAGnetic resonance imaging compilation in acute ischemic stroke

Qi Wang, Gang Wang, Qiang Sun, Di-He Sun

ORCID number: Qi Wang 0000-0001-6613-865X; Gang Wang 0000-0002-8295-0530; Qiang Sun 0000-0003-3963-9779; Di-He Sun 0000-0001-7122-7462.

Author contributions: Wang Q and Wang G designed and coordinated the study; Sun Q and Sun HD treated the patients.

Institutional review board statement: The study was reviewed and approved for publication by our Institutional Reviewer.

Informed consent statement: All study participants or their legal guardian provided informed written consent about personal and medical data collection before study enrollment.

Conflict-of-interest statement: All the authors have no conflict of interest related to the manuscript.

Data sharing statement: No additional data are available.

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

Supported by Wu Jieping Medical

Abstract

BACKGROUND
Synthetic magnetic resonance imaging (MRI) MAGnetic resonance imaging compilation (MAGiC) is a new MRI technology. Conventional T1, T2, T2-fluid-attenuated inversion recovery (FLAIR) contrast images, quantitative images of T1 and T2 mapping, and MAGiC phase sensitive inversion recovery (PSIR) Vessel cerebrovascular images can be obtained simultaneously through post-processing at the same time after completing a scan. In recent years, studies have reported that MAGiC can be applied to patients with acute ischemic stroke. We hypothesized that the synthetic MRI vascular screening scheme can evaluate the degree of cerebral artery stenosis in patients with acute ischemic stroke.

AIM
To explore the application value of vascular images obtained by synthetic MRI in diagnosing acute ischemic stroke.

METHODS
A total of 64 patients with acute ischemic stroke were selected and examined by MRI in the current retrospective cohort study. The scanning sequences included traditional T1, T2, and T2-FLAIR, three-dimensional time-of-flight magnetic resonance angiography (3D TOF MRA), diffusion-weighted imaging (DWI), and synthetic MRI. Conventional contrast images (T1, T2, and T2-FLAIR) and intracranial vessel images (MAGiC PSIR Vessel) were automatically reconstructed using synthetic MRI raw data. The contrast-to-noise ratio (CNR) values of traditional T1, T2, and T2-FLAIR images and MAGiC reconstructed T1, T2, and T2-FLAIR images in DWI diffusion restriction areas were measured and compared. MAGiC PSIR Vessel and TOF MRA images were used to measure and calculate the stenosis degree of bilateral middle cerebral artery stenosis areas. The consistency of MAGiC PSIR Vessel and TOF MRA in displaying the degree of vascular stenosis with computed tomography angiography (CTA) was compared.
RESULTS
Among the 64 patients with acute ischemic stroke, 79 vascular stenosis areas showed that the correlation between MAGiC PSIR Vessel and CTA (r = 0.90, P < 0.01) was higher than that between TOF MRA and CTA (r = 0.84, P < 0.01). With a degree of vascular stenosis > 50% assessed by CTA as a reference, the area under the receiver operating characteristic (ROC) curve of MAGiC PSIR Vessel [area under the curve (AUC) = 0.906, P < 0.01] was higher than that of TOF MRA (AUC = 0.790, P < 0.01). Among the 64 patients with acute ischemic stroke, 39 were scanned for traditional T1, T2, and T2-FLAIR images and MAGiC images simultaneously, and CNR values in DWI diffusion restriction areas were measured, which were: Traditional T2 = 21.2, traditional T1 = -6.7, and traditional T2-FLAIR = 11.9; and MAGiC T2 = 7.1, MAGiC T1 = -3.9, and MAGiC T2-FLAIR = 4.5.

CONCLUSION
The synthetic MRI vascular screening scheme for patients with acute ischemic stroke can accurately evaluate the degree of bilateral middle cerebral artery stenosis, which is of great significance to early thrombolytic interventional therapy and improving patients’ quality of life.

Key Words: Acute ischemic stroke; Magnetic resonance angiography; Computed tomography angiography; Phase sensitive inversion recovery

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INTRODUCTION
Cerebrovascular disease is the second deadliest disease globally, and acute cerebrovascular disease also has a higher disability rate than any other single disease, which brings heavy burdens to society[1-4]. In recent years, imaging has played an increasingly prominent key role in preventing and treating cerebrovascular disease[5]. For example, in treating acute stroke, the treatment time window of some patients with macrovascular diseases can be extended by 6-24 h using image evaluation[6,7]. The long-term survival rate and recurrence rate after acute ischemic stroke also vary significantly with the different causes of the first stroke. The 5-year survival rate of small vessel disease is the highest in both males and females, and the 5-year recurrence rate is the lowest in female patients with small vessel disease and male patients with large vessel diseases[8]. The traditional magnetic resonance imaging (MRI) technology, three-dimensional time-of-flight magnetic resonance angiography (3D TOF MRA), has been widely used in screening cerebrovascular diseases because of its advantages, including non-invasiveness, non-radiation, and no need to inject contrast media[9,10]. However, in the imaging examination of patients with acute stroke, saving time can save the brain, so the shorter the examination process, the better the outcome. Traditional sequences such as T1, T2, T2-fluid-attenuated inversion recovery (FLAIR), TOF MRA, and diffusion-weighted imaging (DWI) require separate scanning, so it
usually takes more than 10 min to complete all the examinations. Furthermore, 3D TOF MRA may overestimate the degree of vascular stenosis due to the hemodynamic changes in stenotic vessels.

MAGnetic resonance imaging compilation (MAGIC) is a newly emerging synthetic MRI technology. While completing one scan, the technician can acquire conventional T1, T2, T2-FLAIR, and other contrast images, quantitative T1 mapping and T2 mapping images, as well as MAGIC phase-sensitive inversion recovery (PSIR) Vessel cerebrovascular images simultaneously through post-processing, which significantly shortens the scanning time required for magnetic resonance examination\[11-14\]. In recent years, some researchers reported that MAGIC can be used to reconstruct various contrast images that can be applied in patients with acute ischemic stroke, and T2 mapping images acquired by MAGIC can more accurately evaluate stroke onset time\[15,16\]. However, studies evaluating the clinical application of intracranial vascular images acquired by MAGIC have not been reported.

This study aimed to compare the accuracy of MAGIC PSIR Vessel and TOF MRA in evaluating the stenosis degree of bilateral middle cerebral arteries, and to further explore the application value of MAGIC in acute ischemic stroke.

**MATERIALS AND METHODS**

**General information**
A total of 64 patients with acute ischemic stroke diagnosed at the neurology department of our hospital (The Stroke Hospital of Liaoning Province, Liaoning Province, China) from November 2020 to May 2021 were retrospectively analyzed (all conforming to the 2018 edition of Chinese Guidelines for Diagnosis and Treatment of Acute Ischemic Stroke), including 44 males and 20 females, aged from 41 to 78 years (average age: 58 years). Upon admission, all patients underwent multi-sequence brain MRI scanning (including DWI, TOF MRA, and MAGIC), and computed tomography angiography (CTA) scanning was performed within 3 d after MRI examination. The post-processing images of DWI, TOF MRA, synthetic MRI, and CTA were retrospectively analyzed. All patients signed an informed consent form before examinations.

**Scanning equipment and parameters**
In this study, a SIGNAPioneer 3.0T MR scanner (GE, USA) with a 21-channel head phased-array coil was used. The main scanning sequences are shown in Table 1.

**Image post-processing and analysis**
MAGIC original image and images (T1, T2, T2-FLAIR, T2 mapping, and MAGIC PSIR Vessel) automatically generated with the post-processing software supplied with the GE host after scanning were analyzed (Figure 1).

The 3D TOF MRA and MAGIC PSIR Vessel images were post-processed with Reformat software of GE ADW4.7 workstation. The consistency of the two examination methods with CTA in evaluating the degrees of intracranial vascular stenosis was investigated.

The degree of vascular stenosis was calculated as (1-diameter of the lumen at stenosis/diameter of an adjacent normal blood vessel) × 100%.

With CTA vascular stenosis degree greater than 50% as the classification point, receiver operating characteristic (ROC) curves were plotted for the two examination methods to calculate the area under the curve (AUC).

The method for measuring contrast-to-noise ratio (CNR) values in DWI diffusion restriction areas of traditional T1, T2, and T2-FLAIR images as well as MAGIC T1, T2, and T2-FLAIR images was as follows: CNR = (mean intensity of stroke lesion - mean intensity of thalamus)/standard deviation of the thalamus.

**Statistical analysis**
All quantitative data were analyzed and processed with SPSS25.0 statistical software. With CTA as the control, the consistency and correlation of the two examination methods TOF MRA and MAGIC PSIR Vessel with CTA in evaluating the degree of vascular stenosis were evaluated by Bland-Altman plots and Spearman correlation analysis, respectively. The significant difference was set as \( P < 0.05 \).
Table 1 3.0T magnetic resonance skull scanning sequences and parameters

<table>
<thead>
<tr>
<th></th>
<th>Slice thickness (mm)</th>
<th>Matrix (mm)</th>
<th>TR (ms)</th>
<th>TE (ms)</th>
<th>Acquisition time (min)</th>
<th>FOV (cm)</th>
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<tr>
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<tr>
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<td>7365</td>
<td>12.9/90.1</td>
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</table>

MAGiC: MAGnetic resonance imaging compilation; TOF MRA: Time-of-flight magnetic resonance angiography; DWI: Diffusion weighted imaging (b value = 1000); TR: Repetition time; TE: Echo time; FOV: Field of view.

RESULTS

Figure 2 and Figure 3 show the evaluation of intracranial vascular stenosis degree by 3D TOF MRA, MAGiC PSIR Vessel, and CTA. The correlation between MAGiC PSIR Vessel and CTA (\(r = 0.90, P < 0.01\)) was higher than that between TOF MRA and CTA (\(r = 0.84, P < 0.01\)). The area under the ROC curve of MAGiC PSIR Vessel (AUC = 0.906, \(P < 0.01\)) was higher than that of TOF MRA (AUC = 0.790, \(P < 0.01\)), as shown in Figure 4.

MAGiC-reconstructed multi-contrast images had reduced CNR values of DWI diffusion restriction areas than the traditional multi-contrast images (traditional T2 = 21.2, traditional T1 = -6.7, and traditional T2-FLAIR = 11.9; MAGiC T2 = 7.1, MAGiC T1 = -3.9, and MAGiC T2-FLAIR = 4.5; Figure 5). In addition, two experienced diagnosticians respectively evaluated whether the images obtained by the two methods could meet the clinical diagnostic requirements of stroke. The results showed that both methods could meet the clinical diagnostic requirements.

DISCUSSION

Synthetic MRI MAGiC is a quantitative MRI technique, which can generate a variety of conventional contrast images (T1, T2, T2-FLAIR, etc.), quantitative images (T1 mapping and T2 mapping), and intracranial vessel images (PSIR Vessel) simultaneously in a single scan by acquiring the T1 relaxation rate, T2 relaxation rate, and PD density value of tissues, and has been applied in many sites such as nerves and joints [17-26]. Among them, research has been conducted on the application of T2 mapping in the nervous system, such as the evaluation of edema around tumors and showed epileptic lesions. In recent years, in the imaging diagnosis of stroke, many studies have been conducted to apply synthetic MRI imaging technology. For example, T2 mapping quantitative images acquired by MAGiC could more accurately evaluate stroke onset time[27-29].

MRI can provide important imaging evidence in the prevention, diagnosis, and treatment of cerebrovascular diseases. However, its long scanning time, especially in patients with hyperacute stroke, contradicts the clinical need to carry out treatment as soon as possible. For example, the evaluation of vascular stenosis degree in acute...
stroke is of great value in defining the etiology and responsible vessels and guiding the selection of subsequent clinical treatment regimens. However, traditional TOF MRA scanning usually takes 3 to 5 min; therefore, a vascular imaging technique with a shorter scanning time is needed in MRI examination. MAGIC PSIR Vessel intracranial blood vessel images are generated simultaneously with conventional T1, T2, and other contrast images, as well as T1 mapping, T2 mapping, and other quantitative images, which can be initially used for screening intracranial blood vessels without occupying additional scanning time. Its imaging principle is based on the use of difference in phase information between flowing blood flow and stationary tissues to image blood vessels, reducing the influence of hemodynamics on blood vessel imaging. In contrast, traditional TOF MRA imaging technology uses the enhancement effect of blood inflow to obtain blood vessel images, which will be affected by changes in hemodynamics. In the area of vascular stenosis, the degree of stenosis may be overestimated due to turbulent or slow blood flow[30-34]. This study revealed that with CTA results as a reference, the area under ROC curve of MAGIC PSIR Vessel examination was higher than that of traditional TOF MRA examinations in patients with vascular stenosis greater than 50%. Some patients with vascular occlusion not displayed by TOF MRA only showed moderate to severe stenosis on MAGIC PSIR Vessel and CTA images. In terms of scanning time, the scanning time of MAGIC was about 4.5 min, and the scanning time of MAGIC combined with DWI was about 5 min, which was significantly less than that of the traditional scanning schemes of TOF MRA and DWI combined with T1, T2, and T2-FLAIR (usually more than 10 min), which is conducive to improving the MRI examination efficiency for patients with acute stroke and treatment window for clinical thrombolytic intervention as soon as possible.

To obtain a clear enough blood vessel display, the slice thickness of the MAGIC image was set at 1.6 mm, which made the CNR values of T1, T2, and T2-FLAIR images generated by MAGIC decrease compared with traditional images due to the influence...
Figure 4 Bland-Altman and receiver operating characteristic curve evaluation of vascular stenosis degrees obtained by MAGnetic resonance imaging compilation phase-sensitive inversion recovery Vessel and time-of-flight magnetic resonance angiography. A: MAGnetic resonance imaging compilation-computed tomography angiography; B: Time-of-flight magnetic resonance angiography; C: Receiver operating characteristic curves. TOF: Time-of-flight; CTA: Computed tomography angiography; ROC: Receiver operating characteristic.

There were some limitations to this study. First, this is a retrospective study, and some patients needed to complete CTA and MRI examinations simultaneously, which might result in selection bias. Meanwhile, due to this reason, not all the patients could be scored by the National Institute of Health stroke scale. Second, the number of cases was relatively small, which was mainly because MRI is not widely used in the diagnosis and treatment of acute stroke in clinical departments, as it is considered that the scanning time of this technique is relatively long, which may delay the diagnosis and treatment time of patients. Third, this study did not evaluate the long-term outcomes of patients, e.g., the proportion of recurrent stroke in patients treated with vascular recanalization. The evaluation of long-term outcomes of patients can further clarify the relationships of vascular stenosis degree judgment with cerebrovascular recanalization treatment and stroke recurrence.
CONCLUSION

In conclusion, MAGiC can simultaneously obtain a variety of conventional contrast images (T1, T2, T2-FLAIR, etc.), intracranial vessel images (MAGiC PSIR Vessel), and both T2 and T1 relaxation time quantitative images (T2 mapping and T1 mapping) in one scan, which can accurately determine the onset time of stroke, preliminarily screen intracranial vessels, and further shorten the MRI examination time in patients with acute stroke, thereby guiding clinical thrombolytic intervention as early as possible and improve patients’ quality of life.

ARTICLE HIGHLIGHTS

Research background

Synthetic magnetic resonance imaging (MRI) MAGnetic resonance imaging compilation (MAGiC) is a new MRI technology. While completing one scan, the technician can acquire conventional T1, T2, T2-fluid-attenuated inversion recovery (FLAIR), and other contrast images, quantitative T1 mapping and T2 mapping images, as well as MAGiC phase-sensitive inversion recovery (PSIR) Vessel cerebrovascular images simultaneously through post-processing, which significantly shortens the scanning time required for MRI examination.

Research motivation

This study evaluated the application value of vascular images obtained by synthetic MRI in diagnosing acute ischemic stroke.

Research objectives

We hypothesized that the synthetic MRI vascular screening scheme can evaluate the degree of cerebral artery stenosis in patients with acute ischemic stroke.

Research methods

The contrast-to-noise ratio (CNR) values of traditional T1, T2, and T2-FLAIR images and MAGiC reconstructed T1, T2, and T2-FLAIR images in DWI diffusion restriction areas were measured and compared. MAGiC PSIR Vessel and time-of-flight magnetic resonance angiography (TOF MRA) images were used to measure and calculate the stenosis degree of bilateral middle cerebral artery stenosis areas. The consistency of MAGiC PSIR Vessel and TOF MRA in displaying the degree of vascular stenosis with computed tomography angiography was compared.

Research results

Magnetic resonance imaging can provide important imaging evidence in the prevention, diagnosis, and treatment of cerebrovascular diseases. However, its long scanning time, especially in patients with hyperacute stroke, contradicts the clinical need to carry out treatment as soon as possible. MAGiC PSIR Vessel images are...
generated simultaneously with conventional T1, T2, and other contrast images, as well as T1 mapping, T2 mapping, and other quantitative images, which can be initially used for screening intracranial blood vessels without occupying additional scanning time.

**Research conclusions**

MAGiC can simultaneously obtain a variety of conventional contrast images (T1, T2, T2-FLAIR, etc.), intracranial vessel images (MAGiC PSIR Vessel), and both T2 and T1 relaxation time quantitative images (T2 mapping, T1 mapping) in one scan, which can accurately determine the onset time of stroke, preliminarily screen intracranial vessels, and further shorten the magnetic resonance imaging examination time in patients with acute stroke.

**Research perspectives**

The evaluation of long-term outcomes of patients can further clarify the relationships of vascular stenosis degree judgment with cerebrovascular recanalization treatment and stroke recurrence.

**ACKNOWLEDGEMENTS**

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**REFERENCES**

11. Blystad I, Wramtjes JBM, Smedby Ø, Lundberg P, Larsson EM, Tisel A. Quantitative MRI for...


31 Dündar TT, Aralasman A, Özdemir H, Seyithanoğlu MH, Uysal O, Toprak H, Kitiş S, Özek E, ...


Retrospective Study

Ninety-four thousand-case retrospective study on antibacterial drug resistance of *Helicobacter pylori*

Yu Zhang, Fei Meng, Jie Jin, Jun Wang, Bin-Bin Gu, Jin-Bang Peng, Li-Ping Ye

**Abstract**

**BACKGROUND**

The resistance rate to antibacterial drugs is the key inhibitor of *Helicobacter pylori* (*H. pylori*) eradication treatment.

**AIM**

To evaluate the prevalence and drug resistance of *H. pylori* based on big data.

**METHODS**

Gastric mucosal specimens were collected from naive patients undergoing upper gastrointestinal endoscopy for *H. pylori* culture and antimicrobial susceptibility testing (AST), including clarithromycin, levofloxacin, metronidazole and amoxicillin. Every 10 years of age was grouped as an age group. The *H. pylori* infection and resistance were explored based on the age group and gender.

**RESULTS**

The number of *H. pylori*-positive specimen was 94509 in 283823 gastric mucosal specimens, with an infection rate of 33.30%. The infection rate increased with age, and males had a higher infection rate than females. The average resistance rate of *H. pylori* to amoxicillin and metronidazole was 0.21% and 93.72%, which remained stable. The average resistance rate to clarithromycin was 23.99% with an increasing trend from 14.43% to 38.24%. The average resistance rate to levofloxacin was 30.29%, which increased from 17.07% to 39.42% and mostly stabilized after 2017. The resistance rate of *H. pylori* increased with age, except amoxicillin. *H. pylori* in females are at higher risk of resistance to metronidazole, clarithromycin, and levofloxacin.
but not to amoxicillin, regardless of the age group. Meanwhile, *H. pylori* in females are at higher risk of resistance to levofloxacin and clarithromycin in the 21-50 age group. The single, dual, triple and quadruple-drug resistance rate was 54.59%, 29.03%, 11.71% and 0.11%, respectively.

**CONCLUSION**

The resistance of *H. pylori* in Taizhou city is serious. Guided by the consensus report, individualized treatment based on AST is recommended.

**Key Words:** Helicobacter pylori; Infection; Resistance; Age group; Gender

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**Core Tip:** We shared a 10-year data in prevalence and resistance of *Helicobacter pylori* (*H. pylori*) in Taizhou city, Zhejiang province, China. We found that the infection rate increased with age, and males had a higher infection rate than females. The resistance rate of *H. pylori* to metronidazole, clarithromycin and levofloxacin was increased with age. *H. pylori* in females are at higher risk of resistance to metronidazole, but not to amoxicillin, regardless of the age group. Meanwhile, *H. pylori* in females are at higher risk of resistance to levofloxacin and clarithromycin in the 21-50 age group.

**INTRODUCTION**

According to the estimates by GLOBOCAN, 1033701 individuals developed gastric cancer, and an estimated 782685 related deaths occurred in 2018[1]. In China, gastric cancer is ranked second for incidence rate and third for mortality rates among all cancers, while in Western Europe, the incidence rate ranks 9th and the mortality rate ranks 6th. In North America, the incidence rate and mortality rates of gastric cancer rank 13th and 9th respectively[2]. *Helicobacter pylori* (*H. pylori*) is the most important pathogenic factor of gastric cancer which accounted for 44.2% of new gastric cancer cases globally[2]. *H. pylori* was estimated to be responsible for more than 78.00% of new gastric cancer cases in 2018, and the total number of *H. pylori*-related cases is not expected to decrease for decades due to global population growth and aging[3]. Moreover, *H. pylori* causes substantial morbidity from various peptic ulcer diseases, gastritis and even gastric lymphoma. *H. pylori* is classified as carcinogenic (Group 1) to humans by the Monographs program of the International Agency for Research on Cancer[4].

Several recent publications have demonstrated the global prevalence of *H. pylori* infection to be approximately 50%[5,6]. Large differences were observed between areas within large countries, such as China, which is one of the countries with the highest prevalence of *H. pylori* infection[7]. Wuwei city has a much higher *H. pylori* prevalence (72.28%) than all other areas in China, followed by Fengkai city (55.90%). Dali city has the lowest *H. pylori* prevalence of 11.36%[8]. Effective treatment for *H. pylori* infection with a combination of antibacterial drugs, proton pump inhibitors and bismuth all contribute to a decline in peptic ulcer disease incidence and the gastric cancer mortality rate. The resistance rate to antibacterial drugs is the key inhibitor of *H. pylori* eradication treatment. Some data that describe the resistance rates of *H. pylori* indicate a correlation with age[9]. Populations of different ages with various antibiotic usage habits may have different resistances to antibacterial drugs used for *H. pylori* treatment, and this result will be more apparent when examined by big data analysis.

Thus, big data-based *H. pylori* prevalence and drug resistance statistical programs are critical. In this study, we shared a 10-year data analysis on the prevalence and resistance of *H. pylori* in Taizhou city, Zhejiang Province, China.
MATERIALS AND METHODS

Research object
This multicenter retrospective study was conducted from January 2011 to December 2020 in Taizhou city, Zhejiang Province, China. Gastric mucosal specimens were collected from patients undergoing upper gastrointestinal endoscopy for H. pylori culture and in vitro antimicrobial susceptibility testing (AST). Patients in this study followed the enrollment criteria: (1) With gastrointestinal symptoms such as abdominal pain, bloating, acid reflux and nausea, etc.; (2) Gastricoscopically diagnosed as gastric, duodenal peptic ulcer and chronic gastritis with erosion, etc.; (3) No severe damage to heart, liver, and kidney function, and no allergies to antibacterial drugs used in AST; (4) Non-pregnant or breastfeeding women, no gastrointestinal bleeding, perforation, pyloric obstruction, or cancer complications; (5) Have not taken any antibacterial drugs, bismuth, H₂ receptor antagonist or proton-pump inhibitors within half a month; and (6) Agree to conduct gastric mucosal tissue sampling, H. pylori culture and in vitro AST, and signed their informed consent. The study had been approved by the ethics committee of Taizhou Hospital of Zhejiang Province.

Sample collection
A gastric mucosal specimen was collected from lesser curvature of the gastric antrum, greater curvature of the gastric body, or the tissue adjacent to the lesion. After biopsy, the specimen was immersed in H. pylori preservation tube containing brain heart infusion. All specimens were transported on dry ice throughout the entire process to Zhiyuan Medical Inspection Institute Co., Ltd. for H. pylori culture, isolation, identification and AST.

H. pylori isolation, culture and identification
Thawed the gastric mucosal specimen at room temperature and fully ground it into homogenate with 600 μL of brain heart infusion in a glass grinder. Spread the tissue homogenate on a Columbia blood plate (OXOID, England) containing 5% sheep blood by streaking. Cultivated the H. pylori in a 37 °C mixed gas incubator (5% O₂, 10% CO₂ and 85% N₂) for 2-3 d. Extended the culture time to 7 d if there was no growth. Picked out and subcultured the monoclonal colonies with typical colony morphology. Then smeared microscopy with the suspected H. pylori strain and carried out the biochemical experiments with urease (Haibo Biotechnology Co., Ltd., China), oxidase (Beijing Luqiao Technology Co., Ltd., China) and catalase (Haibo Biotechnology Co., Ltd., China). Suspected strains with biological morphology and biochemical reactions were identified as H. pylori, and the patient was diagnosed as positive for H. pylori infection. Extended the culture time to 7 d, and if there was still no H. pylori strain growth on the medium, the patient was diagnosed as negative for H. pylori infection.

AST
The plate incorporation assay was used to test the antimicrobial susceptibility of H. pylori strains[10]. The critical points of antibacterial resistance referred to the value of H. pylori clinical susceptibility test in China[11,12]: 1 μg/mL for clarithromycin (National Institute for Food and Drug Control, China), 2 μg/mL for levofloxacin (National Institute for Food and Drug Control, China), 8 μg/mL for metronidazole (National Institute for Food and Drug Control, China), and 2 μg/mL for amoxicillin (Dr. Ehrenstorfer GmbH, Germany).

We diluted and added these 4 kinds of antibacterial drugs to sterile Columbia culture medium containing 5% sheep blood respectively and ensured the concentration of antibacterial drugs to the critical point. After mixing well, poured into the plate to prepare 4 kinds of blood plates containing the antibacterial drugs.

Collected H. pylori strains with good growth status, and diluted the strains with 0.9% normal saline to a concentration of 0.5 McFarland, about 1.5 × 10⁸/mL[10]. Drew 2 μL of the diluted bacterial solution and inoculated on the conventional Columbia blood plate and the Columbia blood plate containing antibacterial drug, respectively. Cultivated the H. pylori in a 37 °C mixed gas incubator (5% O₂, 10% CO₂ and 85% N₂) for 2 d.

Firstly, we observed the growth of H. pylori strains on the conventional blood plate. The H. pylori strains with good growth status proved that its antimicrobial susceptibility results are credible. The H. pylori strains with poor growth status or not growing needed to undergo a new AST. Secondly, we observed the growth of H. pylori strains on the blood plate containing antibacterial drug. An inhibited growth of the H. pylori strain on the blood plate containing antibacterial drug was judged to be sensitive to
the antibacterial drug, and the uninhibited growth of the *H. pylori* strain was judged to be resistant to the antibacterial drug. The NCTC11637 standard strain was selected as the quality control bacteria.

**Statistical analysis**

SPSS 19.0 software were used. Using chi-square test to perform statistical analysis on count data. Odds ratio (OR) was used to evaluate risk factors. The Mantel-Haenszel chi-square test was used to evaluate a linear relationship. Breslow-Day method was used for the test of Homogeneity of OR. *P* < 0.05 indicated that the difference was statistically significant.

**RESULTS**

**H. pylori infection**

**Basic information**: From 2011 to 2020, a total of 283823 gastric mucosal specimens were cultured from patients with peptic ulcer disease. The ratio of males to females was 1.01:1.00. The ages of the participants ranged from 3 to 97, and the average age was 48.52 ± 14.04. The number of *H. pylori*-positive specimens was 94509; thus, the overall positive rate of *H. pylori* infection reached 33.30%. The ratio of male to female patients who were positive for *H. pylori* was 1.08:1.00. The ages of these patients ranged from 4 to 96, and the average age was 50.79 ± 12.76. Every 10 years of age was grouped as an age group, resulting in division into 8 age groups: ≤ 20 years, 21-30, 31-40, 41-50, 51-60, 61-70, 71-80 and ≥ 81 years; this division was close to a normal distribution (*P* = 0.383) (Table 1).

**Gender and risk of H. pylori infection**: A total of 142851 males and 140972 females were tested for *H. pylori* infection; of these, 49139 males and 45370 females tested positive for *H. pylori* infection. Compared with females, males had a higher rate of *H. pylori* infection (OR = 1.105, 95% confidence interval (CI): 1.088-1.122).

**Relationship between age and H. pylori infection**: The results of the Mantel-Haenszel chi-square test showed that there was a linear relationship between age and the rate of *H. pylori* infection (*χ² = 2577.812, *P* < 0.001). The Pearson-related results showed that *r* = 0.095, *P* < 0.001, indicating that the *H. pylori* infection rate increased with age.

**Multivariable analysis of H. pylori infection**: The homogeneity of OR test showed *P* = 0.003, suggesting that the OR values between age groups were heterogeneous, and it was not appropriate to combine the OR values. Therefore, after stratifying according to age group, male gender was determined to be a risk factor for *H. pylori* infection, except for the population aged ≥ 81-years-old (OR = 1.044, 95%CI: 0.844-1.292, *P* = 0.690). For the ≤ 20-years-old age group, the risk of *H. pylori* infection was 1.240 times higher in males than in females (OR = 1.240, 95%CI: 1.082-1.421, *P* = 0.002). For different age groups between 21-years-old and 80-years-old, the risk of *H. pylori* infection was 1.073, 1.103, 1.117, 1.165, 1.050, and 1.123 times higher in males than in females, respectively (Table 1).

**Antibacterial resistance of H. pylori**

**The overall resistance rate of H. pylori**: The average resistance rate of *H. pylori* to amoxicillin was 0.21% and slightly increased in 2017 and 2018 to 1.15% and 0.87%, respectively. The average resistance rate of *H. pylori* to metronidazole was 93.72%, remained at a high level and fluctuated in the range of 92.71% to 96.92%, except for when the rate fell to 86.64% in 2016. Different from the trends of these two antibacterial drugs, the average resistance rate of *H. pylori* to clarithromycin was 23.99% and had an increasing trend (from 14.43% in 2013 to 38.24% in 2020) (Figure 1). The average resistance rate of *H. pylori* to levofloxacin was 30.29%, which increased over time (from 17.07% in 2013 to 39.42% in 2017) and mostly stabilized after 2017. The results of the Mantel-Haenszel chi-square test and Pearson-related results showed a linear increase for resistance to clarithromycin (*χ² = 2389.117, *r* = 0.159, *P* < 0.001) and for resistance to levofloxacin (*χ² = 1901.809, *r* = 0.142, *P* < 0.001).

**Gender and risk of H. pylori resistance rates**: The number of males infected with *H. pylori* who were resistant to levofloxacin was 14051, and the resistance rate was 28.59%, while the number of females infected with *H. pylori* who were resistant was 14578, with a resistance rate of 32.13%. Compared with that of males, the *H. pylori* resistance rate was higher in females (OR = 1.182, 95%CI: 1.159-1.216). The resistance
Zhang Y et al. Study on resistance rate of *H. pylori*

Table 1 Basic information of specimen tested for *H. pylori* infection (n)

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<th>Infection rate (%)</th>
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<td>46803</td>
<td>23720</td>
<td>23083</td>
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<tr>
<td>41-50</td>
<td>29.76</td>
<td>80907</td>
<td>39271</td>
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<td>72229</td>
<td>35077</td>
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<td>61-70</td>
<td>43.33</td>
<td>40951</td>
<td>21065</td>
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<tr>
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<td>18.65</td>
<td>2488</td>
<td>1621</td>
<td>867</td>
</tr>
</tbody>
</table>

*95% confidence interval (lower bound, upper bound).
CI: Confidence interval; *H. pylori*: Helicobacter pylori.*

Figure 1 Trends of *Helicobacter pylori* resistance to four antibacterial drugs with years.

rates to clarithromycin in males and females were 22.93% and 25.14%, respectively, and the *H. pylori* resistance rate to clarithromycin in females was higher than that in males (OR = 1.129, 95%CI: 1.095-1.163). Similarly, the *H. pylori* resistance rate to metronidazole in females (94.44%) was higher than that in males (93.05%) (OR = 1.267, 95%CI: 1.202-1.337). There was no significant difference in the resistance rate of *H. pylori* to amoxicillin between different genders (OR = 0.880, 95%CI: 0.663-1.169).

**Relationship between age and *H. pylori* resistance rates**: Overall, the resistance rate to amoxicillin was low (< 0.35%). The resistance rate to metronidazole mostly stabilized after increasing from 75.39% to 96.49% in the population < 60-years-old, and the resistance rate of the population ≥ 61-years-old remained at approximately 98%. The resistance rate to clarithromycin increased rapidly in the population ≥ 61 years of age, changing from 21.02% to 39.01%. The resistance rate to levofloxacin continuously increased from 10.32% to 48.71% with increasing age. The results from the Mantel-Haenszel chi-square test and the Pearson relationship showed that there was a linear and positive relationship between age and resistance rate of *H. pylori* to the three kinds
of antibacterial drugs, except for a negative relationship to amoxicillin resistance ($\chi^2 = 1356.563$, $r = 0.120$, $P < 0.001$ for levofloxacin; $\chi^2 = 153.312$, $r = 0.040$, $P < 0.001$ for clarithromycin; $\chi^2 = 3685.476$, $r = 0.197$, $P < 0.001$ for metronidazole; and $\chi^2 = 24.710$, $r = -0.016$, $P < 0.001$ for amoxicillin) (Figure 2).

**Multivariable analysis of resistance rates:** Furthermore, we conducted an analysis on the correlation of age and gender with the *H. pylori* resistance rates to levofloxacin, clarithromycin and metronidazole (Figure 3).

Resistance rate to levofloxacin: The homogeneity of OR test showed $P < 0.001$, suggesting that the OR values between age groups are heterogeneous, and it is not appropriate to combine OR values. Therefore, after stratifying according to age group, there was no significant difference in the resistance rate of *H. pylori* to levofloxacin between female and male, aged ≤ 20-years-old and aged ≥ 51-years-old ($P > 0.05$). However, for the 21-50 age group, *H. pylori* in female was at a higher risk of resistance to levofloxacin than in male. For the 21-30 age group, the risk of *H. pylori* developing resistance to levofloxacin was 1.525 times higher in females than in males (OR = 1.525, 95%CI: 1.330-1.748, $P < 0.001$). For the 31-40 age group, the risk of *H. pylori* developing resistance to levofloxacin was 1.604 times higher in females than in males (OR = 1.604, 95%CI: 1.483-1.735, $P < 0.001$), and for the 41-50 age group, the risk was 1.325 times higher in females than in males (OR = 1.325, 95%CI: 1.253-1.400, $P < 0.001$).

Resistance rate to clarithromycin: The homogeneity of OR test showed $P < 0.001$. After stratifying according to age group, there was no significant difference in the resistance rate of *H. pylori* to clarithromycin between females and males, aged ≤ 20-years-old and aged ≥ 51-years-old ($P > 0.05$). For the 21-50 age groups, *H. pylori* in females was at a higher risk of resistance to clarithromycin than in males. For the 21-30 age group, the risk of *H. pylori* developing resistance to clarithromycin was 1.356 times higher in females than in males (OR = 1.356, 95%CI: 1.192-1.544, $P < 0.001$). For the 31-40 age group, the risk of *H. pylori* developing resistance to clarithromycin 1.495 times higher in females than in males (OR = 1.495, 95%CI: 1.379-1.622, $P < 0.001$). For the 41-50 age group, the risk of *H. pylori* developing resistance to clarithromycin was 1.175 times higher in females than in males (OR = 1.175, 95%CI: 1.107-1.246, $P < 0.001$).

Resistance rate to metronidazole: The homogeneity of OR test showed $P = 0.056$, suggesting that the OR values between the age groups are homogeneous. Therefore, after controlling the age groups, *H. pylori* in females was at a higher risk of the resistance to metronidazole (OR = 1.257, 95%CI: 1.330-1.748, $P < 0.001$). For the 31-40 age group, the risk of *H. pylori* developing resistance to metronidazole was 1.325 times higher in females than in males (OR = 1.325, 95%CI: 1.253-1.400, $P < 0.001$). Thus, regardless of the age group, the *H. pylori* resistance rate to metronidazole was approximately 1.257 times in females than that in males.

**Multidrug resistance of *H. pylori***

Multidrug resistance of *H. pylori* to the four antibacterial drugs is shown in Table 2. Among the 94509 positive specimens, the overall resistance rate to the four antibacterial drugs reached 95.44%, of which the single-drug resistance rate was 54.59%, the dual-drug resistance rate was 29.03%, the triple-drug resistance rate was 11.71%, and the quadruple-drug resistance rate was 0.11%. According to the comparison of gender, the single-drug resistance rate in females was significantly higher than that of males ($\chi^2 = 44.337$, $P < 0.001$), while the multidrug resistance rate in females was higher than that in males, especially the triple-drug resistance rate ($\chi^2 = 188.305$, $P < 0.001$).

**DISCUSSION**

The infection rate of *H. pylori* in China is approximately 55%[13], while the detection rate of *H. pylori* culture is only approximately 30%. A variety of reasons may affect the positivity rate of *H. pylori* culture, including the colonization of *H. pylori* at the biopsy site[14], the influence of PPIs and antibacterial drugs on microbial cultures[15], and even contamination in the process of microbial culture. However, the drug susceptibility test based on *H. pylori* culture can provide doctors with guidance for prescribing clinical medication and is the key to individualized treatment. With an annually increasing rate of antibacterial resistance, individualized treatment based on drug susceptibility results is recommended in China. Therefore, the cultivation of *H. pylori* is still important and is the gold standard for detecting *H. pylori* infection.

In this study, we shared a 10-year data analysis on the infection and resistance of *H. pylori* in Taizhou city, Zhejiang Province, China. A total of 283823 gastric mucosal specimens were examined, and the *H. pylori* infection rate was 33.30%. Age was determined to be related with the *H. pylori* infection. The population aged ≤ 20-years-
Table 2 The multiple-drug resistance of *H. pylori* to the four antibacterial drugs, n

<table>
<thead>
<tr>
<th>Antibacterial drugs</th>
<th>Total</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitive</td>
<td>4314</td>
<td>2485</td>
<td>1829</td>
</tr>
<tr>
<td>LEV</td>
<td>626</td>
<td>362</td>
<td>264</td>
</tr>
<tr>
<td>CLA</td>
<td>557</td>
<td>332</td>
<td>225</td>
</tr>
<tr>
<td>MTR</td>
<td>50413</td>
<td>26642</td>
<td>23771</td>
</tr>
<tr>
<td>AMX</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>LEV + CLA</td>
<td>444</td>
<td>234</td>
<td>210</td>
</tr>
<tr>
<td>LEV + MTR</td>
<td>16419</td>
<td>8343</td>
<td>8076</td>
</tr>
<tr>
<td>LEV + AMX</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>CLA + MTR</td>
<td>10551</td>
<td>5599</td>
<td>4952</td>
</tr>
<tr>
<td>CLA + AMX</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>MTR + AMX</td>
<td>17</td>
<td>14</td>
<td>3</td>
</tr>
<tr>
<td>LEV + CLA + MTR</td>
<td>10990</td>
<td>5035</td>
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</tr>
<tr>
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<td>0</td>
</tr>
<tr>
<td>LEV + MTR + AMX</td>
<td>48</td>
<td>25</td>
<td>23</td>
</tr>
<tr>
<td>CLA + MTR + AMX</td>
<td>28</td>
<td>16</td>
<td>12</td>
</tr>
<tr>
<td>LEV + CLA + MTR + AMX</td>
<td>101</td>
<td>51</td>
<td>50</td>
</tr>
</tbody>
</table>

*Sensitive to all four antibacterial drugs.
CLA: Clarithromycin; LEV: Levofloxacin; MTR: Metronidazole; AMX: Amoxicillin.

Figure 2 Trends of *Helicobacter pylori* resistance to four antibacterial drugs with age groups.

old had the lowest infection rate of 22.49%, and the population aged 61-70 years had the highest infection rate of 43.33%. The infection rate increased with age; however, the prevalence of *H. pylori* infection in children and adolescents is worthy of attention. The reported rates of *H. pylori* infection among children and adolescents in different areas of China range from 18.62% to 72.28% [16,17]. The "Kyoto global consensus report on *H. pylori* gastritis" proposes that *H. pylori* infection is an infectious disease [18], and it can be transmitted through mouth-to-mouth, stomach-to-mouth, feces-to-mouth and other routes. Thus, in addition to the limited awareness of hygiene and health, the

Figure 3 Helicobacter pylori resistance rate to four antibacterial drugs. A: The resistance to levofloxacin; B: The resistance to clarithromycin; C: The resistance to metronidazole; D: The resistance to amoxicillin. *P* < 0.05. There were significant differences of the resistance between males and females.

Figure 3 Helicobacter pylori resistance rate to four antibacterial drugs. A: The resistance to levofloxacin; B: The resistance to clarithromycin; C: The resistance to metronidazole; D: The resistance to amoxicillin. *P* < 0.05. There were significant differences of the resistance between males and females.

traditional eating style (sharing food from the same plates) observed in China may play a role in the transmission of *H. pylori*. The diagnosis and treatment of *H. pylori* infection in children and adolescents requires special attention. In the absence of effective treatment, an *H. pylori* infection may be lifelong.

On the other hand, males were found to have a higher risk of *H. pylori* infection than that for females, and Dutta et al.[19] reported the same results. Some habits, such as smoking, may be indirectly related to this result[20]. In Taizhou city, 48.00% of males smoke, while only 1.19% of females smoke[21]. The habit of smoking may lead to an increase in the secretion of gastric acid and pepsin, thereby destroying the health of the gastric mucosa and promoting the colonization of *H. pylori*.

*H. pylori* has high resistance rates to antibacterial drugs in Taizhou city, and these rates have gradually increased over time. The resistance of *H. pylori* to amoxicillin remains low (0.21%), while that to metronidazole is high (93.72%) throughout China[22,23]. In the 10 years examined in this study, the resistance rates to clarithromycin and levofloxacin significantly increased by 23.81% and 22.35%, respectively. The resistance rate of *H. pylori* increases with age[9]. In this study, the resistance rate to clarithromycin and metronidazole for the population aged ≥ 81-years-old was 15.60% and 21.59% higher, respectively, than those for the population aged ≤ 20-years-old, and the difference in levofloxacin resistance reached 38.38%. The application of antibacterial drugs in the population is one of the external factors contributing to the development of *H. pylori* resistance, and the resistance of *H. pylori* detected for the population aged ≤ 20-years-old, who seldom use antibacterial drugs, may be related to the resistance of the *H. pylori* itself.

After controlling for age group, females showed a higher incidence of *H. pylori* resistance to metronidazole[24], which was approximately 1.257 times higher than that of males. This result is in agreement with data presented by Mirzaei et al.[25]. Metronidazole is used in a wide variety of applications and is typically used in the treatment of anaerobic infections in the female reproductive system or for treating *Trichomonas vaginalis* infections[26]. In this study, *H. pylori* in females was at a higher risk of resistance to clarithromycin and levofloxacin for the population aged 21-50 years; this finding is different from the data presented by Shu et al.[27]. A study by Shao et al.[24] reported results in agreement with ours. In addition, the incidence of multidrug resistance in females was higher than that in males. These phenomena may be related to hormones, genetic differences, and the frequency of antibiotic use. For levofloxacin and clarithromycin, the younger population, aged ≤ 20-years-old, had a similar medication background. For the population aged ≥ 51-years-old, the physical fitness and immunity of individuals decreases with age, and medications increase and vary. Due to the accumulation of medication over the years, the difference between female and male decreases, while the difference between age group increases. For the
population in the middle-aged 21-50 group, their physical fitness is relatively healthy, and their immunity is strong. Therefore, the use of antibacterial agents will affect the resistance rates in *H. pylori*. Some research indicates that for some less serious infections, such as colds, females are relatively more willing to receive antibiotic treatment, while males are often accustomed to relying on their own immunity. Therefore, female medication habits may be one of the reasons why the resistance rate in females is higher than that in males\textsuperscript{28}.

Resistance to antibacterial drugs poses a huge challenge to *H. pylori* eradication therapy. Experts from all over the world have jointly issued some consensus reports, and a number of consensus reports have been published based on the resistance rates of *H. pylori* in China. The “Fifth Chinese National Consensus Report on the management of *H. pylori* infection” (“Fifth Chinese National Consensus Report”) indicated that quadruple therapy containing clarithromycin and metronidazole was not recommended in empirical therapy when the dual-drug resistance rate is over 15.00\%\textsuperscript{29}. In Taizhou city, the dual-drug resistance rate to clarithromycin and metronidazole is 11.16\%, although resistance rates to each drug individually are high. Furthermore, the “Fifth Chinese National Consensus Report”, published in December 2016, proposed that treatment therapy containing levofloxacin was not recommended for initial *H. pylori* eradication because of its high resistance rate\textsuperscript{28}. Following the consensus recommendations, the resistance rate to levofloxacin decreased slightly and remained stable after 2017 in Taizhou, which was an obvious result.

**Limits of study**
The purpose of this study is to study the prevalence and drug resistance of *H. pylori*. The detection methods for *H. pylori* infection include microbial culture, pathological testing, $^{13}$C urease breath test, nucleic acid testing, etc., and the combined detection of multiple methods can improve the detection rate of *H. pylori*. However, some of these methods were not widely and continuously used in the early stages of this study. In this paper, we mainly analyzed the data obtained through microbial culture, which can reflect the changes of *H. pylori* prevalence to a certain extent.

**CONCLUSION**
The prevalence and resistance of *H. pylori* in Taizhou city are serious. The prevalence of *H. pylori* increased with age, and the male was at a higher risk of *H. pylori* prevalence. The resistance rate increased with age, and *H. pylori* in females, age 21-years-old to 50-years-old, was at a higher risk of resistance to levofloxacin and clarithromycin. Guided by the consensus report, individualized treatment based on an AST is recommended.

**ARTICLE HIGHLIGHTS**

*Research background*
The trend of *Helicobacter pylori* (*H. pylori*) prevalence and antibacterial drug resistance is getting more serious.

*Research motivation*
To provide guidance on the use of antimicrobial drugs for *H. pylori* eradication treatment based on the trend of antimicrobial resistance.

*Research objectives*
Big data-based research of *H. pylori* prevalence and antimicrobial resistance trends in Taizhou, Zhejiang Province were performed.

*Research methods*
Carried out the statistical analysis of the results of gastric mucosal tissue sample culture and drug susceptibility tests in Taizhou in the past 10 years, and explored the differences between different age groups and gender of the *H. pylori* prevalence and antibacterial drug resistance rates.
Zhang Y et al. Study on resistance rate of H. pylori

Research results
The prevalence of H. pylori increased with age, and males were at a higher risk of H.
pylori prevalence. The resistance rate increased with age, and H. pylori in females, age
21-years-old to 50-years-old, were at a higher risk of resistance to levofloxacin and
clarithromycin.

Research conclusions
The prevalence and resistance of H. pylori in Taizhou city are serious.

Research perspectives
Guided by the consensus report, individualized treatment based on an AST is
recommended.

REFERENCES
1

2

WJCC

Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018:
GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA
Fitzmaurice C, Abate D, Abbasi N, Abbastabar H, Abd-Allah F, Abdel-Rahman O, Abdelalim A,
Abdoli A, Abdollahpour I, Abdulle ASM, Abebe ND, Abraha HN, Abu-Raddad LJ, Abualhasan A,
Adedeji IA, Advani SM, Afarideh M, Afshari M, Aghaali M, Agius D, Agrawal S, Ahmadi A,
Ahmadian E, Ahmadpour E, Ahmed MB, Akbari ME, Akinyemiju T, Al-Aly Z, AlAbdulKader AM,
Alahdab F, Alam T, Alamene GM, Alemnew BTT, Alene KA, Alinia C, Alipour V, Aljunid SM,
E, Amini S, Amoako YA, Anbari Z, Anber NH, Andrei CL, Anjomshoa M, Ansari F, Ansariadi A,
Appiah SCY, Arab-Zozani M, Arabloo J, Arefi Z, Aremu O, Areri HA, Artaman A, Asayesh H,
Babaee E, Bacha U, Badawi A, Bagherzadeh M, Bagli E, Balakrishnan S, Balouchi A, Bärnighausen
TW, Battista RJ, Behzadifar M, Bekele BB, Belay YB, Belayneh YM, Berfield KKS, Berhane A,
Bernabe E, Beuran M, Bhakta N, Bhattacharyya K, Biadgo B, Bijani A, Bin Sayeed MS, Birungi C,
Bisignano C, Bitew H, Bjørge T, Bleyer A, Bogale KA, Bojia HA, Borzì AM, Bosetti C, Bou-Orm
IR, Brenner H, Brewer JD, Briko AN, Briko NI, Bustamante-Teixeira MT, Butt ZA, Carreras G,
Carrero JJ, Carvalho F, Castro C, Castro F, Catalá-López F, Cerin E, Chaiah Y, Chanie WF, Chattu
VK, Chaturvedi P, Chauhan NS, Chehrazi M, Chiang PP, Chichiabellu TY, Chido-Amajuoyi OG,
Chimed-Ochir O, Choi JJ, Christopher DJ, Chu DT, Constantin MM, Costa VM, Crocetti E, Crowe
CS, Curado MP, Dahlawi SMA, Damiani G, Darwish AH, Daryani A, das Neves J, Demeke FM,
Demis AB, Demissie BW, Demoz GT, Denova-Gutiérrez E, Derakhshani A, Deribe KS, Desai R,
Desalegn BB, Desta M, Dey S, Dharmaratne SD, Dhimal M, Diaz D, Dinberu MTT, Djalalinia S,
Sayed I, Zaki MES, El-Jaafary SI, El-Khatib Z, Elemineh DA, Elkout H, Ellenbogen RG, Elsharkawy
A, Emamian MH, Endalew DA, Endries AY, Eshrati B, Fadhil I, Fallah Omrani V, Faramarzi M,
Gebrehiwot TT, Gebremeskel GG, Gedefaw GA, Gelaw BK, Geta B, Getachew S, Gezae KE,
M, Gomez RS, Gopalani SV, Gorini G, Goulart BNG, Grada A, Ribeiro Guerra M, Guimaraes ALS,
Islami F, Jafari Balalami N, Jafarinia M, Jahangiry L, Jahani MA, Jahanmehr N, Jakovljevic M,
James SL, Javanbakht M, Jayaraman S, Jee SH, Jenabi E, Jha RP, Jonas JB, Jonnagaddala J, Joo T,
Kasahun GG, Kassa B, Kassa TD, Kassaw MW, Kaul A, Keiyoro PN, Kelbore AG, Kerbo AA,
M, Khazaee-Pool M, Khazaei S, Khoja AT, Khosravi MH, Khubchandani J, Kianipour N, Kim D,
Kugbey N, Kumar V, Kuupiel D, La Vecchia C, Lad DP, Lake EA, Lakew AM, Lal DK, Lami FH,
Lopez AD, Lopukhov PD, Lunevicius R, Madadin M, Magdeldin S, El Razek HMA, Majeed A,
Maleki A, Malekzadeh R, Manafi A, Manafi N, Manamo WA, Mansourian M, Mansournia MA,
Mantovani LG, Maroufizadeh S, Martini SMS, Mashamba-Thompson TP, Massenburg BB, Maswabi
MT, Mathur MR, McAlinden C, McKee M, Meheretu HAA, Mehrotra R, Mehta V, Meier T, Melaku
YA, Meles GG, Meles HG, Melese A, Melku M, Memiah PTN, Mendoza W, Menezes RG, Merat S,
Meretoja TJ, Mestrovic T, Miazgowski B, Miazgowski T, Mihretie KMM, Miller TR, Mills EJ, Mir

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Retrospective Study

Adjacent segment disease following Dynesys stabilization for lumbar disorders: A case series of mid- and long-term follow-ups


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Author contributions: Chen KJ and Lai CY conceptualized the study; Chen HT conceptualized, reviewed, and supervised the entire study; Chen KJ wrote and reviewed the manuscript; Chen KJ and Lai CY contributed equally to the work; all authors have read and approved the final version of the submitted manuscript.

Institutional review board statement: The study was approved by our institutional review board, Research Ethics Committee China Medical University and Hospital, Taichung, Taiwan (Protocol No.: CMUH108-REC2-133).

Informed consent statement: The institutional review board waived the need for informed consent.

Conflict-of-interest statement: This
Adjacent segment degeneration; Adjacent segment disease; Degenerative December 16, 2021

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Abstract

BACKGROUND
Radiologic adjacent segment degeneration (ASDeg) can occur after spinal surgery. Adjacent segment disease (ASDis) is defined as the development of new clinical symptoms corresponding to radiographic changes adjacent to the level of previous spinal surgery. Greater pre-existing ASDeg is generally considered to result in more severe ASDis; nonetheless, whether the ASDeg status before index surgery influences the postoperative risk of revision surgery due to ASDis warrants investigation.

AIM
To identify possible risk factors for ASDis and verify the concept that greater preexisting ASDeg leads to more severe ASDis.

METHODS
Data from 212 patients who underwent posterior decompression with Dynesys stabilization from January 2006 to June 2016 were retrospectively analyzed. Patients who underwent surgery for ASDis were categorized as group A (n = 13), whereas those who did not were classified as group B (n = 199). Survival analysis and Cox proportional hazards models were used to compare the modified Pfirrmann grade, University of California-Los Angeles grade, body mass index, number of Dynesys-instrumented levels, and age.

RESULTS
The mean time of reoperation was 7.22 (1.65–11.84) years in group A, and the mean follow-up period was 6.09 (0.10–12.76) years in group B. No significant difference in reoperation risk was observed: Modified Pfirrmann grade 3 vs 4 (P = 0.53) or 4 vs 5 (P = 0.46) for the upper adjacent disc, University of California-Los Angeles grade 2 vs 3 for the upper adjacent segment (P = 0.66), age of < 60 vs > 60 years (P = 0.9), body mass index < 25 vs > 25 kg/m² (P = 0.3), and sex (P = 0.8).

CONCLUSION
Greater preexisting upper ASDeg was not associated with a higher rate of reoperation for ASDis after Dynesys surgery. Being overweight tended to increase reoperation risk after Dynesys'surgery for ASDis.

Key Words: Adjacent segment degeneration; Adjacent segment disease; Degenerative lumbar spondylolisthesis; Dynamic stabilization; Dynesys; Spinal stenosis

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Core Tip: Preoperative degeneration status of the adjacent segment did not affect the rate of mid- and long-term follow-up for adjacent segment disease. Dynesys is a reliable implant with respect to preserving the motion of the adjacent segment and reducing the progression of adjacent segment disease.

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DOI: https://dx.doi.org/10.12998/wjcc.v9.i35.10850

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World J Clin Cases
INTRODUCTION

Fusion surgery remains the gold standard for degenerative lumbar disorders with instability. The rate of surgical interventions for adjacent segment disease (ASDs) following fusion has been reported to be 3.9% annually and 25%–35% after 10 years[1].

The Dynesys® dynamic stabilization system (Zimmer Inc., Warsaw, IN, United States) was developed to maintain partial motion of instrumented levels and reduce the occurrence of ASDs. This system, which consists of titanium alloy screws connected by an elastic synthetic compound, controls motion in any plane. Several studies have obtained good short- and long-term results after Dynesys surgery when clinical parameters such as the Oswestry Disability Index (ODI), visual analog scale (VAS) score, disc height, and even Cobb’s angle were evaluated. Nonetheless, data on long-term adjacent degeneration from large cohort studies are lacking[2-9]. While the risk of ASDs remains controversial, it most frequently affects the upper adjacent segment after fusion surgery[3].

This study aims to analyze clinical and radiologic outcomes in order to identify possible risk factors for ASDs and verify whether greater preexisting adjacent segment degeneration (ASDeg) could lead to more severe ASDs.

MATERIALS AND METHODS

This retrospective study was approved by the institutional review board, the Research Ethics Committee of China Medical University and Hospital in Taichung, Taiwan (protocol no. CMUH108-REC2-133); the need for acquisition of informed consent from patients was waived owing to the retrospective nature of the study. A total of 227 patients with lumbar degenerative disorder (of at least 3 mo duration) refractory to medications or rehabilitation underwent posterior decompression and Dynesys instrumentation surgery from January 2006 to June 2016. Indications for Dynesys surgery are listed in Table 1[10].

All surgeries were performed by the same surgeon; reoperation for ASDs was conducted in the same hospital. Exclusion criteria were as follows: Previous spinal implantation, combination with other implants in the same surgery, and reoperation not performed for ASDs. Overall, 212 patients were included in this study.

The endpoints of this study were reoperation for ASDs or imaging examination at the last follow-up prior to November 2019. Patients’ upper ASDeg grade before Dynesys surgery and the rate of reoperation for ASDs were analyzed.

Clinical evaluation

Age, sex, body mass index (BMI), VAS score for back and leg pain, and ODI were recorded[11].

Radiologic evaluation

Plain radiography and magnetic resonance imaging were performed prior to Dynesys surgery. The upper ASDeg grade was recorded and compared with that determined by the imaging examination conducted either at the last follow-up or before reoperation for ASDs. The modified Pfirrmann[12] and University of California-Los Angeles (UCLA) grades[1] were used in this study. Analysis of adjacent disc degeneration according to the modified Pfirrmann grade was performed before Dynesys surgery on the upper adjacent segment. Figure 1 shows the magnetic resonance images before Dynesys instrumentation.

Statistical analysis

The risk of surgical interventions for ASDs was calculated for each year, and Kaplan-Meier survival curves and Cox proportional hazards models with 95% confidence intervals were constructed to determine the independent variables that contributed to the rate of ASDs. Independent variables included age, BMI, and number of Dynesys-instrumented levels.

RESULTS

A total of 212 patients (76 men, 136 women) were included in this study. The mean age was 60.78 (range, 21–82) years. The number of Dynesys-instrumented levels was 2 in
Table 1 Indications for Dynesys surgery

<table>
<thead>
<tr>
<th>Indications</th>
<th>Patient number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumbar spondylosis with stenosis</td>
<td>77</td>
</tr>
<tr>
<td>Degenerative spondylolisthesis Meyerding[10] grade I</td>
<td>98</td>
</tr>
<tr>
<td>Degenerative disc disease</td>
<td>3</td>
</tr>
<tr>
<td>Recurrent disc herniation</td>
<td>9</td>
</tr>
<tr>
<td>Adjacent degenerative disease</td>
<td>1</td>
</tr>
<tr>
<td>Degenerative lumbar scoliosis</td>
<td>2</td>
</tr>
<tr>
<td>HIVD (large disc extrusion)</td>
<td>22</td>
</tr>
</tbody>
</table>

HIVD: Herniated intervertebral disc.

Figure 1 Magnetic resonance images of patients. Arrow points at the adjacent level.

83 patients, 3 in 104 patients, and 4 in 25 patients. The UCLA grade for the upper adjacent segment in these patients was I in 92 patients (43.4%), II in 25 patients (11.8%), grade III in 76 patients (35.8%), and IV in 19 patients (9.0%).

The distribution of modified Pfirrmann grade for the upper adjacent disc was as follows: Grade 1, 20 patients (10%); grade 2, 41 patients (20%); grade 3, 62 patients (30%); grade 4, 54 patients (26%); grade 5, 20 patients (10%); grade 6, 9 patients (4%). No patients with modified Pfirrmann grade 7 or 8 before Dynesys instrumentation were identified in this study. Thirteen patients underwent reoperation for ASDs.
With respect to the association between ASDis and the number of Dynesys-instrumented levels, 9 patients had upper ASDis, 2 had lower ASDis, and 2 had both upper and lower ASDis. Among the 212 patients, the mean UCLA grade was 2.1, mean modified Pfirrmann grade was 3.19, mean age was 60.78 years, mean BMI was 26.29 kg/m², and mean preoperative ODI was 30.04.

Among patients who did not undergo reoperation, the mean UCLA grade was 2.11, mean modified Pfirrmann grade was 3.19, mean age was 60.89 years, mean BMI was 26.16 kg/m², preoperative ODI was 30.04, and mean follow-up period was 6.09 years. Among those who underwent reoperation, the mean UCLA grade was 2.08, mean modified Pfirrmann grade was 3.17, mean age was 59.15 years, mean BMI was 28.28 kg/m², mean preoperative ODI was 30.08, and mean time to reoperation was 7.22 years (Table 2). Indications for reoperation were adjacent stenosis (n = 3), adjacent degenerative spondylolisthesis (n = 5), adjacent disc degeneration (n = 1), and adjacent disc herniation (n = 4). Figure 2 shows patients’ survival distribution. Fifty-four patients were followed for more than 10 years.

Patients with a modified Pfirrmann grade ≤ 3 vs ≥ 4 or ≤ 4 vs ≥ 5 for the upper adjacent segment exhibited no significant difference according to the crude hazard ratio determined by the Cox model. The Kaplan-Meier survival analysis of the revision risk revealed no significant difference in the cumulative risk in either comparison, with P values of 0.53 and 0.46, respectively. In the comparison of UCLA grades 1, 2 vs 3, 4, neither the hazard ratio nor the Kaplan-Meier survival analysis revealed significant differences (Table 2 and Figure 5).

No significant difference was observed between 2 and 3 Dynesys-instrumented levels, with a hazard ratio of 0.51 (0.11–2.43). The P value was 0.41 for the probability of revision. In the comparison of patients aged ≤ 60 and > 60 years, the hazard ratio was 0.94 (0.31–2.82), and the survival probability indicated no significance. In the comparison between BMI ≤ 25 kg/m² and BMI > 25 kg/m², the hazard ratio was 2.01 (0.55–7.36), which was also not significant. Moreover, in the Kaplan-Meier survival analysis of revision, BMI > 25 kg/m² tended to a higher rate of reoperation for ASDis; however, the trend was not significant. Sex and instrumentation of 2 vs 3 levels had no significant effect on the reoperation rate (Table 3, Figures 4 and 5).

**DISCUSSION**

Preoperative degeneration status of the adjacent disc did not affect the risk of occurrence of ASDis. Furthermore, age, BMI, and sex did not significantly increase the risk of developing ASDis.

**Grading method selection**

Many image grading systems are available to assess degenerative changes. However, the Pfirrmann grading system cannot provide good discrimination in the spine of the elderly, especially in cases of decreased disc height but good T2 signal intensity. Therefore, we applied a modified Pfirrmann grading system as the grading method[1, 12,13].

**Comparison of ASDis outcomes after Dynesys surgery, fusion, and microdiscectomy**

In this study, the mean time to reoperation for ASDis was 7.22 years. For comparison, in a study by Lee et al[5], the time interval from fusion to later non-fusion surgery was 5.6 ± 3 (range, 0.5–10) years. Yeh et al[14] compared the radiologic outcomes of decompression with Dynesys instrumentation with those of microdiscectomy for L4-5 spinal stenosis. The patients in the Dynesys surgery group had a higher grade of facet degeneration than those in the microdiscectomy group. A higher facet fusion rate and decreased range of motion (ROM) at the instrumented level were noted 2 years after surgery. Higher grades of facet degeneration played an important role in increasing the facet fusion rate and decreasing the ROM at the instrumented level. In the same study, which involved more than 3 years of follow-up, the grade of facet degeneration in the Dynesys group was positively correlated with and increased by time[14]. In order to achieve the same ROM, it is necessary for the remaining spinal levels to accept greater load following elimination of motion from the instrumented level, leading to hypomobility and increased stress in the adjacent segments[15]. The use of non-fusion devices is associated with a significantly lower rate of reoperation for ASDis, which has been proven by a meta-analysis[16]. Dynesys implantation lowers the incidence of ASDeg to 9.1% (vs 24.0% in the isolated fusion group)[17].
### Table 2 Baseline characteristics of participants who did and did not undergo reoperation

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No reoperation (n = 199)</th>
<th>Reoperation (n = 13)</th>
<th>Total patients (n = 212)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Mean</td>
<td>min</td>
</tr>
<tr>
<td>Before Dynesys surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper adjacent modified Pfirrmann grade</td>
<td>194</td>
<td>3.19</td>
<td>1</td>
</tr>
<tr>
<td>Upper UCLA classification</td>
<td>199</td>
<td>2.11</td>
<td>1</td>
</tr>
<tr>
<td>Before reoperation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper adjacent modified Pfirrmann grade</td>
<td>/</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>Upper UCLA classification</td>
<td>/</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>Age</td>
<td>199</td>
<td>60.89</td>
<td>21</td>
</tr>
<tr>
<td>Male</td>
<td>72</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Female</td>
<td>127</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>VAS score, back</td>
<td>/</td>
<td>7.67</td>
<td>0</td>
</tr>
<tr>
<td>VAS score, leg</td>
<td>/</td>
<td>8.01</td>
<td>2</td>
</tr>
<tr>
<td>BMI</td>
<td>/</td>
<td>26.16</td>
<td>16</td>
</tr>
<tr>
<td>Preoperative ODI</td>
<td>189</td>
<td>30.04</td>
<td>9</td>
</tr>
<tr>
<td>Last imaging follow-up yr (before reoperation)</td>
<td>199</td>
<td>6.09</td>
<td>0.10</td>
</tr>
</tbody>
</table>

Data are shown as the mean and minimum and maximum values. BMI: Body mass index; ODI: Oswestry Disability Index; UCLA: University of California-Los Angeles; VAS: Visual analog scale.

**Interpretation of ASDis considering facets, discs, and biomechanics**

ASDeg more frequently occurs in the cephalad than caudal direction[1,3]. Lee et al.[3] revealed that facet degeneration is a significant risk factor for ASDis. Adjacent disc degeneration is not a risk factor for ASDis in fusion surgery[18]. Degenerative changes affect the bony and soft tissue structures of the spine and may ultimately result in modifications in the spinal motion segment and instantaneous axis of rotation. Considering the functional spinal unit, osteophytes develop as the annulus is distorted and pulled from its bony attachments, resulting in an unstable functional spinal unit and, potentially, in low back pain. The fused spinal segment stress-strain curve indicates that the slope of the elastic zone is steeper than that of the normal functional spinal unit. The ROM increases in early stages but diminishes in later stages of degeneration. Greater ROM is found at the adjacent levels[15,19].
Table 3 Cox model measuring the hazard ratios of reoperation associated with adjacent discs in patients with Dynesys surgery

<table>
<thead>
<tr>
<th>Variables</th>
<th>Reoperation after Dynesys surgery</th>
<th>Crude HR (95%CI)</th>
<th>Adjusted HR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/patients</td>
<td>Event/patients</td>
<td>PY</td>
</tr>
<tr>
<td>Upper adjacent modified</td>
<td>12/206</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pfirrmann grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 3</td>
<td>8/123</td>
<td>734.36</td>
<td>10.89</td>
</tr>
<tr>
<td>≥ 4</td>
<td>4/83</td>
<td>539.21</td>
<td>7.42</td>
</tr>
<tr>
<td>Upper adjacent modified</td>
<td>12/206</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pfirrmann grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 4</td>
<td>11/177</td>
<td>1081.26</td>
<td>10.17</td>
</tr>
<tr>
<td>≥ 5</td>
<td>1/129</td>
<td>192.31</td>
<td>5.20</td>
</tr>
<tr>
<td>Upper UCLA classification</td>
<td>13/212</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1, 2</td>
<td>8/117</td>
<td>737.28</td>
<td>10.85</td>
</tr>
<tr>
<td>3, 4</td>
<td>5/95</td>
<td>569.17</td>
<td>8.78</td>
</tr>
<tr>
<td>Dynesys level</td>
<td>13/212</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>6/83</td>
<td>468.05</td>
<td>12.82</td>
</tr>
<tr>
<td>3</td>
<td>7/104</td>
<td>695.30</td>
<td>10.07</td>
</tr>
<tr>
<td>4</td>
<td>0/25</td>
<td>143.10</td>
<td>0.00</td>
</tr>
<tr>
<td>Age, yr</td>
<td>13/212</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 60</td>
<td>7/92</td>
<td>642.72</td>
<td>10.89</td>
</tr>
<tr>
<td>≥ 60</td>
<td>6/120</td>
<td>663.73</td>
<td>9.04</td>
</tr>
<tr>
<td>Sex</td>
<td>13/212</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>4/76</td>
<td>456.05</td>
<td>8.77</td>
</tr>
<tr>
<td>Female</td>
<td>9/136</td>
<td>850.41</td>
<td>10.58</td>
</tr>
<tr>
<td>BMI</td>
<td>13/212</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 25</td>
<td>3/80</td>
<td>460.16</td>
<td>6.52</td>
</tr>
<tr>
<td>≥ 25</td>
<td>10/132</td>
<td>846.29</td>
<td>11.82</td>
</tr>
</tbody>
</table>

Hazard ratio adjusted for age, sex, visual analog scale scores for the back and legs, body mass index, medical comorbidities, and preoperative ODI. BMI: Body mass index; CI: Confidence interval; HR: Hazard ratio; IR: Incidence rate per 1000 person-years; PY: Person-years; UCLA: University of California-Los Angeles; VAS: Visual analog scale.

Current studies on ASDis
A meta-analysis reported that the rate of reoperation for ASDis was significantly lower in patients treated with a non-fusion device than in those treated with fusion[16]. St-Pierre et al[20] showed that prior ASDis was a significant factor for progressive ASDis after Dynesys surgery.

The risk of revision due to ASDis is twice as high in men as in women[21]. However, in this study, sex did not appear to be significantly related to the reoperation rate. No progression of spondylolisthesis occurred over a 2-year follow-up after dynamic stabilization in addition to decompression for lumbar spinal stenosis with degenerative spondylolisthesis; only 1 patient with Dynesys instrumentation at L4-5 had adjacent level instability[6]. Another study reported 1 patient with adjacent instability after instrumentation at L4-5[5].

Nevertheless, in contrast, one report indicated that floating fusion (L4-5) accelerates adjacent degeneration. Radiologic ASDeg at L5-S1 is mostly asymptomatic[22]. In our postoperative 12-year study, the number of levels treated with posterior instrumentation was not a significant indication for revision for ASDis.

BMI
BMI > 25 kg/m² is a risk factor for ASDeg and ASDis[23]. However, BMI cannot be confirmed as a risk factor for reoperation for ASDis[21]. Our results further indicate
Figure 2 Kaplan-Meier survival analysis of cumulative reoperation risk. A total of 54 patients were followed-up for more than 10 years.

Figure 3 Probability of reoperation for upper adjacent segments with different modified Pfirrmann and University of California-Los Angeles grades. No significant difference was observed between adjacent degenerative grades.

that BMI > 25 kg/m² was not significantly associated with ASDis but showed a higher tendency for reoperation.

Study limitations
This study has some limitations. First, it is a retrospective review of medical records at
one hospital, representing a single surgeon’s clinical experience with non-fusion dynamic stabilization for degenerative lumbar spine disease, and involves patient follow-up for reoperation at a single hospital. Second, the rate of reoperation for ASDis was relatively low. Strict compliance with conservative measures, such as spinal braces and adjustment of daily activity, is believed to significantly decrease ASDis progression. Third, only 13 patients underwent reoperation; an analysis of a larger number of patients would allow drawing of more precise conclusions. Fourth, before the secondary endpoint of our study (November 2019), more than 20 elderly patients had died due to age, cancer, cardiovascular disease, cardiopulmonary trauma, and other non-Dynesys surgery-related conditions.

**CONCLUSION**

The concept of patients with more degenerative changes in adjacent segments being more prone to revision for ASDis appears reasonable. Nonetheless, our results indicate that the modified Pfirrmann grade was not a significant factor that influenced the rate of revision for ASDis. In addition, the number of stabilized levels tended not to affect the rate of reoperation for ASDis and was not a risk factor. Finally, BMI was not a risk factor.
factor for ASDis reoperation but displayed a higher tendency towards reoperation; thus, BMI should be considered before surgery. Greater preexisting upper ASDeg was not related to a higher rate of reoperation for ASDis after Dynesys surgery. Being overweight tended to increase the reoperation risk after Dynesys surgery for ASDis.

ARTICLE HIGHLIGHTS

Research background
Dynesys surgery is believed to decrease adjacent segment disease compared to fusion surgery.

Research motivation
The main topics, key problems to be solved, and significance of solving these problems for future research in this field should be described in detail.

Research objectives
To determine the relationship between preoperative adjacent degeneration condition and adjacent segment disease requiring surgery.

Research methods
This is a retrospective study involving 212 patients. Data on University of California-Los Angeles and modified Pfirrmann grading were analyzed with Kaplan-Meier survival curves and Cox proportional hazards models.

Research results
No static significant difference exists between higher vs lower University of California-Los Angeles grades of adjacent segment degeneration (ASDeg). No static significant difference exists between higher vs lower modified Pfirrmann grades of ASDeg.

Research conclusions
Greater preexisting upper ASDeg was not related to a higher rate of reoperation for adjacent segment disease following Dynesys surgery.

Research perspectives
A cohort study on the relationship between pre-existing ASDeg and surgery for adjacent segment disease is lacking.

REFERENCES

Chen H et al. ASDeg following Dynesys stabilization for lumbar disorders

[PMID: 30381586 DOI: 10.4103/0366-6999.244107]


10 Meyerding HW. Spondylolisthesis; surgical fusion of lumbosacral portion of spinal column and interarticular facets; use of autogenous bone grafts for relief of disabling backache. *J Int Coll Surg* 1956; 26: 566-591 [PMID: 13367505]


Retrospective Study

Identification of independent risk factors for intraoperative gastroesophageal reflux in adult patients undergoing general anesthesia

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Author contributions: Zhao X and Wang HJ conceived and coordinated the study, designed, performed, and analyzed the experiments, and wrote the paper; Liu K, Wang HJ, Liu K, Li ST, Chen LH, and Fang YJ carried out the data collection and data analysis and revised the paper. All authors reviewed the results and approved the final version of the manuscript.

Institutional review board statement: This study was approved by the ethics committee of Shanghai General Hospital of Nanjing Medical University (2019KY037).

Informed consent statement: Informed consent was waived by the committee because of the retrospective nature of the study.

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

Data sharing statement: The data

Abstract

BACKGROUND
Gastroesophageal reflux (GER) affects up to 20% of the adult population and is defined as troublesome and frequent symptoms of heartburn or regurgitation. GER produces significantly harmful impacts on quality of life and precipitates poor mental well-being. However, the potential risk factors for the incidence and extent of GER in adults undergoing general anesthesia remain unclear.

AIM
To explore independent risk factors for the incidence and extent of GER during general anesthesia induction.

METHODS
A retrospective study was conducted, and 601 adult patients received general anesthesia intubation or laryngeal mask surgery between July 2016 and January 2019 in Shanghai General Hospital of Nanjing Medical University. This study recruited a total of 601 adult patients undergoing general anesthesia, and the characteristics of patients and the incidence or extent of GER were recorded. The potential risk factors for the incidence of GER were explored using multivariate logistic regression, and the risk factors for the extent of GER were evaluated using multivariate linear regression.
Gastroesophageal reflux; Intraoperative period; Risk factors; Anesthesia

INTRODUCTION

Gastroesophageal reflux (GER) affects up to 20% of the adult population and is defined as troublesome and frequent symptoms of heartburn or regurgitation [1-3]. GER produces significantly harmful impacts on health-related quality and increases the risk for esophageal adenocarcinoma [4-6]. Currently, the identified risk factors for GER include overweight, tobacco smoking, low socioeconomic status, and heredity [7-9]. Moreover, GER is the most likely complication in perioperative patients, and early detection, diagnosis, and treatment can prevent serious adverse consequences. Acidic gastric juice reflux is associated with chemical damage to the airway mucosa and lung tissue, damages the normal respiratory membrane structure, and causes different degrees of bronchospasm, atelectasis, aspiration pneumonia, and even respiratory failure. Therefore, early identification of potential risk factors for the progression of GER in patients undergoing general anesthesia should be explored to improve the quality of anesthesia.

RESULTS

The current study included 601 adult patients, 82 patients with GER and 519 patients without GER. Overall, we noted significant differences between GER and non-GER for pharyngitis, history of GER, other digestive tract diseases, history of asthma, and the use of sufentanil (P < 0.05), while no significant differences between groups were observed for sex, age, type of surgery, operative time, body mass index, intraoperative blood loss, smoking status, alcohol intake, hypertension, diabetes mellitus, psychiatric history, history of respiratory infection, history of surgery, the use of lidocaine, palliative strategies, propofol, or rocuronium bromide, state anxiety inventory, trait anxiety inventory, and self-rating depression scale (P > 0.05). The results of multivariate logistic regression indicated that female sex [odds ratio (OR): 2.702; 95% confidence interval (CI): 1.144-6.378; P = 0.023], increased age (OR: 1.031; 95% CI: 1.008-1.056; P = 0.009), pharyngitis (OR: 31.388; 95% CI: 15.709-62.715; P < 0.001), and history of GER (OR: 11.925; 95% CI: 4.184-33.989; P < 0.001) were associated with an increased risk of GER, whereas the use of propofol could protect against the risk of GER (OR: 0.942; 95% CI: 0.892-0.994; P = 0.031). Finally, age (P = 0.004), operative time (P < 0.001), pharyngitis (P < 0.001), history of GER (P = 0.024), and hypertension (P = 0.017) were significantly associated with GER time.

CONCLUSION

This study identified the risk factors for GER in patients undergoing general anesthesia including female sex, increased age, pharyngitis, and history of GER.

Key Words: Gastroesophageal reflux; Intraoperative period; Risk factors; Anesthesia, General; Surgery; Retrospective studies

Core Tip: The study included 82 patients who reported gastroesophageal reflux (GER) and 519 patients without GER. The results of multivariate logistic regression indicated sex, increased age, pharyngitis, and history of GER were associated with increased risk of GER, whereas the use of propofol could protect against the risk of GER. Finally, age, operative time, pharyngitis, history of GER, and hypertension were significantly associated with GER time.

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URL: https://www.wjgnet.com/2307-8960/full/v9/i35/10861.htm
DOI: https://dx.doi.org/10.12998/wjcc.v9.i35.10861
Several studies have explored the potential risk factors for GER. Taraszewska\cite{10} indicated that intermediate physical activity might be associated with a reduced risk of GER in obese individuals, while this significant association was not observed in non-obese people. Maret-Ouda et al\cite{11} suggested that older age, female sex, and comorbidity were associated with an increased risk of recurrent GER in patients who underwent antireflux surgery. Wang et al\cite{12} recruited 56 patients who underwent peroral endoscopic myotomy and found that full-thickness myotomy and low post-operative 4-s integrated relaxation pressure induced more GER. Lindam et al\cite{13} investigated 25844 participants and found that the relationship between sleep disturbances and GER seems to be bidirectional, and sleep disturbances seem to be a stronger risk factor for GER than the reverse. However, no study has focused on patients undergoing general anesthesia to identify the independent risk factors for the risk of GER and total GER time. Therefore, the current study was conducted to explore the potential risk factors for the progression of GER during general anesthesia induction.

### MATERIALS AND METHODS

#### Patients inclusion and exclusion criteria

A retrospective study was conducted in 601 adult patients who underwent general anesthesia intubation or laryngeal mask surgery between July 2016 and January 2019 at the Shanghai General Hospital of Nanjing Medical University. The exclusion criteria of this study included patients diagnosed with nasal or upper esophageal obstruction, severe and uncontrolled clotting disease, bullae disease of the esophageal mucosa, unstable heart disease, or other poor tolerance to vagal stimulation. The general characteristics of the enrolled patients were collected using a pre-defined questionnaire, and the detailed medical history was collected through an anesthesiologist who made preoperative visits. This study was approved by the ethics committee of Nanjing Medical University. The purpose and procedures of the study were carefully explained, and written informed consent was obtained from all participants.

#### GER and variables

The definition of GER was based on assessment by Orion II-ohmega portable pH dynamic monitoring recorder (MMS, Enschede, The Netherlands), which was used to monitor the pH of the middle and lower esophagus, to observe whether reflux occurred, and to measure the occurrence frequency and duration\cite{14}. The general characteristics of the patients included sex, age, body mass index, smoking status, and alcohol intake. The detailed medical history included pharyngitis, history of GER, other digestive tract diseases, hypertension, diabetes mellitus, history of asthma, psychiatric history, history of respiratory infection, history of surgery, state anxiety inventory (SAI), trait anxiety inventory (TAI), and self-rating depression scale (SDS). Moreover, the intraoperative parameters included type of surgery, operative time, intraoperative blood loss, and the use of lidocaine, palliative strategies, sufentanil, propofol, and rocuronium bromide.

#### Statistical analysis

The continuous data of patients’ characteristics are presented as medians and quartiles because these data did not meet the normal distribution. Moreover, the category data are presented as event rates. Comparisons of continuous variables between non-GER and GER patients were calculated using Kruskal-Wallis tests due to the non-normal distributions, while the frequencies of data between groups were calculated using chi-squared tests. Multivariate logistic regression was applied to explore the risk factors for GER incidence after continued adjustment for potential confounders, and odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. Moreover, the impact factors of GER time were explored using multivariate linear analyses. All reported $P$ values were two-sided, and $P < 0.05$ was considered statistically significant. The data were analyzed using IBM SPSS Statistics for Windows, version 19.0 (SPSS 19.0, Armonk, NY, United States).
RESULTS

The characteristics of the enrolled patients are presented in Table 1. In total, 601 adult patients were enrolled, 82 patients with GER and 519 patients without GER. Overall, we noted significant differences between GER and non-GER for pharyngitis, history of GER, other digestive tract diseases, history of asthma, and the use of sufentanil ($P < 0.05$), while no significant differences were observed between groups for sex, age, type of surgery, operative time, body mass index, intraoperative blood loss, smoking status, alcohol intake, hypertension, diabetes mellitus, psychiatric history, history of respiratory infection, history of surgery, the use of lidocaine, palliative strategies, propofol, rocuronium bromide, SAI, TAI, and SDS ($P > 0.05$).

The results of logistic regression with multivariate adjustment for potential confounders indicated that female sex (OR: 2.702; 95%CI: 1.144-6.378; $P = 0.023$), older age (OR: 1.031; 95%CI: 1.008-1.056; $P = 0.009$), pharyngitis (OR: 31.388; 95%CI: 15.709-62.715; $P < 0.001$), and history of GER (OR: 11.925; 95%CI: 4.184-33.989; $P < 0.001$) were associated with an increased risk of GER, whereas increased propofol use was associated with a reduced risk of GER (OR: 0.942; 95%CI: 0.892-0.994; $P = 0.031$) (Table 2).

The results of the impact factors on GER time were evaluated using multivariate linear analyses and are shown in Table 3. Overall, we noted that older age ($P = 0.004$), longer operative time ($P < 0.001$), pharyngitis ($P < 0.001$), and history of GER ($P = 0.024$) were associated with longer GER time. Moreover, patients with hypertension were associated with a shorter GER time ($P = 0.017$).

DISCUSSION

This study reported that 13.6% of patients had GER. Risk factors for the incidence of GER include female sex, older age, pharyngitis, and history of GER, whereas the use of propofol was a protective factor. Moreover, older age, longer operative time, pharyngitis, and a history of GER produced longer GER time, whereas patients with hypertension were associated with shorter GER time.

The current study suggested that female sex was a potential risk factor for the incidence of GER; this result was consistent with a previous study[15] that recruited 23557 World Trade Center responders and found that women were associated with a greater risk of GER than men (hazard ratio: 1.25; 95%CI: 1.13-1.38). The potential reason for this could be that women present with more severe symptoms, leading to an easier diagnosis, whereas GER in men is mild compared to women, which may lead to a missed diagnosis[16,17]. Moreover, older age was associated with an increased risk of GER, which is consistent with a previous study[11]. The potential reason for this is that comorbidities of patients could affect the risk of GER. Furthermore, older people have poor esophageal acid clearance and decreased defense mechanisms against reflux of acid gastric contents on the esophageal mucosa[18,19].

Moreover, we noted that pharyngitis and a history of GER were associated with a greater risk of GER in patients undergoing general anesthesia. The 24-h pH monitoring for these patients should be employed to detect pathological reflux, and medical antireflux treatment should be used to prevent the progression of GER[20]. Moreover, the bidirectional associations of GER and pharyngitis, erosive esophagitis, esophageal strictures, Barrett’s esophagus, and esophageal adenocarcinoma could be used to interpret these risk factors.

We noted that the use of propofol was associated with a lower risk of GER, whereas this result was variable compared with previous studies. Chawla et al[21] conducted 48-h pH tracings in 88 children and found that an increase in GER risk during the post-anesthesia period correlated with a direct effect of propofol or other related factors. However, the study conducted by Turan et al[22] found similar effects of dexmedetomidine and propofol on lower esophageal sphincter pressure and gastroesophageal pressure gradient. However, although a decrease in lower esophageal sphincter pressure at high concentrations was detected, there was no evidence that this effect could promote GER during sedation. Therefore, these effects should be verified in future prospective studies.

Numerous factors were not associated with the risk of GER, including type of surgery, operative time, body mass index, intraoperative blood loss, smoking status, alcohol intake, other digestive tract diseases, hypertension, diabetes mellitus, history of asthma, psychiatric history, history of respiratory infection (within 2 mo), history of surgery, lidocaine, the use of palliative strategies (dexmedetomidine vs midazolam),...
### Table 1 Baseline characteristics of recruited patients, n (%)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non-GER</th>
<th>GER</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>519</td>
<td>82</td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>260 (50.10)</td>
<td>32 (39.02)</td>
<td>0.085</td>
</tr>
<tr>
<td>Female</td>
<td>259 (49.90)</td>
<td>50 (60.98)</td>
<td></td>
</tr>
<tr>
<td><strong>Age (yr)</strong></td>
<td>49.00 (35.00, 61.00)</td>
<td>60.00 (42.00, 68.00)</td>
<td></td>
</tr>
<tr>
<td><strong>Type of surgery</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orthopedics</td>
<td>117 (22.54)</td>
<td>24 (29.27)</td>
<td>0.169</td>
</tr>
<tr>
<td>Abdominal</td>
<td>402 (77.46)</td>
<td>58 (70.73)</td>
<td></td>
</tr>
<tr>
<td><strong>Operative time (min)</strong></td>
<td>85.00 (50.00, 140.00)</td>
<td>120.00 (75.00, 190.00)</td>
<td></td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>23.63 (20.96, 26.30)</td>
<td>24.77 (20.28, 26.22)</td>
<td></td>
</tr>
<tr>
<td><strong>Intraoperative blood loss (mL)</strong></td>
<td>200.00 (100.00, 300.00)</td>
<td>250.00 (50.00, 350.00)</td>
<td></td>
</tr>
<tr>
<td><strong>Smoking status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>446 (85.93)</td>
<td>64 (78.05)</td>
<td>0.116</td>
</tr>
<tr>
<td>Current or former</td>
<td>73 (14.07)</td>
<td>18 (21.95)</td>
<td></td>
</tr>
<tr>
<td><strong>Alcohol intake</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>477 (91.91)</td>
<td>73 (89.02)</td>
<td>0.436</td>
</tr>
<tr>
<td>Yes</td>
<td>42 (8.09)</td>
<td>9 (10.98)</td>
<td></td>
</tr>
<tr>
<td><strong>Pharyngitis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>472 (90.94)</td>
<td>23 (28.05)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Yes</td>
<td>47 (9.06)</td>
<td>59 (71.95)</td>
<td></td>
</tr>
<tr>
<td><strong>History of GER</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>506 (97.50)</td>
<td>66 (80.49)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Yes</td>
<td>13 (2.50)</td>
<td>16 (19.51)</td>
<td></td>
</tr>
<tr>
<td><strong>Other digestive tract diseases</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>497 (95.76)</td>
<td>71 (86.59)</td>
<td>0.023</td>
</tr>
<tr>
<td>Yes</td>
<td>22 (4.24)</td>
<td>11 (13.41)</td>
<td></td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>413 (79.58)</td>
<td>66 (80.49)</td>
<td>0.846</td>
</tr>
<tr>
<td>Yes</td>
<td>106 (20.42)</td>
<td>16 (19.51)</td>
<td></td>
</tr>
<tr>
<td><strong>Diabetes mellitus</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>457 (88.05)</td>
<td>70 (85.37)</td>
<td>0.523</td>
</tr>
<tr>
<td>Yes</td>
<td>62 (11.95)</td>
<td>12 (14.63)</td>
<td></td>
</tr>
<tr>
<td><strong>History of asthma</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>501 (96.53)</td>
<td>73 (89.02)</td>
<td>0.041</td>
</tr>
<tr>
<td>Yes</td>
<td>18 (3.47)</td>
<td>9 (10.98)</td>
<td></td>
</tr>
<tr>
<td><strong>Psychiatric history</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>510 (98.27)</td>
<td>79 (96.34)</td>
<td>0.375</td>
</tr>
<tr>
<td>Yes</td>
<td>9 (1.73)</td>
<td>3 (3.66)</td>
<td></td>
</tr>
<tr>
<td><strong>History of respiratory infection (within 2 mo)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>510 (98.27)</td>
<td>80 (97.56)</td>
<td>0.696</td>
</tr>
<tr>
<td>Yes</td>
<td>9 (1.73)</td>
<td>2 (2.44)</td>
<td></td>
</tr>
</tbody>
</table>
Table 1. Characteristics of study patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Never (96.34%)</th>
<th>Yes (3.66%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of surgery</td>
<td>500 (92.68)</td>
<td>6 (7.32)</td>
<td>0.229</td>
</tr>
<tr>
<td>Lidocaine (2% mL)</td>
<td>3.00 (2.20, 3.50)</td>
<td>3.00 (2.30, 3.55)</td>
<td>0.000</td>
</tr>
<tr>
<td>Palliative</td>
<td>360 (69.36)</td>
<td>64 (78.05)</td>
<td>0.071</td>
</tr>
<tr>
<td>Midazolam</td>
<td>159 (30.64)</td>
<td>18 (21.95)</td>
<td>0.071</td>
</tr>
<tr>
<td>Sufentanil (g)</td>
<td>10 (1.93)</td>
<td>0 (0.00)</td>
<td>0.032</td>
</tr>
<tr>
<td>15</td>
<td>169 (32.56)</td>
<td>36 (43.90)</td>
<td>0.071</td>
</tr>
<tr>
<td>20</td>
<td>340 (65.51)</td>
<td>46 (56.10)</td>
<td>0.071</td>
</tr>
<tr>
<td>Propofol (mg)</td>
<td>100.00 (100.00, 100.00)</td>
<td>100.00 (90.00, 100.00)</td>
<td>0.000</td>
</tr>
<tr>
<td>Rocuronium bromide</td>
<td>50.00 (40.00, 50.00)</td>
<td>50.00 (40.00, 50.00)</td>
<td>0.000</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>10.00 (10.00, 30.00)</td>
<td>30.00 (10.00, 30.00)</td>
<td>0.000</td>
</tr>
</tbody>
</table>
| BMI: Body mass index; GER: Gastroesophageal reflux; SAI: State anxiety inventory; SDS: Self-rating depression scale; TAI: Trait anxiety inventory.

A previous study indicated that anxiety and depression levels were significantly higher in subjects with GER and pointed out that the potential reasons for this could be that psychological factors always precede the clinical manifestations of GER. Moreover, anxiety can induce acid reflux by lowering the pressure of the lower esophageal sphincter, changing esophageal motility or increasing gastric acid secretion.

The results of this study indicated that older age, longer operative time, pharyngitis, and history of GER produce longer GER time. The greater incidence of GER in patients during general anesthesia induction, which is associated with longer GER time, potentially leads to the longer operative time. Moreover, older age, pharyngitis, and history of GER are associated with a higher risk of GER, which correlates with longer GER time. Interestingly, the results of this study indicated that hypertensive patients were associated with shorter GER time, which might be due to a potential beneficial effect of GER on hypertension in terms of inducing changes in the dietary habits of patients.

A strength of this study is that we systematically explored the risk factors for the incidence of GER in patients undergoing general anesthesia. Furthermore, this study is the first to explore factors affecting GER time, and the cohort data used in this study were of high completeness, accuracy, and quality. However, several limitations of this study should be mentioned: (1) The study design was retrospective, which might introduce uncontrolled biases that might lead to overestimated associations; (2) The severity of GER during general anesthesia induction was not explored in this study; and (3) Stratified analyses based on patients’ characteristics were not conducted because all factors entered the regression models. Therefore, the specific factors affecting the risk of GER in patients with specific characteristics during general anesthesia should be explored in future prospective studies.

## CONCLUSION

Among patients who underwent general anesthesia, 12.8% had one GER event, and 0.8% had two GER events. We noted that female sex, older age, pharyngitis, and history of GER were associated with an increased risk of GER, whereas the use of propofol could protect against the risk of GER. In addition, older age, longer operative time, pharyngitis, and history of GER produced longer GER time, whereas patients...
Table 2 The risk factors for the incidence of gastroesophageal reflux by multivariate logistic regression analysis

<table>
<thead>
<tr>
<th>Variables</th>
<th>β value</th>
<th>SD</th>
<th>Wald chi-square</th>
<th>OR (95%CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept 1</td>
<td>-10.518</td>
<td>182.127</td>
<td>0.003</td>
<td>0.954</td>
<td>0.954</td>
</tr>
<tr>
<td>Intercept 2</td>
<td>-14.558</td>
<td>182.128</td>
<td>0.006</td>
<td>0.936</td>
<td>0.936</td>
</tr>
<tr>
<td>Gender (female vs male)</td>
<td>0.994</td>
<td>0.438</td>
<td>5.144</td>
<td>2.702 (1.144-6.378)</td>
<td>0.023</td>
</tr>
<tr>
<td>Age (yr) (continuous)</td>
<td>0.031</td>
<td>0.012</td>
<td>6.824</td>
<td>1.031 (1.008-1.056)</td>
<td>0.009</td>
</tr>
<tr>
<td>Type of surgery</td>
<td>-0.018</td>
<td>0.382</td>
<td>0.002</td>
<td>0.982 (0.464-2.077)</td>
<td>0.963</td>
</tr>
<tr>
<td>Operative time (min) (continuous)</td>
<td>0.003</td>
<td>0.004</td>
<td>0.904</td>
<td>1.003 (0.996-1.010)</td>
<td>0.342</td>
</tr>
<tr>
<td>BMI (kg/m²) (continuous)</td>
<td>-0.049</td>
<td>0.069</td>
<td>0.516</td>
<td>0.952 (0.832-1.089)</td>
<td>0.472</td>
</tr>
<tr>
<td>Intraoperative blood loss (mL) (continuous)</td>
<td>-0.000</td>
<td>0.001</td>
<td>0.081</td>
<td>1.000 (0.998-1.002)</td>
<td>0.776</td>
</tr>
<tr>
<td>Smoking status</td>
<td>0.802</td>
<td>0.474</td>
<td>2.859</td>
<td>2.230 (0.880-5.650)</td>
<td>0.091</td>
</tr>
<tr>
<td>Alcohol intake</td>
<td>0.602</td>
<td>0.565</td>
<td>1.135</td>
<td>1.826 (0.603-5.524)</td>
<td>0.287</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>3.446</td>
<td>0.353</td>
<td>95.234</td>
<td>31.388 (15.709-62.715) &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>History of GER</td>
<td>2.479</td>
<td>0.534</td>
<td>21.513</td>
<td>11.925 (4.184-33.989) &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Other digestive tract diseases</td>
<td>0.028</td>
<td>0.570</td>
<td>0.002</td>
<td>1.028 (0.336-3.145)</td>
<td>0.961</td>
</tr>
<tr>
<td>Hypertension</td>
<td>-0.661</td>
<td>0.437</td>
<td>2.294</td>
<td>0.516 (0.219-1.215)</td>
<td>0.130</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>-0.854</td>
<td>0.533</td>
<td>2.568</td>
<td>0.426 (0.150-1.210)</td>
<td>0.109</td>
</tr>
<tr>
<td>History of asthma</td>
<td>0.313</td>
<td>0.594</td>
<td>0.278</td>
<td>1.368 (0.427-4.383)</td>
<td>0.598</td>
</tr>
<tr>
<td>Psychiatric history</td>
<td>0.467</td>
<td>0.827</td>
<td>0.319</td>
<td>1.596 (0.315-8.072)</td>
<td>0.572</td>
</tr>
<tr>
<td>History of respiratory infection (within 2 mo)</td>
<td>-0.560</td>
<td>1.155</td>
<td>0.235</td>
<td>0.571 (0.059-5.492)</td>
<td>0.628</td>
</tr>
<tr>
<td>History of surgery</td>
<td>1.181</td>
<td>0.692</td>
<td>2.915</td>
<td>3.258 (0.840-12.642)</td>
<td>0.088</td>
</tr>
<tr>
<td>Lidocaine (2% mL) (continuous)</td>
<td>0.016</td>
<td>0.121</td>
<td>0.018</td>
<td>1.017 (0.802-1.289)</td>
<td>0.892</td>
</tr>
<tr>
<td>Palliative (d vs midazolam)</td>
<td>0.005</td>
<td>0.416</td>
<td>0.000</td>
<td>1.005 (0.445-2.272)</td>
<td>0.990</td>
</tr>
<tr>
<td>Sufentanil (g)</td>
<td>0.134</td>
<td>0.031</td>
<td>0.497</td>
<td>1.011 (0.976-1.044)</td>
<td>0.647</td>
</tr>
<tr>
<td>15</td>
<td>10.378</td>
<td>182.118</td>
<td>0.003</td>
<td>32155.18 (0.000-3.36E159)</td>
<td>0.955</td>
</tr>
<tr>
<td>20</td>
<td>10.653</td>
<td>182.121</td>
<td>0.003</td>
<td>42315.00 (0.000-4.44E159)</td>
<td>0.953</td>
</tr>
<tr>
<td>Propofol (mg) (continuous)</td>
<td>-0.060</td>
<td>0.028</td>
<td>4.680</td>
<td>0.942 (0.892-0.994)</td>
<td>0.031</td>
</tr>
<tr>
<td>Arden (mg) (continuous)</td>
<td>-0.185</td>
<td>0.236</td>
<td>0.619</td>
<td>0.831 (0.523-1.318)</td>
<td>0.431</td>
</tr>
<tr>
<td>Rocuronium bromide (continuous)</td>
<td>-0.005</td>
<td>0.050</td>
<td>0.009</td>
<td>0.995 (0.902-1.098)</td>
<td>0.926</td>
</tr>
<tr>
<td>Sufentanil (continuous)</td>
<td>0.016</td>
<td>0.025</td>
<td>0.383</td>
<td>1.016 (0.967-1.067)</td>
<td>0.536</td>
</tr>
<tr>
<td>SAI (continuous)</td>
<td>0.134</td>
<td>0.031</td>
<td>0.497</td>
<td>1.011 (0.976-1.044)</td>
<td>0.647</td>
</tr>
<tr>
<td>TAI (continuous)</td>
<td>0.006</td>
<td>0.029</td>
<td>0.516</td>
<td>1.004 (0.962-1.051)</td>
<td>0.712</td>
</tr>
<tr>
<td>SDS (continuous)</td>
<td>-0.072</td>
<td>0.013</td>
<td>0.311</td>
<td>0.982 (0.948-1.035)</td>
<td>0.562</td>
</tr>
</tbody>
</table>

BMI: Body mass index; CI: Confidence interval; GER: Gastroesophageal reflux; OR: Odds ratio; SAI: State anxiety inventory; SD: Standard deviation; SDS: Self-rating depression scale; TAI: Trait anxiety inventory.

with hypertension were associated with shorter GER time. These results require further prospective studies of patients undergoing general anesthesia.
Table 3 The factors associated with gastroesophageal reflux time by multivariate linear regression analyses

<table>
<thead>
<tr>
<th>Variables</th>
<th>$\beta$ value</th>
<th>SE</th>
<th>t value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>12.061</td>
<td>17.616</td>
<td>0.685</td>
<td>0.494</td>
</tr>
<tr>
<td>Gender</td>
<td>1.732</td>
<td>3.079</td>
<td>0.563</td>
<td>0.574</td>
</tr>
<tr>
<td>Age (yr) (continuous)</td>
<td>0.277</td>
<td>0.951</td>
<td>2.903</td>
<td>0.004</td>
</tr>
<tr>
<td>Type of surgery</td>
<td>-0.898</td>
<td>3.178</td>
<td>-0.283</td>
<td>0.778</td>
</tr>
<tr>
<td>Operative time (min) (continuous)</td>
<td>0.103</td>
<td>0.031</td>
<td>3.378</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>BMI (kg/m$^2$) (continuous)</td>
<td>-0.667</td>
<td>0.517</td>
<td>-1.290</td>
<td>0.197</td>
</tr>
<tr>
<td>Intraoperative blood loss (mL) (continuous)</td>
<td>-0.007</td>
<td>0.007</td>
<td>-1.057</td>
<td>0.291</td>
</tr>
<tr>
<td>Smoking status</td>
<td>6.843</td>
<td>3.821</td>
<td>1.791</td>
<td>0.074</td>
</tr>
<tr>
<td>Alcohol intake</td>
<td>3.309</td>
<td>4.692</td>
<td>0.705</td>
<td>0.481</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>33.566</td>
<td>3.418</td>
<td>9.820</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>History of gastroesophageal reflux</td>
<td>13.809</td>
<td>6.111</td>
<td>2.260</td>
<td>0.024</td>
</tr>
<tr>
<td>Other digestive tract diseases</td>
<td>1.165</td>
<td>5.896</td>
<td>0.198</td>
<td>0.844</td>
</tr>
<tr>
<td>Hypertension</td>
<td>-8.575</td>
<td>3.593</td>
<td>-2.386</td>
<td>0.017</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>-2.448</td>
<td>4.280</td>
<td>-0.572</td>
<td>0.568</td>
</tr>
<tr>
<td>History of asthma</td>
<td>-2.465</td>
<td>6.177</td>
<td>-0.399</td>
<td>0.690</td>
</tr>
<tr>
<td>Psychiatric history</td>
<td>-5.423</td>
<td>9.060</td>
<td>-0.599</td>
<td>0.550</td>
</tr>
<tr>
<td>History of respiratory infection (within 2 mo)</td>
<td>-7.538</td>
<td>9.566</td>
<td>-0.788</td>
<td>0.431</td>
</tr>
<tr>
<td>History of surgery</td>
<td>4.426</td>
<td>6.443</td>
<td>0.687</td>
<td>0.492</td>
</tr>
<tr>
<td>Lidocaine (2% mL) (continuous)</td>
<td>-1.224</td>
<td>0.927</td>
<td>-1.320</td>
<td>0.187</td>
</tr>
<tr>
<td>Palliative (d vs midazolam)</td>
<td>4.683</td>
<td>3.009</td>
<td>1.556</td>
<td>0.120</td>
</tr>
<tr>
<td>Sufentanil (g)</td>
<td>10</td>
<td>ref</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>1.823</td>
<td>11.849</td>
<td>0.154</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>2.301</td>
<td>13.692</td>
<td>0.168</td>
</tr>
<tr>
<td>Propofol (mg) (continuous)</td>
<td>-0.174</td>
<td>0.160</td>
<td>-1.093</td>
<td>0.275</td>
</tr>
<tr>
<td>Arden (mg) (continuous)</td>
<td>1.408</td>
<td>1.857</td>
<td>0.758</td>
<td>0.449</td>
</tr>
<tr>
<td>Rocuronium bromide (continuous)</td>
<td>-0.061</td>
<td>0.337</td>
<td>-0.182</td>
<td>0.856</td>
</tr>
<tr>
<td>Sufentanil (continuous)</td>
<td>-0.086</td>
<td>0.214</td>
<td>-0.401</td>
<td>0.689</td>
</tr>
<tr>
<td>SA1 (continuous)</td>
<td>-0.053</td>
<td>0.031</td>
<td>-0.253</td>
<td>0.546</td>
</tr>
<tr>
<td>TAI (continuous)</td>
<td>-0.027</td>
<td>0.087</td>
<td>-0.436</td>
<td>0.658</td>
</tr>
<tr>
<td>SDS (continuous)</td>
<td>0.011</td>
<td>0.053</td>
<td>0.211</td>
<td>0.432</td>
</tr>
</tbody>
</table>

BMI: Body mass index; GER: Gastroesophageal reflux; SAI: State anxiety inventory; SE: Standard error; SDS: Self-rating depression scale; TAI: Trait anxiety inventory.

ARTICLE HIGHLIGHTS

Research background
Gastroesophageal reflux (GER) is the most likely complication in perioperative patients, and early detection, diagnosis, and treatment can prevent serious adverse consequences.

Research motivation
No previous study had investigated the independent risk factors for the risk of GER and total GER time for patients undergoing general anesthesia.
Research objectives
To explore independent risk factors for the incidence and extent of GER during general anesthesia induction.

Research methods
This is a retrospective study, and 601 adult patients who received general anesthesia intubation or laryngeal mask surgery were involved. The definition of GER was based on assessment by Orion II-ohmega portable pH dynamic monitoring recorder, which was used to monitor the pH of the middle and lower esophagus to observe whether reflux occurred and to measure the occurrence frequency and duration. The potential risk factors for the incidence of GER were explored using multivariate logistic regression, and the risk factors for the extent of GER were evaluated using multivariate linear regression.

Research results
This study found female sex, increased age, pharyngitis, and history of GER were associated with an increased risk of GER, whereas the use of propofol could protect against the risk of GER. Moreover, age, operative time, pharyngitis, history of GER, and hypertension were significantly associated with GER time.

Research conclusions
This study identified the risk factors for the incidence of GER in patients undergoing general anesthesia, including female sex, increased age, pharyngitis, and history of GER.

Research perspectives
Further prospective studies should be performed to verify these findings owing to the retrospective design of this study.

REFERENCES
6 Pandeya N, Webb PM, Sadeghi S, Green AC, Whiteman DC; Australian Cancer Study. Gastroesophageal reflux symptoms and the risks of oesophageal cancer: are the effects modified by smoking, NSAIDs or acid suppressants? Gut 2010; 59: 31-38 [PMID: 19875392 DOI: 10.1136/gut.2009.190827]
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Retrospective Study

Value of the controlling nutritional status score and psoas muscle thickness per height in predicting prognosis in liver transplantation

Xing Dai, Ben Gao, Xin-Xin Zhang, Jiang Li, Wen-Tao Jiang

Abstract

BACKGROUND
Patients with end-stage liver disease usually have varying degrees of malnutrition, and severe malnutrition may affect the prognosis of patients after liver transplantation (LT). However, there is no recommended standard for the nutrition assessment of patients waiting for LT, and it is unknown whether malnutrition has an impact on the occurrence of postoperative complications.

AIM
The study aim was to investigate the value of the controlling nutritional status (CONUT) score and psoas muscle thickness per height (PMTH) in predicting prognosis in LT.

METHODS
We retrospectively analyzed the clinical data of 313 patients who underwent classic orthotopic LT from January 2016 to December 2018 in Tianjin First Central Hospital affiliated with Tianjin Medical University. The CONUT score is derived from the preoperative serum albumin and total cholesterol levels, and total lymphocyte count. Patients were divided into low (≤4), medium (5–8), and high (9–12) CONUT score groups periparterative characteristics, Clavien-Dindo grade III/IV/V postoperative complications, graft loss and infection, and cumulative postoperative survival in the three groups were compared 3 mo after LT. PMTH was calculated as the ratio of the transverse thickness of the psoas muscle in the umbilical plane to the height of the patient. The cutoff values of receiver operating characteristic curves were determined separately for men and women. The values
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INTRODUCTION

Previous studies have demonstrated that malnutrition is an independent predictor of death in patients with end-stage liver disease[1], indicating that nutrition levels are important for the progression of disease. The incidence of malnutrition in patients undergoing liver transplantation (LT) for end-stage liver disease can be as high as 50%-90%, and malnutrition can lead to a poor prognosis[2]. At present, there are no uniform nutritional assessments for patients awaiting LT. To better evaluate the nutritional status of patients with liver diseases and explore the relationship between malnutrition and complications after LT, we analyzed the controlling nutritional status score (CONUT) score and psoas muscle thickness per height (PMTH) in LT patients.

The CONUT score has been used to assess patient nutritional status by considering nutritional-related indicators, including serum albumin, serum total cholesterol, and total lymphocyte count[3]. The CONUT score has been verified and used as an independent risk factor for death in the prediction of patients with rectal and stomach cancer[4,5]. The PMTH is defined as the ratio of the transverse thickness of the psoas muscle to the height of the patient at the umbilical level. It requires no additional tools and is relatively easy to calculate[6]. The PMTH has been used to diagnose sarcopenia, which is an important manifestation of malnutrition[7], and to predict mortality in patients with cirrhosis on waiting lists[8]. In this study, we explored the role of the CONUT score and PMTH in predicting prognosis in LT patients.

RESULTS

Patients with medium and high CONUT scores had lower preoperative serum hemoglobin, more intraoperative red blood cell (RBC) transfusions, longer postoperative intensive care unit stay and hospital stays, higher 7 and 14 preoperative-day serum bilirubin levels, and a higher incidence of postoperative grade III/IV complications and infections than patients with low CONUT scores. Differences in the 3-mo cumulative survival among the three groups were not significant. Patients with a low PMTH had higher preoperative serum urea nitrogen, more intraoperative packed RBC and frozen plasma transfusions, longer times to postoperative ventilator extubation, higher incidence of total postoperative complications, and a lower 3-mo cumulative survival than those with a high PMTH.

CONCLUSION

A CONUT score ≥ 5 and a low PMTH were both associated with poor prognosis in LT. The CONUT score had no predictive value for short-term patient survival after LT, but the PMTH was predictive of short-term patient survival after LT.

Key Words: Liver transplantation; Controlling nutritional status score; Psoas muscle thickness per height; Nutrition assessment; Complications; Prognosis

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DOI: https://dx.doi.org/10.12998/wjcc.v9.i35.10871
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MATERIALS AND METHODS

A total of 313 patients seen from January 2016 to December 2018 at the Tianjin First Central Hospital Affiliated with Tianjin Medical University were included. Patients eligible for inclusion were: (1) 18-65 years of age with orthotopic LT for the first time; (2) With graft livers obtained from a postmortem donation; (3) With hepatocellular carcinoma meeting the UCSF criteria[9] (i.e. solitary tumors ≤ 6.5 cm or ≤ 3 nodules with the largest lesion ≤ 4.5 cm and total tumor diameter ≤ 8 cm); (4) With cirrhosis diagnosed by liver biopsy or imaging including B-ultrasonography, liver stiffness measurement, or abdominal computed tomography (CT); and (5) With acute liver failure diagnosed by evidence of coagulation abnormality [international normalized ratio (INR) > 1.5] and any degree of mental alteration (encephalopathy) in a patient without preexisting cirrhosis and with an illness of < 26 wk duration[10].

Patients (1) undergoing retransplantation, salvage LT or multiple organ transplantation; (2) with preoperative severe pneumonia; (3) with preoperative cardiac cerebrovascular disease; and (4) undergoing LT from marginal donors such as elderly liver donors > 65 years of age, fatty liver donors, split liver transplant donors, hepatitis B or hepatitis C donors, unstable hemodynamic donors, and donors with potential infection were excluded.

Grouping was based on the CONUT score, which was calculated from the last postoperative tests, obtained within 3 d before LT, and including albumin ≥ 35.0 g/L, score 0; 30.0-34.9 g/L, score 2; 25.0-29.9 g/L, score 4, < 25.0 g/L, score 6; total cholesterol ≥ 180 mg/dL, score 0; 140-179 mg/dL, score 1; 100-139 mg/dL, score 2; < 100 mg/dL, score 3; total lymphocytes ≥ 1600/μm³, score 0; 1200-1599/μm³, score 1; 800-1199/μm³, score 2; < 800/μm³, score 3[11]. Patients were divided into low, medium, and high CONUT score groups by low scores of ≤ 4, medium scores of 5–8, and high scores of 9–12. A total of 281 patients were eligible, but 32 were excluded because of a lack of serum total cholesterol.

For measurement, calculation, and grouping by PMTH, patients were routinely examined by abdominal CT within 2 mo of LT with a GE revolution CT 64-slice scanner. PMTH was defined as the ratio of the transverse thickness of the psoas muscle in the umbilical plane to the height of the patient. The transverse thickness of the right psoas muscle at the umbilical level was measured on CT images perpendicular to the axial diameter, and the axial psoas thickness was the maximum diameter of the psoas in the axial view (Figure 1). Because it has been reported that the PMTH is correlated with the sex and mortality of cirrhosis patients[6], receiver operating characteristic (ROC) curves were generated for men and women according to postoperative patient mortality. PMTH cutoff values were determined by the optimal Youden index. Patients were divided into high PMTH and a low PMTH groups. A total of 254 patients were eligible, but 59 who lacked CT scans obtained within 2 mo of LT were excluded from the analysis.

Perioperative indicators included patient age, sex, body mass index (BMI), preoperative model for end-stage liver disease (MELD) score, urea nitrogen (BUN), hemoglobin, albumin, white blood cell (WBC) count, platelet (PLT) count, total cholesterol, total lymphocyte count, receipt of intraoperative packed red blood cell (RBC) or frozen plasma transfusion, intraoperative blood loss, anhepatic phase and operation time, postoperative ventilator extubation time, length of intensive care unit (ICU) and hospital stays, postoperative serum total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase, creatinine, and BUN on postoperative days 7 and 14.

Postoperative Clavien-Dindo complications of grade III and greater severity were collected[12]: Grade III complications require surgical, endoscopic, or radiological intervention, grade IV complications are life-threatening and require ICU management, including single and multiorgan dysfunction, and grade V complications are fatal. Grade III included vascular complications such as portal vein stenosis, thrombosis, hepatic artery thrombosis, splenorenal shunt, and splenic arterial steal syndrome; biliary complications such as bile leakage, bile drainage obstruction, and bile duct stenosis. Other complications include retransplantation, pleural effusion requiring thoracentesis, peritoneal effusion requiring abdominocentesis, abdominal bleeding, placement of a drainage tube at the site of T-tube outlet leakage, and nasointestinal tube insertion, etc. Grade IV complications included respiratory, heart, liver, and renal failure, requiring treatment tracheotomy, extracorporeal membrane

patients.
oxygenation, artificial extracorporeal liver support and hemodialysis. Grade V complications were those causing death, including septic shock, hemorrhagic shock, heart failure, liver failure, renal failure, and intracranial hemorrhage. Graft loss and infection were observed; the diagnosis of infection was made following infection diagnosis guidelines[13], and the patients were followed up for 3 mo.

Statistical methods
The statistical analysis were performed with SPSS 20.0. Normally distributed data were reported as means ± SD, and the independent sample t-test was used for intergroup comparisons. Data that did not have a normal distribution were reported as medians and quartiles, and the Mann-Whitney U or Kruskal-Wallis tests were used for intergroup comparisons. Classification data were reported as numbers and percentages (%), and χ² or Fisher’s exact tests were used for intergroup comparisons. The area under the ROC curve (AUC) and 95% confidence intervals (CIs) were used to find the optimal values of the PMTH. Survival rates were estimated by the Kaplan-Meier method. P < 0.05 indicated statistical significance for all tests.

RESULTS
Grouping by the CONUT score resulted in 65 low-score, 173 medium-score, and 43 high-score patients (Tables 1 and 2). Comparison of the perioperative data found that patients in medium and high CONUT score groups had lower serum hemoglobin levels, more intraoperative RBC transfusions, longer ICU and hospital times and higher serum bilirubin levels on postoperative days 7 and 14 than patients in the low-score group. No differences were observed between the medium- and high-score groups (P < 0.05). There were no significant differences in sex, age, BMI, MELD score, etiology, serum BUN level, WBC and PLT counts, anhepatic phase, operation time, postoperative ventilator extubation time, or postoperative serum AST or Cr levels on the postoperative days 7 and 14 among the three groups (P > 0.05).

Comparison of the incidence of complications in the three groups (Table 3) found that patients in the low-score group had a lower incidence of grade III/IV/V complications and infections than patients in the medium- and high-score groups (grade III, 12.3% vs 35.3% vs 44.2%; grade IV, 1.5% vs 9.2% vs 11.6%; grade V, 1.5% vs 9.8% vs 7.0%; and infections, 26.1% vs 47.4% vs 58.1%, all P < 0.05). No significant differences were observed between the medium- and high-score groups (P > 0.05). There were no significant differences in graft loss among the three groups (P = 1.000).

Cumulative 3-mo survival rates at postoperative month 3 were 98.5%, 90.2%, and 93% in the low-, medium-, and high-score groups, respectively. No significant differences were observed among the three groups (P > 0.05, 95%CI: 0.831-0.873). The PMTH of male patients was 20.11 ± 3.68 cm/m², and the AUC of the ROC curve for male patients (Figure 2A) was 0.703 (P = 0.02, 95%CI: 0.633-0.767). The optimal Youden index was 0.387, and the cutoff point was 17.9 cm/m². The male high PMTH group consisted of 127 male patients with scores higher than 17.9 cm/m² and the male
Table 1 Relationship between the controlling nutritional status score and general patient clinical data

<table>
<thead>
<tr>
<th>Group</th>
<th>Low CONUT</th>
<th>Medium CONUT</th>
<th>High CONUT</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>49.7 ± 9.9</td>
<td>50.2 ± 9.8</td>
<td>46.6 ± 10.1</td>
<td>0.102</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>48:17</td>
<td>128:45</td>
<td>34:9</td>
<td>0.801</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.5 (21.2-25.4)</td>
<td>23.7 (21.6-27.0)</td>
<td>24.3 (21.8-28.0)</td>
<td>0.515</td>
</tr>
<tr>
<td>MELD score</td>
<td>14 (10-20)</td>
<td>15 (10-21)</td>
<td>18 (13-21)</td>
<td>0.155</td>
</tr>
<tr>
<td>Etiology</td>
<td></td>
<td></td>
<td></td>
<td>0.386</td>
</tr>
<tr>
<td>HBV (n)</td>
<td>42</td>
<td>90</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>HCV (n)</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Alcohol (n)</td>
<td>4</td>
<td>20</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>NASHE(n)</td>
<td>4</td>
<td>10</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Autoimmune diseases (n)</td>
<td>8</td>
<td>23</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Cryptogenic (n)</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Other (n)</td>
<td>4</td>
<td>26</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

BMI: Body mass index; CONUT: Controlling nutritional status; F: Female; HBV: Hepatitis B virus; HCV: Hepatitis C virus; M: Male; MELD: Model for end-stage liver disease; NASH: Nonalcoholic steatohepatitis.

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DISCUSSION

There are many nutritional assessments for liver cirrhosis patients, including BMI, Nutrition Risk Screening 2002 (NRS 2002), the Royal Free Hospital Nutritional Prioritizing Tool (RFH-NPT), upper arm circumference, the laboratory-related index, and muscle mass. BMI is thought to lack accuracy for LT patients because patients with end-stage liver disease usually have varying degrees of ascites that results in weight measurements that do not accurately reflect their nutritional status. In addition, some patients lack accurate weight data before surgery because of a long-term bedridden status. NRS 2002 and the RFH-NPT require assessment of body weight changes and food intake over a long period[14,15]. For patients with poor compliance, accurate data might be difficult to obtain, and some patients require emergency LT
Table 2 Relationship between the controlling nutritional status score and general patient laboratory data

<table>
<thead>
<tr>
<th>Group</th>
<th>Low CONUT</th>
<th>Medium CONUT</th>
<th>High CONUT</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HB (g/L)</td>
<td>122.6 ± 25.5</td>
<td>96.8 ± 26.52</td>
<td>89.2 ± 17.9</td>
<td>&lt; 0.001; &lt; 0.001; 0.074</td>
</tr>
<tr>
<td>WBC (cells/mm³)</td>
<td>4.95 (3.24-6.54)</td>
<td>4.63 (3.43-6.94)</td>
<td>4.8 ± 3.3</td>
<td>0.101</td>
</tr>
<tr>
<td>PLT (cells/mm³)</td>
<td>113.0 (58.0-116.5)</td>
<td>105.0 (46.5-166.0)</td>
<td>111.1 ± 79.1</td>
<td>0.493</td>
</tr>
<tr>
<td>Albumen (g/L)</td>
<td>38.8 ± 4.53</td>
<td>31.8 (29.0-34.4)</td>
<td>26.34 ± 2.65</td>
<td>&lt; 0.001; &lt; 0.001; &lt; 0.001</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>148.08 (117.75-178.81)</td>
<td>102.67 (81.39-113.68)</td>
<td>80.7 ± 29.81</td>
<td>&lt; 0.001; &lt; 0.001; &lt; 0.001</td>
</tr>
<tr>
<td>Total lymphocytes (cells/mm³)</td>
<td>700 (440-1170)</td>
<td>530 (380-770)</td>
<td>350 (220-510)</td>
<td>&lt; 0.001; &lt; 0.001; &lt; 0.001</td>
</tr>
</tbody>
</table>

Intraoperative data

| Packed red cell transfusion (units) | 6.0 (4.0-10.0) | 10.0 (8.0-12.0) | 10.0 (8.0-16.0) | < 0.001; < 0.001; 0.158 |
| Frozen plasma transfusion (mL)     | 1800.0 (1000.0-2100.0) | 2000.0 (1600.0-2000.0) | 2078.6 ± 638.4 | 0.180; 0.018; 0.319 |
| Blood loss (mL)                    | 1600.0 (800.0-2000.0) | 2000.0 (1500.0-2400.0) | 2000.0 (1500.0-2400.0) | 0.069; 0.004; 1.00 |
| Anhepatic phase (min)              | 42.0 (40.0-50.0) | 45.0 (37.0-50.0) | 45.0 ± 11.4 | 0.849 |
| Operation time (h)                 | 7.5 (6.7-8.3) | 7.5 (7.0-8.4) | 7.5 (6.6-9.0) | 0.542 |

Postoperative data

| Time of ventilator extubation (h)   | 6.0 (4.0-9.0) | 10.5 (5.0-31.4) | 6.5 (3.5-24.0) | 0.237 |
| ICU stay (d)                        | 3.0 (2.0-4.0) | 4.0 (3.0-4.9) | 3.0 (3.0-4.96) | < 0.001; 0.049; 1.00 |
| hospital stay (d)                   | 25.0 (21.0-30.0) | 35.0 (26.0-37.3) | 33.0 (27.0-38.0) | < 0.001; < 0.001; 0.94 |
| Day 7 Tbil (µmol/L)                 | 30.0 (18.09-43.5) | 48.0 (27.5-75.5) | 55.6 ± 37.9 | 0.21; 0.011; 1.00 |
| Day 14 Tbil (µmol/L)                | 19.0 (13.25-32.0) | 33.0 (19.0-51.9) | 42.0 (22.0-72.0) | 0.01; < 0.001; 1.00 |
| Day 7 AST (U/L)                     | 27.0 (19.5-35.8) | 24.0 (15.5-39.1) | 26.3 ± 16.5 | 0.180 |
| Day 14 AST (U/L)                    | 25.0 (20.1-38.0) | 26.0 (18.0-39.5) | 26.0 ± 17.40.00 | 0.809 |
| Day 7 ALT (U/L)                     | 79.0 (56.5-104.0) | 65.0 (39.0-97.5) | 57.0 (34.0-93.0) | 0.685; 0.019; 0.069 |
| Day 14 ALT (U/L)                    | 61.0 (35.0-81.5) | 47.0 (25.2-72.3) | 43.0 (21.0-70.0) | 0.153 |
| Day 7 INR                           | 1.31 (1.14-1.47) | 1.30 (1.15-1.51) | 1.27 (1.15-1.34) | 0.719 |
| Day 14 INR                          | 1.26 (1.08-1.27) | 1.34 (1.15-1.51) | 1.34 (1.13-1.71) | 0.499 |
| Day 7 Cr (µmol/L)                   | 55.0 (46.2-63.0) | 62.0 (49.0-80.5) | 57.0 (40.0-71.0) | 0.097 |
| Day 14 Cr (µmol/L)                  | 58.0 (45.5-68.0) | 62.0 (49.0-73.5) | 59.1 ± 23.4 | 0.161 |
| Day 7 BUN (mmol/L)                  | 7.71 (5.04-9.45) | 8.2 (6.1-11.5) | 7.5 (5.8-10.7) | 0.71 |
| Day 14 BUN (mmol/L)                 | 5.28 (4.30-6.75) | 7.13 (5.20-9.52) | 6.0 (4.6-8.9) | 0.13; 0.01; 0.796 |

<sup>a</sup>Low controlling nutritional status (CONUT) and medium CONUT group.

<sup>b</sup>Low CONUT and high CONUT group.

<sup>c</sup>Medium CONUT group and high CONUT group. ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BUN: Blood urea nitrogen; CONUT: Controlling nutritional status; Cr: Creatinine; HB: Hemoglobin; ICU: Intensive care unit; INR: International normalized ratio; PLT: Platelet; Tbil: Total bilirubin; WBC: White blood cell.

because of the severity of their condition, leading to difficulty in completing long-term monitoring. Upper arm circumference is an objective nutritional assessment index that cannot be affected by ascites and peripheral edema. It has been recommended as a screening index for chronic liver disease[16]. However, it is not included in routine preoperative examinations for LT at our center, and there may be some errors that result from variability among those who measure the arm circumference. Therefore, the CONUT score and muscle mass, as objective and convenient assessments, were used to predict the prognosis of LT patients.

The CONUT score is calculated from three indices, albumin, total cholesterol and total lymphocyte count, and represents the energy reserve and immune status of the body. The study results showed that patients with the medium and high CONUT scores had more intraoperative RBC transfusions than those with low CONUT scores, but the operation time and anhepatic period were not significantly different among the
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Table 3 Relationship between controlling nutritional status score and postoperative complications

<table>
<thead>
<tr>
<th>Group</th>
<th>Low CONUT</th>
<th>Medium CONUT</th>
<th>High CONUT</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>65</td>
<td>173</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>Grade III complications</td>
<td>8 (12.3)</td>
<td>61 (35.3)</td>
<td>19 (44.2)</td>
<td>&lt; 0.01; 0.01; 0.278</td>
</tr>
<tr>
<td>Grade IV complications</td>
<td>1 (1.5)</td>
<td>16 (9.2)</td>
<td>5 (11.6)</td>
<td>0.04; 0.023; 0.054</td>
</tr>
<tr>
<td>Grade V complications</td>
<td>1 (1.5)</td>
<td>17 (9.8)</td>
<td>3 (7.0)</td>
<td>0.031; 0.143; 0.564</td>
</tr>
<tr>
<td>Graft loss</td>
<td>1 (1.5)</td>
<td>4 (2.3)</td>
<td>1 (2.3)</td>
<td>1.000</td>
</tr>
<tr>
<td>Infections</td>
<td>17 (26.1)</td>
<td>82 (47.4)</td>
<td>25 (58.1)</td>
<td>0.03; 0.01; 0.207</td>
</tr>
</tbody>
</table>

*aLow controlling nutritional status (CONUT) and medium CONUT group.

*bLow CONUT and high CONUT group.

*cMedium CONUT group and high CONUT group. CONUT: Controlling nutritional status.

Table 4 Relationship between psoas muscle thickness/height and general patient clinical data

<table>
<thead>
<tr>
<th>Group</th>
<th>Low PMTH</th>
<th>High PMTH</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>81</td>
<td>173</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>50.6 ± 9.8</td>
<td>50.7 ± 8.8</td>
<td>0.765</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>63:18</td>
<td>127:46</td>
<td>0.455</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.0 (20.9-26.0)</td>
<td>24.1 (21.8-26.4)</td>
<td>0.069</td>
</tr>
<tr>
<td>MELD score</td>
<td>16 (11-21.5)</td>
<td>14 (10-20)</td>
<td>0.237</td>
</tr>
<tr>
<td>Etiology</td>
<td></td>
<td></td>
<td>0.712</td>
</tr>
<tr>
<td>HBV (n)</td>
<td>41</td>
<td>99</td>
<td></td>
</tr>
<tr>
<td>HCV (n)</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Alcohol (n)</td>
<td>11</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>NASH (n)</td>
<td>5</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Autoimmune disease (n)</td>
<td>10</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Cryptogenic (n)</td>
<td>0</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Other (n)</td>
<td>12</td>
<td>26</td>
<td></td>
</tr>
</tbody>
</table>

BMI: Body mass index; F: Female; HBV: Hepatitis B virus; HCV: Hepatitis C virus; M: Male; MELD: Model for end-stage liver disease; NASH: Nonalcoholic steatohepatitis. PMTH: Psoas muscle thickness per height.

Three groups, which may be related to anemia before surgery. Anemia is a surrogate marker for hypersplenism, portal hypertension, and malnutrition in cirrhosis patients because an enlarged spleen inactivates RBCs, and esophageal varicose veins caused by portal hypertension lead to upper digestive bleeding. In addition, long-term loss of appetite and protein malabsorption lead to nutritional anemia. Hypersplenism, portal hypertension and malnutrition gradually aggravate anemia as the disease develops. Patients with medium and high CONUT scores had higher postoperative day 7 and day 14 bilirubin and BUN levels. The increase in bilirubin may be highly correlated with postoperative complications, and the high BUN may have been associated with postoperative short-term fasting, which leads to hypercatabolism in patients. Low lymphocyte counts might have been associated with chronic hepatitis B and C virus infections and immune system disorders caused by autoimmune hepatitis, which lead to decreased immunity and increased susceptibility to pneumonia and infection. Enzymes for the synthesis of cholesterol are reduced because of impaired liver function in patients with end-stage liver disease, which leads to a decrease in cholesterol. Cholesterol is a major component of cell membranes and is closely related to cell surface molecules and structural functions and is also required for the synthesis of steroid hormones[17]. Cholesterol reduction may affect the repair function of cells and the stability of the internal environment, which can lead to some complic-
Table 5 Relationship between psoas muscle thickness per height and general patient laboratory data

<table>
<thead>
<tr>
<th>Group</th>
<th>Low PMTH</th>
<th>High PMTH</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BUN (mmol/L)</td>
<td>5.98 (4.06-10.22)</td>
<td>4.64 (3.52-6.03)</td>
<td>0.001</td>
</tr>
<tr>
<td>HB (g/L)</td>
<td>97.22 ± 21.84</td>
<td>102.77 ± 23.35</td>
<td>0.085</td>
</tr>
<tr>
<td>WBC (cells/mm³)</td>
<td>5.14 (3.71-8.26)</td>
<td>4.73 (3.14-6.22)</td>
<td>0.066</td>
</tr>
<tr>
<td>PLT (cells/mm³)</td>
<td>120.0 (55.5-171.5)</td>
<td>112.0 (51.0-161.0)</td>
<td>0.505</td>
</tr>
<tr>
<td>Album (g/L)</td>
<td>33.6 ± 6.1</td>
<td>37.1 ± 5.6</td>
<td>0.067</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>1050.2 ± 520.4</td>
<td>1010.1 ± 550.9</td>
<td>0.624</td>
</tr>
<tr>
<td>Total lymphocytes (cells/mm³)</td>
<td>820 (510-1320)</td>
<td>720 (490-1000)</td>
<td>0.124</td>
</tr>
<tr>
<td><strong>Intraoperative data</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Packed red cell transfusion (units)</td>
<td>10.0 (8.0-12.0)</td>
<td>8.0 (6.0-10.0)</td>
<td>0.003</td>
</tr>
<tr>
<td>Frozen fresh/plasm transfusion (mL)</td>
<td>2000.0 (1800.0-2350.0)</td>
<td>1800.0 (1400.0-2000.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Blood loss (mL)</td>
<td>2000 (1500-2350.0)</td>
<td>1900.0 (1500.0-2000.0)</td>
<td>0.180</td>
</tr>
<tr>
<td>Anhepatic phase (min)</td>
<td>45 (35.5-50)</td>
<td>45.0 (40.0-50.0)</td>
<td>0.932</td>
</tr>
<tr>
<td>Operation time (h)</td>
<td>7.75 (7.0-8.6)</td>
<td>7.5 (7.0-8.5)</td>
<td>0.649</td>
</tr>
<tr>
<td><strong>Postoperative data</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time of ventilatorextubation (h)</td>
<td>7.0 (4.0-32.5)</td>
<td>6.0 (4.0-12.5)</td>
<td>0.043</td>
</tr>
<tr>
<td>ICU stay (d)</td>
<td>4.0 (2.5-4.7)</td>
<td>3.0 (2.0-4.0)</td>
<td>0.113</td>
</tr>
<tr>
<td>Hospital stay (d)</td>
<td>29.0 (23.0-31.5)</td>
<td>28.0 (23.0-35.7)</td>
<td>0.968</td>
</tr>
<tr>
<td>Day 7 TBil (μmol/L)</td>
<td>41.0 (20.0-63.7)</td>
<td>37.0 (24.3-62.0)</td>
<td>0.774</td>
</tr>
<tr>
<td>Day 14 TBil (μmol/L)</td>
<td>29.0 (16.0-43.9)</td>
<td>27.1 (16.9-44.5)</td>
<td>0.998</td>
</tr>
<tr>
<td>Day 7 AST (U/L)</td>
<td>18.0 (13.5-32.5)</td>
<td>25.0 (17.1-38.0)</td>
<td>0.005</td>
</tr>
<tr>
<td>Day 14 AST(U/L)</td>
<td>24.0 (16.0-27.0)</td>
<td>28.0 (19.0-42.5)</td>
<td>0.008</td>
</tr>
<tr>
<td>Day 7 ALT (U/L)</td>
<td>55.0 (32.5-83.5)</td>
<td>74.0 (48.5-102.5)</td>
<td>0.002</td>
</tr>
<tr>
<td>Day 14 ALT (U/L)</td>
<td>41.0 (26.0-48.5)</td>
<td>57.0 (34.0-88.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>Day 7 INR</td>
<td>1.28 (1.15-1.49)</td>
<td>1.24 (1.13-1.43)</td>
<td>0.291</td>
</tr>
<tr>
<td>Day 14 INR</td>
<td>1.29 (1.13-1.29)</td>
<td>1.31 (1.12-1.51)</td>
<td>0.891</td>
</tr>
<tr>
<td>Day 7 Cr (μmol/L)</td>
<td>57.0 (50.3-67.8)</td>
<td>60.0 (50.5-73.0)</td>
<td>0.196</td>
</tr>
<tr>
<td>Day 14 Cr (μmol/L)</td>
<td>61.0 (48.5-69.0)</td>
<td>60.0 (48.0-75.0)</td>
<td>0.982</td>
</tr>
<tr>
<td>Day 7 BUN (mmol/L)</td>
<td>8.47 (5.95-11.4)</td>
<td>7.83 (6.05-10.41)</td>
<td>0.264</td>
</tr>
<tr>
<td>Day 14 BUN (mmol/L)</td>
<td>7.2 (4.9-9.0)</td>
<td>6.04 (4.75-8.15)</td>
<td>0.203</td>
</tr>
</tbody>
</table>


The pathogenesis of sarcopenia in patients with end-stage liver disease is complex and associated with inadequate intake, changes in energy metabolism, chronic inflammation, hyperammonemia, insulin resistance, and so on. Hyperammonemia and portosystemic shunts can occur in patients with end-stage liver disease, and hyperammonemia can upregulate myostatin, which inhibits protein synthesis and muscle regeneration. Hyperammonemia also promotes oxidative stress and damages mitochondrial function, resulting in impaired protein synthesis [18]. In addition, patients with end-stage liver disease often have insulin resistance, especially in the context of metabolic-related fatty liver disease, leading to reduced muscle protein synthesis and increased catabolism [2]. In patients with end-stage liver disease, the body is in a proinflammatory state, with elevated levels of the proinflammatory cytokines interleukin 6 and tumor necrosis factor, which activate the ubiquitin-proteasome pathway, leading to increased autophagy of skeletal muscle cells and a
Table 6 Relationship between psoas muscle thickness/height and postoperative complications

<table>
<thead>
<tr>
<th>Group</th>
<th>Low PMTH</th>
<th>High PMTH</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>81</td>
<td>173</td>
<td></td>
</tr>
<tr>
<td>Grade III complications</td>
<td>25 (30.9)</td>
<td>43 (24.9)</td>
<td>0.313</td>
</tr>
<tr>
<td>Grade IV complications</td>
<td>8 (9.9)</td>
<td>12 (6.9)</td>
<td>0.630</td>
</tr>
<tr>
<td>Grade V complications</td>
<td>14 (17.3)</td>
<td>5 (2.9)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Total complications</td>
<td>47 (58.0)</td>
<td>60 (34.7)</td>
<td>0.001</td>
</tr>
<tr>
<td>Graft loss</td>
<td>2 (2.5)</td>
<td>3 (1.7)</td>
<td>1.000</td>
</tr>
<tr>
<td>Infection</td>
<td>36 (44.4)</td>
<td>65 (37.6)</td>
<td>0.297</td>
</tr>
</tbody>
</table>

PMTH: Psoas muscle thickness per height.

Figure 2 Receiver operating characteristic curves. A: Male death-risk prediction model; B: Female death-risk prediction model. AUC: Area under the curve.

Figure 3 Kaplan-Meier curve of 3-mo postoperative survival. PMTH: Psoas muscle thickness per height.

significant reduction in muscle mass and strength[19]. Measurement of the skeletal muscle of the whole body is the gold standard for diagnosing sarcopenia, but because of the complexity of the measurement, the skeletal muscle at the level of the third lumbar spine or the skeletal muscle index (SMI) is commonly used to reflect the skeletal muscle content instead and is calculated by software[20]. Compared with
measurement of the SMI, measurement of the PMTH only requires the transverse thickness of the right psoas at the umbilical plane on CT images. Some studies have shown that the PMTH is highly correlated with the SMI and is an independent risk factor for mortality in patients with cirrhosis. The transverse thickness of the psoas muscle is also correlated with sex, age, and ethnicity. Therefore, PMTH cutoff values of less than $17.9 \text{ cm/m}^2$ for male patients and PMTH less than $14.1 \text{ cm/m}^2$ for female patients were obtained using the study data and were for the diagnosis of sarcopenia. Patients with a low PMTH had a higher preoperative BUN than patients with a high PMTH, which may be related to skeletal muscle loss and protein metabolism imbalance. Patients with a low PMTH had an increased incidence of postoperative complications. Because patients with sarcopenia have low preoperative protein storage, it is difficult to provide sufficient amino acids for the human body, which leads to a deficiency of amino acids in the postoperative tissue recovery stage, and injuries remain unhealed\[^{[21]}\]. Additionally, L-glutamine released by skeletal muscle can activate lymphocytes to strengthen the immune system of muscle, and its reduction leads to a weak immune system\[^{[22]}\]. Meanwhile, the patient’s respiratory muscle volume is reduced, which may cause postoperative respiratory failure and septic shock. It was found that patients with a low PMTH need a much longer ventilator extubation time.

Many studies have shown an association between sarcopenia and recipient mortality. The CONUT score predicts mortality after hepatectomy for hepatocellular carcinoma\[^{[4]}\]. However, our data is consistent with a previous study showing that the CONUT score did not predict mortality after LT\[^{[23]}\]. We think the inconsistent results can be explained by a lack of improvement in some nutrition-related indices after LT, especially an elevation of albumin. The most severe complications (i.e. death) are avoided, but sarcopenia in not improved in the short term.

The two tools used in this study are convenient to use and intuitive for predicting the prognosis of LT. Both have been used in various clinical studies, and the indices considered by the two tools are routinely performed during clinical examinations and are available in clinical practice. As such, we think they have excellent clinical practicability.

There are some study limitations. There were few female patients ($n = 64$), which may have affected the accuracy of the PMTH cutoff values. The PMTH was measured on CT images taken within 2 mo of surgery; however, for patients with severe conditions, the PMTH may change rapidly, which could have affected the accuracy of measurement. Recent studies have shown that sarcopenia is associated not only with the amount of skeletal muscle but also with the quality of skeletal muscle\[^{[24]}\], which can be measured by dual energy X-ray absorption (DEXA), bioelectrical impedance analysis (BIA), grip strength and so on. DEXA and BIA have been used for measurement of skeletal muscle for LT recipients in several studies\[^{[3,25-26]}\]. Unfortunately, we do not have related data; in the early stage of primary biliary cirrhosis and primary sclerosing cholangitis, patients have dyslipidemia that leads to hypercholesterolemia, which then gradually decreases as the disease progresses\[^{[27,28]}\]. That affects the CONUT score in some patients. In addition, studies have shown that patients with alcoholic cirrhosis have a higher incidence of malnutrition than patients with nonalcoholic cirrhosis\[^{[28]}\], probably because ethanol and its metabolites may affect protein synthesis and skeletal muscle autophagy\[^{[29]}\], but whether that leads to sarcopenia needs to be further validated by experience with additional cases.

**CONCLUSION**

A CONUT score $\geq 5$ was associated with the incidence of grade III/IV/V complications and infection after LT. A low PMTH was associated with the incidence of total complications after LT. The CONUT score had no predictive value for short-term patient survival after LT, and the PMTH was predictive of short-term patient survival after LT.

**ARTICLE HIGHLIGHTS**

*Research background*

Patients with end-stage liver disease usually have varying degrees of malnutrition, and severe malnutrition may affect the prognosis of patients after liver transplantation.
(LT). However, whether malnutrition has an impact on the occurrence of postoperative complications in not known, and there is no unified standard for the nutrition assessment of patients waiting for LT. This study included 313 patients from single center in China, and statistically analyzed the predictive value of the two nutrition assessments, the controlling nutritional status (CONUT) score and psoas muscle thickness per height (PMTH) on prognosis in LT.

**Research motivation**
The study aimed to investigate the relationship between nutrition and prognosis of LT.

**Research objectives**
This study was designed to find the right nutrition assessment tools of patients waiting for LT and investigate the predictive value of tools on prognosis in LT.

**Research methods**
This was a retrospective study that included 313 patients from a single center undergoing orthotopic liver transplantation. Patients were divided into two or three groups, independent sample t tests, Mann-Whitney U or Kruskal-Wallis tests were used to compare intergroup perioperative data. Fisher’s exact or 2 tests were used to compare numbers and percentages of cases. Cumulative 3-mo survival rates were estimated by the Kaplan-Meier method.

**Research results**
Patients in the medium and high CONUT score groups had a lower preoperative serum hemoglobin levels, more intraoperative red blood cell (RBC) transfusions, longer postoperative intensive care unit and hospital stays, higher preoperative day 7 and day 14 serum bilirubin levels, and a higher incidence of postoperative grade III/IV complications and infections than patients in the low CONUT score group. There were no significant differences in the 3-mo cumulative survival rate among the three groups. Patients with a low PMTH had higher levels of preoperative serum urea nitrogen, more intraoperative packed RBC and frozen plasma transfusions, longer postoperative ventilator extubation times, an increased incidence of total postoperative complications, and a lower 3-mo cumulative survival rate than those with a high PMTH.

**Research conclusions**
A CONUT score ≥ 5 was associated with the incidence of grade III/IV/V complications and infection after LT, and a low PMTH was associated with the incidence of total complications after LT. The CONUT score had no predictive value for short-term patient survival after LT, and the PMTH was predictive of short-term patient survival after LT.

**Research perspectives**
We hope to develop a predictive model for poor clinical outcomes of LT that combines the CONUT score and PMTH so that the two tools can be used together to predict outcomes in a wider audience.

**REFERENCES**


Dai X et al. Relationship between nutritional status and liver transplantation

10.1007/s10120-017-0744-3


26 Golse N, Bucur PO, Ciacio O, Pittau G, Sacunha A, Adam R, Castaing D, Antonini T, Coilly A,


Retrospective Study

Development of a lipid metabolism-related gene model to predict prognosis in patients with pancreatic cancer

Hong Xu, Jian Sun, Ling Zhou, Qian-Cheng Du, Hui-Ying Zhu, Yang Chen, Xin-Yu Wang

Abstract

BACKGROUND
Pancreatic cancer is a highly heterogeneous disease, making prognosis prediction challenging. Altered energy metabolism to satisfy uncontrolled proliferation and metastasis has become one of the most important markers of tumors. However, the specific regulatory mechanism and its effect on prognosis have not been fully elucidated.

AIM
To construct a prognostic polygene signature of differentially expressed genes (DEGs) related to lipid metabolism.

METHODS
First, 9 tissue samples from patients with pancreatic cancer were collected and divided into a cancer group and a para-cancer group. All patient samples were subjected to metabolomics analysis based on liquid tandem chromatography quadrupole time of flight mass spectrometry. Then, mRNA expression profiles and corresponding clinical data of pancreatic cancer were downloaded from a public database. Least absolute shrinkage and selection operator Cox regression analysis was used to construct a multigene model for The Cancer Genome Atlas.

RESULTS
Principal component analysis and orthogonal projections to latent structures-discriminant analysis (OPLS-DA) based on lipid metabolomics analysis showed a clear distribution in different regions. A Euclidean distance matrix was used to calculate the quantitative value of differential metabolites. The permutation test of the OPLS-DA model for tumor tissue and paracancerous tissue indicated that the established model was consistent with the actual condition based on sample data. A bar plot showed significantly higher levels of the lipid metabolites phosphatidylycholine (PC), phosphatidyl ethanolamine (PE), phosphatidylethanolamine...
Lipid metabolism; Pancreatic cancer; Gene signature; Overall survival; Volume 9; December 16, 2021

INTRODUCTION

Pancreatic cancer is one of the most common malignancies of the digestive system in China. Although the incidence of pancreatic cancer is not high, it is the seventh leading cause of cancer-related death[1]. Despite advances in surgical techniques and adjuvant therapy, mortality and morbidity due to the disease have not changed over the past 40 years. Furthermore, less than 5% of patients with pancreatic cancer have a survival rate of greater than 5 years; even among those who are able to undergo radical resection, the 5-year survival rate is only approximately 20%[2]. Ferlay et al[3] believed that pancreatic cancer would exceed breast cancer as the 3rd leading cause of cancer death in the future. One of the reasons for the low 5-year survival rate for pancreatic cancer is the lack of specific biomarkers for early diagnosis in clinical practice. Therefore, it is of particular importance to identify diagnostic hallmarks of significance for pancreatic cancer.

As the pancreas is an important organ for regulating lipid metabolism in the body, lipids and their metabolites might be used as indicators of health or disease. Lipidomics, proposed by Han in 2003, involves the study of all lipid molecules in the body and their role in the regulation of protein expression and gene expression[4]. Lipidomics has been widely used in the study of biomarkers for various tumors (such as ovarian cancer, prostate cancer, breast cancer)[5-7]. Recently, lipidomics has revealed that plasma concentrations of arachidonic acid, lysophosphatidylcholine, phosphatidylcholine (34:2) and phosphatidylethanolamine (26:0) are increased in patients with early pancreatic cancer[8]. Because lipid metabolism is involved in the proliferation of pancreatic cancer cells, detection of lipid contents in plasma might be helpful for the early diagnosis of pancreatic cancer. However, for pancreatic diseases,
especially pancreatic cancer, lipidomics of pancreatic tissue samples has not been comprehensive.

Although our previous studies suggested that differences in serum lipid metabolites might serve as biomarkers for the early diagnosis of pancreatic cancer[9], tissue samples represent changes in the local environment of the tumor and are less affected by systemic factors. We aimed to investigate the characteristics of lipid metabolism profiles in tumor tissues and paracancerous tissues of pancreatic cancer patients using data from our center. Moreover, mRNA expression profiles and corresponding clinical data of pancreatic cancer patients were downloaded from public databases. A prognostic polygene profile of differentially expressed genes (DEGs) related to lipid metabolism was constructed using pancreatic adenocarcinoma (PAAD) data from The Cancer Genome Atlas (TCGA), and functional enrichment analysis was conducted to explore the underlying mechanisms.

**MATERIALS AND METHODS**

All participants from our center signed an informed consent form, which was checked and verified by the Clinical Research Ethics Committee of Shanghai Fourth People’s Hospital Affiliated to Tongji University School of Medicine (No. 2019057-001).

**Patients**

In total, 9 patients with PAAD who had been treated and underwent surgery at the General Surgery, Shanghai Fourth People’s Hospital Affiliated to Tongji University School of Medicine, between October 2018 and March 2019 were enrolled in the study. All 9 patients were diagnosed with pancreatic cancer by computed tomography or magnetic resonance imaging before surgery and underwent laparoscopic pancreaticoduodenectomy; none of the 9 patients received neoadjuvant chemotherapy before surgery to exclude the influence of chemotherapy on the results. Postoperative pathology confirmed ductal adenocarcinoma of the pancreas. The mean age of the patients was 63, including 6 males and 3 females. Regarding clinical stage, 2 cases were T2N0Mx, 3 cases were T2N1Mx, 3 cases were T2N2Mx, and 1 case was T3N1Mx. Fresh frozen tumor tissues were selected as the experimental group, and adjacent tissues were selected as the control group. The exclusion criteria were diagnosis of benign tumors, chronic pancreatitis, other tumors, and radiotherapy and chemotherapy within 6 mo.

**TCGA data collection**

RNA-seq data and corresponding clinical information for 176 pancreatic cancer patients as of June 1, 2021, were downloaded from TCGA (https://portal.gdc.cancer.gov/); these data are publicly available. Therefore, this study did not involve relevant ethics or require approval of the local ethics committee. Our current study followed the access policy of TCGA and related guidelines. The “limma” package in R software (version R 4.1.0) was used to normalize the downloaded dataset, and the normalized and readable count values were obtained. A total of 197 genes related to lipid metabolism were retrieved from previous literature[10-12].

**Construction of a prognostic lipid metabolism-related gene profile**

DEGs between tumor tissues and adjacent nontumor tissues in TCGA were screened by the “limma” package in R software, with a \( P \) value < 0.05 considered to be significant. Univariate Cox analysis of overall survival (OS) was performed to identify DEGs related to lipid metabolism with prognostic value. To minimize the risk of overfitting, a prognostic model was constructed using least absolute shrinkage and selection operator (LASSO) Cox regression analysis[13,14]. The “glmnet” package in R software was used to select variables and shrink them by the LASSO algorithm. The independent variable for regression was the standardized expression matrix of candidate prognosis-related DEGs. Dependent variables were OS and survival status of the pancreatic cancer patients in TCGA. In the LASSO regression model, the parameter \( \lambda \) value of the penalty was used to select the value with the minimum cross-validation error through tenfold cross-validation. The risk score value of patients was calculated according to the standardized expression level of each gene and the corresponding regression coefficient: risk score= \( \sum (\text{each gene’s expression} \times \text{corresponding coefficient}) \). Patients were divided into high-risk and low-risk groups according to the median risk score. Principal component analysis (PCA) was performed using the “prcomp” function of the “stats” package in R software according to the gene expression in the gene profile.
Xu H et al. Based on TCGA cohort analysis

Figure 1 Identification of differential lipid metabolites. A: Score scatter plot of the PCA model for the cancer group vs. the paracarcinoma tissue group; B: Score scatter plot of the orthogonal projections to latent structures-discriminant analysis (OPLS-DA) model for the cancer group vs. the paracancer group; C: Permutation test of the OPLS-DA model for the cancer group vs. the para-cancer group; D: Bar plot for the cancer group vs. the para-cancer group. TAG: triacylglycerols; SM: sphingomyelin; SHeXcer: sulfatide; PS: phosphatidylserines; PMeOH: phosphatidylmethanol; PG: phosphatidylglycerols; PEtOH: phosphatidylethanolamines; PC: phosphatidylcholines; MAG: myelin-associated glycoprotein; LPE: lysosphosphatidylethanol; LPC: lysosphosphatidylcholine; LDGTS: lysosphosphatidylglycerol; HexCer: hexosylceramide; ACar: acarabenz; DGTS: diacylglycerol trimethylhomoserine; DGDG: digalactosyl diacylglycerols; DAG: diacylglycerols; Cer: ceramide; CE: cholesteryl esters; BMP: bis(monoacylglycerol)phosphate.

Furthermore, the “Rtsne” package in R software was used to determine the distribution of each group by the t-distributed stochastic neighbor embedding (t-SNE) method. Survival analysis of each differentially expressed gene was performed with the “surv_cutpoint” function of the “survminer” package in R software to obtain the optimal cutoff value. Time-dependent receiver operating characteristic (ROC) curves were plotted using the “survivalROC” package in R software to assess the predictive power of the gene profile.

Functional enrichment analysis

The “clusterProfiler” package in R software was used to perform Gene Ontology (GO) enrichment and Kyoto Encyclopedia of Genes and Genomes (KEGG) functional analyses for DEGs between the high-risk and low-risk groups based on a P value < 0.05 and false discovery rate (FDR) < 0.05. The corrected P value, or FDR value, was the expected ratio of false rejections (true hypothesis rejections) to the total number of rejected null hypotheses, which was also adjusted for the P value by the BH method. The infiltration scores of 16 types of immune cells and the activities of 13 immune-related pathways were calculated by single sample gene set enrichment analysis (ssGSEA) using the “gsva” package of R software [15].

Statistical analysis

All figures drawn from our central data were generated with SIMCA software (version 15.0.2, Sartorius Stedim Data Analytics AB, Umea, Sweden). SIMCA software was used to conduct data processing LOG conversion plus center formatting and then automatic modeling analysis[16]. Orthogonal projections to latent structures-discriminant analysis (OPLS-DA) can filter out orthogonal variables unrelated to categorical variables in metabolites and analyze nonorthogonal variables and orthogonal variables to obtain more reliable information about intergroup differences of metabolites and the degree of correlation between experimental groups. SIMCA software was employed to perform LOG conversion and UV formatting for the data. First, OPLS-DA modeling analysis was performed on the first principal component, and 7-fold cross-validation was used to verify the quality of the model. Then, the
validity of the model was evaluated by R2Y (the model’s interpretability to the categorical variable Y) and Q2 (the model’s predictability) obtained after cross-validation. Finally, the permutation test was applied to randomly change the arrangement order of the classification variable Y several times to obtain different random Q2 values and further test the validity of the model. Statistical analysis of partial data was performed using SPSS software version 23.0 (IBM Corporation, 2015, Chicago, IL, United States). All continuous variables that followed a normal distribution were compared using Student’s t-test, and the results are shown as the mean ± standard deviation. A bilateral P value < 0.05 was considered statistically significant. The Pearson method was used to calculate the correlation coefficient of the quantitative value of differential metabolites.

All figures drawn with TCGA data were generated using R software (version R 4.1.0). Gene expression values of tumor tissues and adjacent nontumor tissues in TCGA were compared using Student’s t-test. The chi-square test was utilized to compare data for classification variables. ssGSEA scores of immune cells or pathways in the high-risk group and the low-risk group were compared by the Mann-Whitney test with corrected P values. Kaplan-Meier analysis and the log-rank test were used to compare OS between the high-risk group and low-risk group, and potential predictors of OS were identified using Cox regression analysis. A P value < 0.05 was considered statistically significant, unless stated otherwise, and all P values were two-tailed.

RESULTS

PCA
PCA based on lipidomics analysis clearly distinguished between pancreatic cancer and adjacent tissues (Figure 1A). The lipid metabolism of the two groups was distributed in different regions, indicating unique characteristics for the lipid metabolism of the two groups. The samples were all within the 95% confidence interval (Hotelling’s T-Squared Ellipse).

OPLS-DA
To investigate significant differences in lipid metabolites between the pancreatic cancer group and the paracancer group, the multivariate analysis model OPLS-DA was used. Data from the pancreatic group and the paracancer group were distributed in two opposite regions in the OPLS-DA model (Figure 1B). The results of the OPLS-DA score chart showed that the two groups of samples differed significantly. All samples were within the 95% confidence interval (Hotelling’s T-Squared Ellipse).
Figure 3 Candidate genes related to lipid metabolism in The Cancer Genome Atlas. A: Venn diagrams were used to identify differentially expressed genes associated with overall survival between tumor tissues and adjacent normal tissues; B: The forest plot shows the relationship between gene expression and overall survival by univariate Cox regression analysis; C: Correlation coefficients in the correlation network of candidate genes are shown in different colors.

The permutation test established the corresponding OPLS-DA model to obtain $R^2$ and $Q^2$ values of the random model by randomly changing the ranking order of the categorical variable $Y$ several times, with an important role in avoiding overfitting of the test model and evaluating its statistical significance. The $Q^2$ values of the random model were all smaller than the $Q^2$ values of the original model. The intercept of the $Q^2$ regression line and vertical axis was less than zero; as the retention degree of displacement decreased gradually, the proportion of the $Y$ variable of displacement increased, and $Q^2$ of the random model decreased gradually. This indicated good robustness for the original model, and the original model could explain the difference between the two groups of samples (Figure 1C). The original Model $R^2$ was very close to 1, indicating that the established model conformed to the actual state of the sample data. The original Model $Q^2$ was close to 1, indicating that if new samples were added to the model, a more approximate distribution might be obtained. Overall, the original model explained the difference between the two groups of samples well. The $Q^2$ values of the random model were all smaller than those of the original model. The intercept of the $Q^2$ regression line and vertical axis was less than zero. As the retention degree of displacement gradually decreased, the proportion of the $Y$ variable of displacement increased, and $Q^2$ of the random model decreased gradually, indicating that the original model had considerable robustness, with no overfitting observed.

**Bar plot**

The bar plot of the lipid group visualized the results of the cancer group and paracancer group using the change degree of metabolite content and classification information (Figure 1D). As illustrated, the lipid metabolites phosphatidylcholine (PC), phosphatidyl ethanolamine (PE), phosphatidylethanol (PEtOH), phosphatidylinethanol (PEtOH), phosphatidylserines (PS) and diacylglycerol trimethylhomoserine (DGTS) were significantly higher in tumor tissues than in paracancerous tissues.
**Bubble plot**
A bubble plot was visualized by the degree of metabolite content change, difference significance and classification information of the cancer group and the paracancer group (Figure 1E). Each point in the bubble represents a metabolite, and the size of the point represents the $P$ value of Student’s t-test (-log10 $P$ value): the larger the dot, the smaller the $P$ value. Gray points represent nonsignificant differences with a $P$ value not less than 0.05, and colored points represent a $P$ value less than 0.05 (different colors marked according to lipid classification). The relative change percentage of the content was 0, indicating the same content of the metabolite in the two groups. A negative percentage change in relative content indicated a higher content of the metabolite in the paracancer group. Thus, we concluded that the lipid metabolites PE, PEtOH, PMeOH, PS and DGTS were significantly higher in tumor tissues than in paracancer tissues.

**TCGA-PAAD cohort baseline data**
The research flow chart for TCGA is depicted in Figure 2. A total of 176 pancreatic cancer patients from the PAAD cohort of TCGA were enrolled. Baseline clinical data for these patients are shown in Table 1.

**Identification of prognostic lipid metabolism-related DEGs in TCGA**
A total of 12.3% (25/197) of genes related to lipid metabolism were differentially expressed between tumor tissues and adjacent paracancerous tissues, and 6 of them were associated with OS in univariate Cox regression analysis (Figure 3A). A group of six prognostic DEGs related to lipid metabolism was revealed (Figure 3B), $P$ value < 0.05. Among the DEGs, the ABO gene was highly expressed in tumor tissues, whereas MAFB, GALNT16, FADS3, CERS4 and BEST1 were expressed at low levels. The correlation between these genes is shown in Figure 3C. The network of interactions among these genes indicated GALNT16 to be the hub gene.

**Development of a prognostic model in TCGA**
The above 6 lipid metabolism-related gene expression profiles were used to construct a prognostic model for pancreatic cancer patients by LASSO regression analysis. Four gene signature models were determined based on the optimal $\lambda$. Survival analysis showed that high expression of these genes was closely associated with poor prognosis in patients with pancreatic cancer according to the optimal cutoff expression value of each gene. The calculation formula of the risk score was as follows: 

$$
\text{risk score} = -0.551 \times \text{expression level of GALNT16} - 0.135 \times \text{expression level of FADS3} - 0.001 \times \text{expression level of CERS4} - 1.554 \times \text{expression level of MAFB} - 0.875 \times \text{expression level of ABO}
$$

Patients were divided into a high-risk group ($n = 88$) and a low-risk group ($n = 88$) based on the median cutoff value (Figure 4A); baseline clinical characteristics for the groups are shown in Table 2. For TCGA pancreatic cancer data, PCA and t-SNE analyses showed that patients in different risk groups were distributed in two directions; the high- and low-risk groups could be distinguished according to these two analyses (Figure 4B and 4C). Figure 4D shows that patients in the high-risk group (63.6%) had a higher probability of death than those in the low-risk group (40.9%), a difference that was significant ($P = 0.003$). Kaplan-Meier curves showed that patients in the high-risk group had significantly worse OS than those in the low-risk group (Figure 4E, $P = 0.004$). The prediction performance of the OS risk score was evaluated by ROC curve analysis, and the area under the curve was 0.647 for 1 year, 0.636 for 2 years and 0.651 for 3 years (Figure 4F).

**Prognostic value of the 4-gene signature**
Univariate Cox regression analysis was performed for available variables to determine whether the risk score can serve as a prognostic predictor of OS. In univariate Cox regression analysis, TCGA data analysis for pancreatic cancer indicated a significant correlation between risk score and OS ($HR = 3.720$, 95% CI = 1.873-7.386, $P < 0.001$) (Figure 5A).

**Functional analyses in TCGA**
To further clarify the biological functions and pathways related to the risk score, GO function enrichment and KEGG pathway analyses were performed on DEGs between the high-risk group and the low-risk group. Based on GO functional enrichment analysis, DEGs were enriched in molecular functions related to transmembrane transport, including phagocytosis, receptor ligand activity, signaling receptor activator activity, and G protein-coupled receptor binding (Figure 5B, $P$ value < 0.05). DEGs were also enriched in certain lipid metabolism-related signaling pathways, such as the
<table>
<thead>
<tr>
<th>Variables</th>
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<tr>
<td>Number of patients</td>
<td>176</td>
</tr>
<tr>
<td>Age (median, range)</td>
<td>65 (35-88)</td>
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<tr>
<td>Sex (%)</td>
<td></td>
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<tr>
<td>Female</td>
<td>80 (45.5%)</td>
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<tr>
<td>Male</td>
<td>96 (54.5%)</td>
</tr>
<tr>
<td>Grade (%)</td>
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<tr>
<td>Grade 1</td>
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</tr>
<tr>
<td>Grade 2</td>
<td>94 (53.4%)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>48 (27.3%)</td>
</tr>
<tr>
<td>Grade 4</td>
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</tr>
<tr>
<td>Unknown</td>
<td>2 (1.1%)</td>
</tr>
<tr>
<td>Stage (%)</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>21 (11.9%)</td>
</tr>
<tr>
<td>II</td>
<td>145 (82.4%)</td>
</tr>
<tr>
<td>III</td>
<td>3 (1.7%)</td>
</tr>
<tr>
<td>IV</td>
<td>4 (2.3%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>3 (1.7%)</td>
</tr>
<tr>
<td>Survival status</td>
<td></td>
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<tr>
<td>OS days (median)</td>
<td>464.5</td>
</tr>
<tr>
<td>Censored (%)</td>
<td>92 (52.3%)</td>
</tr>
</tbody>
</table>

TCGA: The Cancer Genome Atlas; OS: Overall survival.

Adipocytokine signaling pathway, regulation of lipolysis in adipocytes and other lipid metabolism-related signaling pathways in TCGA (Figure 5C, \( P \) value < 0.05).

To further explore the correlation between the risk score and immune status, we used ssGSEA to quantify enrichment scores for different immune cell subsets and related functions or pathways. In the cohort from TCGA, differences in scores for 16 immune cells were found between the low-risk and high-risk groups, including aDCs, B cells, CD8+ T cells, DCs, iDCs, macrophages, mast cells, neutrophils, NK cells, pDCs, T helper cells, Ths, Th1 cells, Th2 cells, TILs and Tregs. Overall, significant differences in all immune cells were observed (Figure 5D, all adjusted \( P \) value < 0.05). Surprisingly, except for MHC class I related to antigen presentation and type I IFN response related to immune regulation, which had similar scores in the groups (Figure 5E, \( P \) value > 0.05), other related pathways showed relatively high scores in the low-risk group (Figure 5F, \( P \) value < 0.05).

**DISCUSSION**

The insidious onset, inconspicuous early symptoms, rapid progression and high fatality rate of pancreatic cancer results in considerable difficulties in the early detection, diagnosis and treatment of pancreatic cancer [17]. Although CA199 plays an important role in the diagnosis of pancreatic diseases, it is less sensitive for early pancreatic cancer and precancerous lesions. For example, in one study, CA199 did not serve as a biomarker for the screening of asymptomatic populations but only for the screening of symptomatic patients or clinical differential diagnosis of other diseases [18]. Therefore, finding specific biomarkers for pancreatic cancer has been a hot topic in pancreatic cancer research. In our study, we attempted to search for patient-specific molecular markers of pancreatic cancer by analyzing differences in lipid metabolites between tumor tissues and adjacent tissues. Preliminary analysis results suggest that
The lipid metabolites PC, PE, PEtOH, PMeOH, PS and DGTS are significantly higher in tumor tissues than in paracancerous tissues.

Lipids are involved in regulating various biological processes, including energy conversion, material transport, information recognition and transmission, and abnormal lipid metabolism is closely related to certain diseases, such as diabetes mellitus, Alzheimer's disease, and the occurrence and development of tumors [19-21]. Our results suggest that differences in lipid metabolites exist between tumor tissues and paracancerous tissues in pancreatic cancer patients. Nevertheless, how such differences in lipid metabolites lead to the occurrence and development of tumors is still unknown. Therefore, we systematically investigated the expression of 197 lipid metabolism-related genes in pancreatic cancer tissues and their relationship with OS. We developed a novel prognostic model integrating 4 lipid metabolism-related genes and performed functional analysis and enrichment of immune-related pathways.

The prognostic model proposed in this study consists of four lipid metabolism-related genes: GALNT16, FADS3, CERS4, and ABO. The main functions of these genes can be roughly divided into the following four categories: protein O-linked glycosylation via serine (GALNT16), involvement in the fatty acid biosynthetic process (FADS3), action upstream of or within the lipid metabolic process (CERS4) and involvement in lipid glycosylation (ABO) [22-26]. Tabassum et al [23] reported that GALNT16 is a novel lipid locus associated with cardiovascular diseases (CVDs). GALNT16 was enriched in proteins, lipid metabolism, insulin/IGF pathway-protein kinase B signaling cascade, prolactin signaling pathway, AMPK signaling pathway and other specific biological functions. However, how GALNT16 affects lipid metabolites remains unclear [27]. FADS3 is a novel mammalian membrane-bound fatty acid desaturase gene, and FADS3 single-nucleotide polymorphisms might be associated with changes in plasma levels of triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and sphingolipid metabolism [28]. High expression of FADS3 was associated with higher triglyceride levels. Karsai et al [29] reported a higher level of d18:2 sphingomyelin species (30%) in women than in men and a corresponding higher level of FADS3 activity. Ceramide synthases form a family of six different proteins, and ceramides are components of complex sphingo-

### Table 2 Baseline characteristics of pancreatic cancer patients in different risk groups

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>TCGA-PAAD cohort</th>
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<td></td>
<td>High risk</td>
<td>Low risk</td>
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<tr>
<td>Sex (%)</td>
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<td>0.354</td>
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<tr>
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<td>37</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>51</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>Age (%)</td>
<td></td>
<td></td>
<td>0.450</td>
</tr>
<tr>
<td>≤ 65 yr</td>
<td>44</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>&gt; 65 yr</td>
<td>44</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>Tumor grade (%)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>G1+G2</td>
<td>59</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>G3+G4</td>
<td>27</td>
<td>23</td>
<td></td>
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<tr>
<td>Unknown</td>
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<td>0</td>
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<tr>
<td>TNM stage (%)</td>
<td></td>
<td></td>
<td>0.779</td>
</tr>
<tr>
<td>I + II</td>
<td>84</td>
<td>82</td>
<td></td>
</tr>
<tr>
<td>III + IV</td>
<td>3</td>
<td>4</td>
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<tr>
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<td>2</td>
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<tr>
<td>Survival state</td>
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</tr>
<tr>
<td>Alive</td>
<td>32</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>Deceased</td>
<td>56</td>
<td>36</td>
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</tr>
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</table>

lipids, such as sphingolipid or glucosylceramide. Ebel et al.[30] found that CERS4-deficient mice developed progressive hair loss due to altered sebum composition and that sebum became more viscous. Overexpression of CERS4 and CERS6 in breast and colon cancer cells resulted in increased short-chain (C16:0) and long-chain ceramides (C18:0 and C20:0), inhibited cell proliferation and increased apoptosis[31]. However, in our prognostic model, three genes (GALNT16, FADS3, and CERS4) were underexpressed in pancreatic cancer patients. A large body of evidence supports a link between ABO and CVDs. However, the mechanism of ABO association with atherosclerosis remains unclear. Moreover, ABO glycotransferase was associated with cholesterol metabolism, and there might be a broader effect on atherosclerotic CVD [32]. ABO was overexpressed, indicating a poor prognosis. Whether these genes influence the prognosis of pancreatic cancer patients by affecting lipid metabolism is unknown. Despite few studies on the association between these genes and pancreatic cancer, our findings might pave the way for lipid metabolomics in pancreatic cancer patients.
Figure 5 Construction of the predictive prognostic model and preliminary exploration of the potential mechanism. A: Results of univariate Cox regression analyses of overall survival in The Cancer Genome Atlas cohort; B: Gene Ontology enrichment; C: Kyoto Encyclopedia of Genes and Genomes pathways; D: The scores of 16 immune cells; E: The scores of 13 immune-related functions. ns was $P \geq 0.05$; $^aP < 0.05$; $^bP < 0.01$; $^cP < 0.001$.

Although the mechanisms of tumor susceptibility have been the focus of research recently, the potential regulatory mechanisms between tumor immunity and lipid metabolism remain unknown, especially in pancreatic cancer. We performed GO
analysis of genes related to lipid metabolism based on differences in genes between risk groups and were pleasantly surprised to find that these DEGs are enriched in many immune-related biological processes and pathways. Therefore, we also provide evidence that lipid metabolism might be closely related to tumor immunity. An important finding in our study was significant differences in genes related to transmembrane transport in lipid metabolism between the low-risk group and the high-risk group. As alteration of energy metabolism to allow uncontrolled proliferation and metastasis is one of the most important markers of tumors, one possible hypothesis is that different signals released by lipid metabolism affect energy transfer by influencing transmembrane transport processes[33]. In addition, our study found no difference in MHC class I and type I IFN responses between the high-risk and low-risk groups. MHC class I is mainly related to the antigen presentation process in the immune response. Type I interferons, IFN-α and IFN-β, are mainly secreted by innate immune cells and are important effector molecules of antiviral immunity[34]. Type II interferon, IFN-γ, is primarily secreted by activated T cells[35]. Therefore, we believe that lipid metabolites, as opposed to nonantigens, play an important role in tumor development in pancreatic cancer patients.

The study had some limitations. First, we constructed a prognostic model using a public database; however, more prospective real-world data should be used to verify its clinical validity. Although we also attempted to use other public database data for verification, the sample size of these databases was small, and the available data were very limited. Second, our study developed a prognostic model by considering only one factor, lipid metabolism, and excluded many significant prognostic genes involved in other aspects of pancreatic cancer, which might constitute an inherent flaw. Third, 197 lipid metabolism-related genes mentioned in this paper were only summarized through a literature review, and some rare genes or functions involved in lipid metabolism are not included herein. Fourth, when we performed lipid metabolite analysis, our research only looked for differences in lipid metabolites between cancer tissues and adjacent para-cancer tissues and did not analyze differences between cancer tissues and healthy control pancreatic tissues. Given the high risk of pancreatic surgery, it was difficult to obtain healthy controls for pancreatic tissue. However, our previous studies showed differences in lipid metabolites between pancreatic cancer patients and healthy controls in blood samples[36]. In addition, the association between the risk score and immune activity was not further validated in the corresponding experiments.

CONCLUSION

In conclusion, our study developed a novel prognostic model composed of 4 lipid metabolism-related genes, which was analytically confirmed to be associated with OS in patients with pancreatic cancer and to be an independent risk factor for predicting the prognosis of pancreatic cancer.

ARTICLE HIGHLIGHTS

Research background
Finding specific prognostic markers is important for pancreatic cancer. Understanding the relationship between lipid metabolism-related genes and pancreatic cancer is helpful to improve its prognosis.

Research motivation
To construct a novel model to predict the prognosis of pancreatic cancer.

Research objectives
To investigate the characteristics of lipid metabolites in pancreatic cancer and construct a prognostic polygene signature of differentially expressed genes related to lipid metabolism.

Research methods
Lipid metabolomics analysis was conducted to explore differences in lipid metabolites between pancreatic cancer tissues and paracancerous tissues. A predictive model of
lipid metabolism genes associated with pancreatic cancer was established using a cohort from The Cancer Genome Atlas.

**Research results**

Lipid metabolomics analysis showed that the lipid metabolites phosphatidylcholine, phosphatidylethanolamine, phosphatidylethanol, phosphatidylmethanol, phosphatidylserines and diacylglycerol trimethylhomoserine were significantly higher in cancer tissues. A 4-gene signature model, including GALNT16, FADS3, CERS4 and ABO, was developed to predict the prognosis of pancreatic cancer.

**Research conclusions**

Differentially expressed genes related to lipid metabolism reflected abnormal lipid metabolism in pancreatic cancer. A novel predictive model of a 4-lipid metabolism-related gene signature contributed to the prediction of pancreatic cancer prognosis.

**Research perspectives**

New gene markers and models are needed to predict prognosis because of the high heterogeneity of pancreatic cancer.

**ACKNOWLEDGEMENTS**

The authors would like to thank Prof. Xiang-Dong Wang and Shanghai Zhongshan Hospital for guidance on the design of the study.

**REFERENCES**


Retrospective Study

Serum magnesium level as a predictor of acute kidney injury in patients with acute pancreatitis

Xian-Qiang Yu, Hong-Bin Deng, Yang Liu, Cheng Qu, Ze-Hua Duan, Zhi-Hui Tong, Yu-Xiu Liu, Wei-Qin Li

Abstract

BACKGROUND
Decreased serum magnesium (Mg²⁺) is commonly seen in critically ill patients. Hypomagnesemia is significantly more frequent in patients with severe acute pancreatitis. Acute kidney injury (AKI) in patients with acute pancreatitis (AP) is associated with an extremely high mortality. The association underlying serum Mg²⁺ and AKI in AP has not been elucidated.

AIM
To explore the association between serum Mg²⁺ on admission and AKI in patients with AP.

METHODS
A retrospective observational study was conducted in a cohort of patients (n = 233) with AP without any renal injury before admission to our center from August 2015 to February 2019. Demographic characteristics on admission, severity score, laboratory values and in-hospital mortality were compared between patients with and without AKI.

RESULTS
A total of 233 patients were included for analysis, including 85 with AKI. Compared to patients without AKI, serum Mg²⁺ level was significantly lower in
patients with AKI at admission \( [OR = 6.070, 95\% CI: 3.374-10.921, P < 0.001] \). Multivariate logistic analysis showed that lower serum \( \text{Mg}^{2+} \) was an independent risk factor for AKI \( [OR = 8.47, 95\% CI: 3.02-23.72, P < 0.001] \).

**CONCLUSION**

Our analysis indicates that serum \( \text{Mg}^{2+} \) level at admission is independently associated with the development of AKI in patients with AP and may be a potential prognostic factor.

**Key Words:** Acute pancreatitis; Acute kidney injury; Magnesium (\( \text{Mg}^{2+} \)); Kidney; Predictor of acute kidney injury

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**INTRODUCTION**

Acute pancreatitis (AP) is an autodigestive disease triggered by acinar cells, and about 20% of the patients progress to fatal severe acute pancreatitis (SAP)[1-4]. Acinar cell injury accompanied by intracellular electrolyte imbalance, further aggravating cell damage and even death is the recognized pathogenesis of AP[5,6]. In particular, organella damage caused by intracellular calcium (\( \text{Ca}^{2+} \)) influx into mitochondria is the main risk factor for AP[7]. An in vitro AP model showed that \( \text{Ca}^{2+} \) channel antagonists could effectively reduce \( \text{Ca}^{2+} \) influx and increase mitochondrial membrane potential, thereby protecting acinar cells[8,9]. As an important cation in cells, magnesium (\( \text{Mg}^{2+} \)) is a coenzyme involved in a variety of enzymatic reactions and plays a role in maintaining membrane potential and physiological function[10-12]. In addition, \( \text{Mg}^{2+} \) plays a protective role in AP acinar cells by antagonizing \( \text{Ca}^{2+} \) signals[13]. On the contrary, abnormal regulation of \( \text{Mg}^{2+} \) acts as a pivotal trigger in the pathogenesis of AP[14].

Acute kidney injury (AKI) is a common complication of SAP with poor prognosis, especially when patients require renal replacement therapy, the mortality rate is >75% [15,16]. SAP-associated AKI is related to systemic inflammatory response syndrome (SIRS), hypoxemia, renal microcirculation injury after trypsin release, renal perfusion pressure reduction caused by intraperitoneal high pressure or low blood volume, endotoxins and reactive oxides[17]. Therefore, early prediction of AKI in AP is very important to improve the course and prognosis of the disease.

AKI is often accompanied by complex electrolyte disturbances[18]. However, the relationship between \( \text{Mg}^{2+} \) and the occurrence of AP-associated AKI in AP pathophysiology has not been fully elucidated. Based on the beneficial role of \( \text{Mg}^{2+} \) in acinar cells of AP, we therefore sought to assess the value of serum \( \text{Mg}^{2+} \) on admission in correlation with the incidence of AKI in AP.
MATERIALS AND METHODS

Patient selection
We conducted a retrospective study of patients with AP admitted to the Center of Severe Acute Pancreatitis of Jinling Hospital between August 2015 and February 2019. All the data were extracted from an electronic database, which stored prospectively collected clinical data of all AP patients admitted to our center. We obtained the approval of the Acute Pancreatitis Database Management Committee (2018 JLAPDMC-009), and all the analyses were performed in accordance with the committee’s regulations. Informed consent involving data storage and academic use of data was obtained from each patient during their hospitalization. Patients who met the following criteria were included: (1) Diagnosis of AP (ICD-10, K85) under the 2012 revision of the Atlanta classification; and (2) Admission to our department within one week after the disease onset. The exclusion criteria included any of the following: (1) The time from abdominal pain onset to hospital admission ≥ 7 d; (2) Age younger than 18 years; and (3) Suspected chronic pancreatitis, cancer, and chronic liver diseases such as cirrhosis or viral hepatitis, chronic kidney diseases such as nephritis, or renal failure. AKI (ICD-10: N17) was diagnosed according to the kidney disease: Improving Global Outcomes criteria based on serum/plasma creatinine and urine output. Patients meeting the diagnostic criteria for AP during hospitalization were included in the AKI group. The diagnosis of low serum Mg\textsuperscript{2+} was made by laboratory measurements on the day of admission.

Data collection
Demographic and baseline characteristics on admission included the following: Age, gender, body mass index (BMI), disease severity score (APACHE II), sequential organ failure assessment (SOFA), computed tomography severity index (CTSI), the Atlanta classification, comorbidities (diabetes, hypertension, hyperlipidemia), white blood cells, lymphocytes%, interleukin-6 (IL-6), procalcitonin (PCT), platelets, blood urea nitrogen (BUN), creatinine, HCO\textsubscript{3}−, and Cl\textsuperscript{−}.

Statistical analysis
Statistical analysis was performed using R software, version 3.6.2 (R Foundation for Statistical Computing). The Kolmogorov-Smirnov test was used to test the normality. Continuous variables are presented as means and standard derivations or medians and interquartile ranges. Categorical variables are presented as number (frequency). The Mann-Whitney U test was used to evaluate the differences in baseline characteristics between the two groups. The Chi-square test or Fisher’s exact test was used to analyze categorical variables for group comparisons. All variables with statistically significant prognostic value in univariate analysis were selected for further multivariate analysis. Odds ratio (OR) and 95% confidence intervals (CIs) are presented. Receiver operating characteristic curves were constructed to evaluate the sensitivity and specificity of serum Mg\textsuperscript{2+} in predicting AKI. P value < 0.05 was considered statistically significant.

RESULTS

Baseline characteristics
A total of 233 patients were included for analysis. The participant selection process is shown in Figure 1. The serum Mg\textsuperscript{2+} level of 0.755 mg/dL was identified as an effective cut-off point for in-hospital AKI occurrence (area under curve = 0.704; 95%CI: 0.640-0.775, P < 0.001), with a sensitivity of 77.7%, and specificity of 63.5% (Figure 2). Baseline characteristics of these patients are shown in Table 1. Compared with the non-low serum Mg\textsuperscript{2+} group, the group with low serum Mg\textsuperscript{2+} had higher BMI (P = 0.028) and APACHE II (P = 0.002). With regard to laboratory parameters, patients in the low serum Mg\textsuperscript{2+} group had higher admission IL-6 (P < 0.001), PCT (P < 0.001), and lower HCO\textsubscript{3}− (P < 0.001).

Clinical outcomes
The in-hospital clinical outcomes are shown in Table 2, divided according to admission serum Mg\textsuperscript{2+} level. The serum Mg\textsuperscript{2+} < 0.755 mg/dL group consisted of 87 patients (54 cases in the AKI group and 33 cases in the non-AKI group), and the serum Mg\textsuperscript{2+} ≥ 0.755 mg/dL group consisted of 146 patients (31 cases in the AKI group and
Table 1 Baseline characteristics

<table>
<thead>
<tr>
<th>Mg(^{2+}) (mg/dL)</th>
<th>(\leq 0.755) mg/dL, (n = 87)</th>
<th>(&gt; 0.755) mg/dL, (n = 146)</th>
<th>(P) value</th>
<th>AKI, (n = 85)</th>
<th>Non-AKI, (n = 148)</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>39 (32, 52)</td>
<td>44 (34, 58)</td>
<td>0.063</td>
<td>38 (30, 50)</td>
<td>44.5 (35.5, 54.5)</td>
<td>0.011</td>
</tr>
<tr>
<td>Gender, male, n (%)</td>
<td>59 (67.8)</td>
<td>98 (67.1)</td>
<td>0.913</td>
<td>59 (69.4)</td>
<td>98 (66.2)</td>
<td>0.913</td>
</tr>
<tr>
<td>BMI</td>
<td>27.1 (24.7, 30.1)</td>
<td>25.6 (23.9, 28.1)</td>
<td>0.028</td>
<td>27.6 (24.8, 30.7)</td>
<td>25.4 (23.4, 27.7)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>APACHE II</td>
<td>9 (7, 12)</td>
<td>7 (5, 9)</td>
<td>0.002</td>
<td>11 (8, 14)</td>
<td>7 (4, 9)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>SOFA</td>
<td>3 (3, 4)</td>
<td>5 (2, 4)</td>
<td>0.075</td>
<td>4 (3, 5)</td>
<td>3 (2, 4)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CTSI</td>
<td>6 (3, 6)</td>
<td>6 (3, 6)</td>
<td>0.122</td>
<td>6 (6, 6)</td>
<td>4 (2, 6)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Severity classification, n (%)</td>
<td></td>
<td></td>
<td>0.064</td>
<td></td>
<td>0.913</td>
<td></td>
</tr>
<tr>
<td>MAP</td>
<td>21 (24.1)</td>
<td>50 (34.2)</td>
<td>0.066</td>
<td>20 (23.5)</td>
<td>27 (18.2)</td>
<td>0.066</td>
</tr>
<tr>
<td>MSAP</td>
<td>47 (54.0)</td>
<td>79 (54.1)</td>
<td>0.913</td>
<td>45 (53.0)</td>
<td>81 (54.7)</td>
<td>0.913</td>
</tr>
<tr>
<td>SAP</td>
<td>19 (21.8)</td>
<td>17 (11.6)</td>
<td>0.064</td>
<td>33 (38.8)</td>
<td>3 (2.1)</td>
<td></td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>23 (26.4)</td>
<td>24 (16.4)</td>
<td>0.066</td>
<td>20 (23.5)</td>
<td>27 (18.2)</td>
<td>0.066</td>
</tr>
<tr>
<td>Hypertension</td>
<td>22 (25.3)</td>
<td>36 (24.7)</td>
<td>0.914</td>
<td>22 (25.9)</td>
<td>36 (24.3)</td>
<td>0.914</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>25 (28.7)</td>
<td>36 (24.7)</td>
<td>0.493</td>
<td>21 (24.7)</td>
<td>40 (27.0)</td>
<td>0.493</td>
</tr>
<tr>
<td>Laboratory data</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC</td>
<td>13.4 (10.6, 16.6)</td>
<td>12.8 (10.1, 15.7)</td>
<td>0.336</td>
<td>12.9 (10.9, 16.6)</td>
<td>12.9 (10.3, 16.1)</td>
<td>0.685</td>
</tr>
<tr>
<td>Ly%</td>
<td>8.1 (5.1, 11.2)</td>
<td>6.7 (4.7, 10.6)</td>
<td>0.297</td>
<td>6.9 (4.9, 10.5)</td>
<td>7.2 (5, 11.2)</td>
<td>0.769</td>
</tr>
<tr>
<td>IL-6</td>
<td>199.6 (104.8, 366.4)</td>
<td>115.4 (45.4, 201.5)</td>
<td>&lt; 0.001</td>
<td>228.8 (130.4, 370)</td>
<td>104.8 (45.4, 178.4)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>PCT</td>
<td>1.2 (0.4, 3.3)</td>
<td>0.4 (0.1, 1.6)</td>
<td>&lt; 0.001</td>
<td>2.1 (1.1, 7.7)</td>
<td>0.3 (0.1, 0.8)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Platelets</td>
<td>193 (142, 239)</td>
<td>174 (134, 224)</td>
<td>0.215</td>
<td>199 (132, 236)</td>
<td>176.5 (142, 218)</td>
<td>0.248</td>
</tr>
<tr>
<td>BUN</td>
<td>5.4 (3.7, 6.3)</td>
<td>5.1 (4.6, 9.9)</td>
<td>0.576</td>
<td>6 (4.8, 8.3)</td>
<td>4.8 (3.8, 5.9)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Creatinine</td>
<td>61 (49.8)</td>
<td>63 (53, 8)</td>
<td>0.924</td>
<td>50 (41, 57.3)</td>
<td>51 (46, 59)</td>
<td>0.184</td>
</tr>
<tr>
<td>HCO(^{3-})</td>
<td>18.9 (15.1, 23.5)</td>
<td>22 (18.7, 24.2)</td>
<td>&lt; 0.001</td>
<td>17.8 (13.7, 21.3)</td>
<td>22.6 (19.8, 24.7)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CT</td>
<td>103 (99, 105)</td>
<td>102 (100, 105)</td>
<td>0.825</td>
<td>103.7 (101, 107)</td>
<td>102 (99, 104)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mg(^{2+})</td>
<td>0.7 (0.6, 0.7)</td>
<td>0.885 (0.8, 0.9)</td>
<td>0.091</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mg\(^{2+}\): Magnesium; BMI: Body mass index; AKI: Acute kidney injury; SOFA: Sequential organ failure assessment; CTSI: CT severity index; MAP: Mild acute pancreatitis; MSAP: Mild severe acute pancreatitis; SAP: Severe acute pancreatitis; WBC: White blood cells; Ly\%: Lymphocytes%; IL-6: Interleukin-6; PCT: Procalcitonin; BUN: Blood urea nitrogen.

115 cases in the non-AKI group). Lower serum Mg\(^{2+}\) was correlated with the occurrence of AKI (62.1% vs 21.2%, \(P < 0.001\)). The length of intensive care unit (ICU) stay (\(P < 0.001\)) and hospital stay (\(P < 0.001\)) of patients with low serum Mg\(^{2+}\) level was longer.

Association of admission serum Mg\(^{2+}\) level with AKI occurrence

As shown in Figure 3, compared with the non-AKI group, the AKI group had significantly lower serum Mg\(^{2+}\) level (\(P < 0.001\)). Following univariate logistic regression analysis, BMI (OR = 1.155, \(P < 0.001\)), APACHE II (OR=1.385, \(P < 0.001\)), SOFA (OR = 1.589, \(P < 0.001\)), CTSI (OR = 1.479, \(P < 0.001\)), severity classification (\(P < 0.001\)), IL-6 (OR = 1.006, \(P < 0.001\)), PCT (OR = 1.350, \(P < 0.001\)), BUN (OR = 1.368, \(P < 0.001\)), creatinine (OR = 1.051, \(P < 0.001\)), HCO\(^{3-}\) (OR = 0.843, \(P < 0.001\)), and CT (OR = 1.100, \(P = 0.003\)) were important indicators of AKI in AP patients (Table 3). Multivariate logistic analysis showed that lower serum Mg\(^{2+}\) (OR = 5.525, \(P < 0.001\)) was an independent risk factor for AKI (Table 3).
### Table 2 Influence of low serum magnesium on clinical course

<table>
<thead>
<tr>
<th>Mg(^{2+}) (mg/dL)</th>
<th>&lt; 0.755 mg/dL, n = 87</th>
<th>≥ 0.755 mg/dL, n = 146</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AKI</td>
<td>54 (62.1)</td>
<td>31 (21.2)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Clinical course, days median</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU days</td>
<td>3 (2, 6)</td>
<td>2 (1, 4)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hospital days</td>
<td>6 (4, 10)</td>
<td>4 (3, 7)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Severe outcome, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU mortality</td>
<td>1 (1.15)</td>
<td>3 (2.05)</td>
<td>0.999</td>
</tr>
<tr>
<td>30 d mortality</td>
<td>1 (1.15)</td>
<td>3 (2.05)</td>
<td>0.999</td>
</tr>
</tbody>
</table>

Mg\(^{2+}\): Magnesium; AKI: Acute kidney injury; ICU: Intensive care unit.

**DISCUSSION**

In this research, we examined the involvement of serum Mg\(^{2+}\) and AKI in AP patients. Our results suggest that serum Mg\(^{2+}\) levels detected at admission were significantly lower in AP patients with AKI than in non-AKI patients. Moreover, the low serum Mg\(^{2+}\) group had a longer ICU and hospital stay than the non-low serum Mg\(^{2+}\) group. Furthermore, serum Mg\(^{2+}\) was revealed as an independent risk factor for the development of AKI. Therefore, serum Mg\(^{2+}\) is an effective predictor of AKI after AP.

Mg\(^{2+}\) is a well-known divalent cation abundant in human cells and is concentrated in mitochondria. It mainly plays the role of a cofactor in enzyme reactions and a second messenger in cellular signaling pathways\[^{19-21}\]. In the physiological state of acinar cells, Mg\(^{2+}\) plays an antagonistic role in the influx of Ca\(^{2+}\) channel ions and inhibits the secretion of intracellular enzymes\[^{9,22}\]. In the acinar cell model of AP, the addition of Mg\(^{2+}\) mitigates the effects of AP by inhibiting Ca\(^{2+}\) influx into the mitochondria, thereby reducing the secretion of digestive enzymes and promoting ATP generation\[^{14}\]. In conclusion, Mg\(^{2+}\) plays an important regulatory role in the pathophysiological state of acinar cells. Mitochondria are the key organelles for the energy supply in acinar cells. It is obvious that Mg\(^{2+}\) plays an important role in maintaining mitochondrial homeostasis and ATP generation from this perspective.

The persistent influx of Ca\(^{2+}\) into the mitochondria of acinar cells in AP leads to increased oxygen radicals further triggering cell necrosis, which in turn induces SIRS\[^{23-25}\]. This imbalance leads to further inflammatory response and oxygen radical production, resulting in multiple organ dysfunction including AKI\[^{26}\]. Therefore, it is important to prevent the continuous influx of Ca\(^{2+}\) into mitochondria to reduce acinar cell necrosis and inhibit trypsin activation in AP. This is consistent with research in animal experiments\[^{8,9}\]. In a murine model, the risk of triggering AP was decreased by inhibiting Ca\(^{2+}\) release-activated Ca\(^{2+}\) channels\[^{27}\]. To the best of our knowledge, hypomagnesemia is commonly seen in severely ill patients including those with SAP\[^{28}\]. In our SAP patients, there was a significant negative correlation between the incidence of AKI and adjusted serum Mg\(^{2+}\) on admission.

AKI as a complication, which is associated with increased mortality, occurs in approximately 15%-70% of SAP patients\[^{18,29}\]. Therefore, early prediction of AKI in hospitalized patients with AP is imperative, especially for screening graded treatment strategies\[^{30}\]. Currently, there are various clinical methods to predict the occurrence of AKI in patients with AP. On the whole, current studies on biomarkers for AP-associated AKI are insufficient, and the number of patients included in the analysis was limited. In addition, from the latest clinical evidence on the markers of AKI in AP, PCT showed relatively better clinical predictive value than neutrophil gelatinase-associated lipocalin (NGAL) and cystatin C\[^{31-33}\]. At present, serum or urine NGAL and serum cystatin C are recognized as the best laboratory indicators for predicting AKI in AP with good diagnostic accuracy. However, these single-center clinical data are not convincing enough. Large multicenter clinical studies on biomarkers are of great clinical value in identifying AKI in AP.
However, the relationship between admission serum Mg²⁺ level and AKI incidence in patients with AP has not been fully elucidated. Our results are the first to show that reduced serum Mg²⁺ levels are significantly associated with an increased risk of AKI in patients with AP. We found that Mg²⁺ level of 0.755 mg/dL was an effective cut-off point for in-hospital AKI occurrence, with a sensitivity of 77.7%, and specificity of 63.5%.

However, there are some limitations to our analysis. Firstly, our study did not consider the value of peripheral blood Mg²⁺; thus, the reliability of the actual level of free Mg²⁺ in peripheral blood may be significantly reduced from this perspective. Secondly, the causal relationship between Mg²⁺ and AP-associated AKI still needs to be verified by a large number of prospective studies. Thirdly, our analysis included only one checkup at admission, and as serum Mg²⁺ is a dynamic state, it may not fully reflect the true status of Mg²⁺ in these patients. From this perspective, dynamic serum Mg²⁺ measurement after admission is more objective in predicting AP-associated AKI.

Finally, there may be methodological bias in our analysis, it is necessary to explore new machine models (such as train-validation models) to verify the current analysis results.

CONCLUSION

Our analysis indicates that serum Mg²⁺ level at admission is independently associated the development of AKI in patients with AP and may be a potential prognostic factor.
Yu XQ et al. Serum magnesium and AKI after AP

Figure 1 The flow diagram of patients. A total of 1666 patients were included in the analysis. AKI: Acute kidney injury.

Figure 2 Receiver operating characteristic curve for serum magnesium in predicting acute kidney injury. AUC: Area under the curve.

Figure 3 Serum magnesium in the acute kidney injury group versus the non-acute kidney injury group. AKI: Acute kidney injury.
ARTICLE HIGHLIGHTS

Research background
There is a lack of effective predictors of acute kidney injury (AKI) after acute pancreatitis (AP) in clinical practice.

Research motivation
To investigate the association between serum Mg\(^{2+}\) on admission and AKI after AP.

Research objectives
To determine whether serum Mg\(^{2+}\) is a valid predictor of AP-associated AKI using clinical data from our severe acute pancreatitis center.

Research methods
Our center is one of the largest severe acute pancreatitis treatment centers in China. A total of 233 patients with AP from August 2015 to February 2019 were included in a retrospective analysis. Almost all clinical and laboratory indicators were included in the study.

Research results
Lower serum Mg\(^{2+}\) was correlated with the occurrence of AKI (62.1% vs 21.2%, \(P < 0.001\)). Patients in the low serum Mg\(^{2+}\) level group had a longer intensive care unit (\(P < 0.001\)) and hospital stay (\(P < 0.001\)).

Research conclusions
Serum Mg\(^{2+}\) on admission can effectively predict AKI in AP patients.

Research perspectives
This study provides ideas and a basis for prospective observation of AKI after AP, and provides early warning for effective intervention of the disease.

REFERENCES


Beker BM, Corletto MG, Fieras C, Musso CG. Novel acute kidney injury biomarkers: their characteristics, utility and concerns. Int Urol Nephrol 2018; 50: 705-713. DOI: 10.1007/s11255-017-1811-x


Frick TW. The role of calcium in acute pancreatitis. Surgery 2012; 152: S157-S163. DOI: 22906890


Yu Q et al. Serum magnesium and AKI after AP

The image contains a list of references and citations related to studies on magnesium and its role in pancreatitis, specifically mentioning calcium-magnesium interactions, the effect of magnesium supplementation, and the role of calcium in acute pancreatitis. The text also references studies on acute kidney injury biomarkers and the relationship between magnesium and calcium levels in acute pancreatitis. The references are formatted in APA style, indicating peer-reviewed articles from various journals, ranging from the late 20th century to the early 21st century.
Retrospective Study

Pedicle complex tissue flap transfer for reconstruction of duplicated thumbs with unequal size

De-Hua Wang, Gui-Ping Zhang, Zeng-Tao Wang, Meng Wang, Qin-Yi Han, Fan-Xiao Liu

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Author contributions: Liu FX, Wang DH, and Han QY designed the research study; Wang DH, Zhang GP, Wang ZT, Wang M, Han Q, and Liu FX performed the research; Liu FX and Han QY analyzed the data; Wang DH, Zhang GP, Wang ZT, Wang M, Han QY, and Liu FX wrote the manuscript; Liu FX and Han QY contributed equally in the planning, construction, and writing of the manuscript.

Institutional review board statement: The study was reviewed and approved by the Biomedical Ethic Committee of Shandong Provincial Hospital (Approval No. 2021-018).

Informed consent statement: Written consent was obtained from the patients’ parents for the purpose of publication of case details and images.

Conflict-of-interest statement: The authors declare no potential conflicts of interest with respect to the research, authorship, and/or De-Hua Wang, Zeng-Tao Wang, Meng Wang, Department of Hand and Foot, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan 250021, Shandong Province, China

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Abstract

BACKGROUND
Thumb polydactyly is one of the most common congenital hand deformities, and the Bilhaut-Cloquet procedure or a modified one is often used. However, controversy remains over the rare instances in which both thumbs are not of similar length or far apart in distance.

AIM
To evaluate the clinical outcomes of pedicle complex tissue flap transfer in the treatment of duplicated thumbs with unequal size.

METHODS
From January 2014 to December 2020, 15 patients underwent duplicated thumb reconstruction by pedicle complex tissue flap transfer at our hand surgery center. The technique was used when it was necessary to combine different tissues from both severed and preserved thumbs that were not of similar length or far apart in distance. Subjective parents’ evaluations and functional outcomes (ALURRA and TATA criteria) were obtained. The alignment deviation, instability, range of motion (percent of opposite thumb) of the interphalangeal and metacarpophalangeal joints, and the aesthetic aspects, including circumference, length, nail size, and nail deformity, were used to assess the clinical outcomes.
RESULTS

The average age of patients at the time of surgery was 13 mo, and the mean final follow-up occurred at 42 mo. An appropriate volume with a stable joint and good appearance was obtained in 14 reconstructed thumbs. An unstable interphalangeal joint occurred in one thumb. The flexion-extension arc at the metacarpophalangeal joint was good, while that at the interphalangeal joint was poor. Most of the parents were satisfied with the cosmetic and functional results of the reconstructed thumbs. The mean ALURRA score was 21.8 (range: 20-24), and the Tada score was 6.9 (range: 5-8). Compared with the non-operated side, the length of the operated thumb was approximately 95%, the girth was 89%, and the nail width was 82.9%. The mean ranges of motion were 62.1% of that of the unaffected thumb in the interphalangeal joint and 78.3% in the metacarpophalangeal joint.

CONCLUSION

Harvesting a pedicle flap from a severed thumb is a safe and reliable procedure. Defects of the preserved thumb, such as the skin, nail, and bone, can be effectively restored using the complex tissue flap.

Key Words: Thumb duplication; Deformity; Pedicle flap; Pedicle

Core Tip: We found that an appropriate volume with a stable joint and good appearance was obtained in 14 reconstructed thumbs. An unstable interphalangeal joint occurred in one thumb. The mean ALURRA score was 21.8 (range: 20-24), and the Tada score was 6.9 (range: 5-8). Compared with the non-operated side, the length of the operated thumb was approximately 95%, the girth was 89%, and the nail width was 82.9%. The mean ranges of motion were 62.1% of that of the unaffected thumb in the interphalangeal joint and 78.3% in the metacarpophalangeal joint. Therefore, harvesting a pedicle flap from a severed thumb is a safe and reliable procedure. Defects of the preserved thumb, such as the skin, nail, and bone, can be effectively restored using the complex tissue flap.

INTRODUCTION

Thumb polydactyly is the most prevalent duplication in Caucasian and Asian populations, occurring in approximately 0.8 to 1.4 per 1000 births[1-4], impacting not only the appearance of the affected hand but also the function of thumb flexion and extension and grasping and pinching movements[5-7]. To better restore the function of the thumb, reconstruction surgery for thumb deformities should be performed early in the first year of life[8], which could help children to obtain a thumb similar to normal thumb anatomy with less growth impairment and to reconstruct thumb function during their growth and development.

The surgical strategy should be formulated according to the specific thumb deformity because thumb deformities are different for various children. There are many clinical diagnostic classifications of complex thumb deformity. At present, the Wassel classification is the most commonly used, which divides complex thumb deformity into seven types based on its type and grade of phalangeal division[9]. Currently, for a clear distinction between primary and redundant thumbs, a surgical strategy including resection of the redundant finger and reconstruction of the main thumb is generally adopted when the primary thumb is well developed. The Bilhaut-Cloquet procedure and its modified operation are often used to reconstruct symmetrical or essentially symmetrical thumb polydactyly with the same size as the
supernumerary finger[7,10]. However, reconstruction of thumb polydactyly correction is often associated with several problems, such as a slender and short reserved thumb, unstable joints, nail lateral deviation deformity, and a narrow skin defect in the first web space, which is a challenge for clinicians.

Thumb polydactyly is one of the most common congenital hand deformities; surgery for most conditions usually involves removal of the more hypoplastic thumb and reconstruction of the better thumb. When neither thumb is obviously dominant in all aspects or when a combination of the two thumbs is a better choice, the Bilhaut-Cloquet procedure or a modified one can be used. There are rare instances in which both thumbs are not of similar length or far apart in distance, in which case the Bilhaut-Cloquet procedure or a modified procedure is difficult to implement. In such cases, a useful procedure is to transfer a complex tissue flap on a neurovascular pedicle raised from the severed thumb to overcome the defect in length or distance.

Therefore, the purpose of this article is to deliver our experience on this kind of reconstruction and to report the follow-up outcomes in our series of patients.

MATERIALS AND METHODS

Choice of study participants
This retrospective study included patients who underwent duplicated thumb reconstruction by pedicle complex tissue flap transfer at the Shandong Provincial Hospital Affiliated to Shandong First Medical University from January 2014 to December 2020. The technique was used when it was necessary to combine different tissues from both severed and preserved thumbs that were not of similar length or far apart in distance. The patients had at least one of the following symptoms: There was a skin defect in the preserved thumb (Figure 1A); neither thumb was obviously dominant in all aspects, and there was a difference in length between the two thumbs that were intended to be combined together (Figure 1B); and there was a distance in space between the two thumbs that also had different defects, such as short and slender bulks, unstable joints, and nail deformities (Figure 1C).

Operation process
Detailed clinical assessments and radiological examinations are essential for hand surgeons to design an ideal reconstruction plan for duplicated thumbs. The clinical assessment addresses the soft tissue bulk and shape, the integrity of the nail folds, and the stability and the range and motion (ROM) in both interphalangeal joints (IPJs) and metacarpophalangeal joints (MCPJs). An X-ray of the opposite thumb is beneficial, especially when accompanied by the findings of the clinical examination to obtain as accurate information as possible. Ultrasound may assist in the assessment of neurovascular conditions of the thumbs but is not employed routinely.

The surgery was performed under general anesthesia and tourniquet control. Generally, the procedures are divided into three steps. First, preoperative assessments must determine which digit will provide the best thumb with an essentially stable osteoarticular structure, especially an adequate carpometacarpal joint. Second, tense skin relaxation and first web space broadening, partial cutoff of the deformed nail, diverse transverse or longitudinal osteotomy of metacarpal or phalangeal bones, and K-wire internal fixation are performed on the chosen thumb (Figures 2-4). Then, the defects are evaluated in all aspects. Finally, pedicle complex tissue flaps, according to the defects in all aspects, are carefully designed and elevated from the abandoned thumb to reconstruct the chosen thumb. Clinical manifestations, operating methods, and follow-up results are discussed by way of typical case reports in the following report.

Postoperative treatment
Spasmolysis and blood circulation-promoting drugs were routinely applied after the operation, and the digit was bandaged with external brace fixation. Six weeks after surgery, the internal fixation K-wires and external fixation were removed. Rehabilitation activities were allowed, including active and passive functional exercises of the operated digit.

Efficacy evaluation
The survival of pedicled tissue flaps was observed after the operation. The length and diameter of the reconstructed thumb and the contralateral healthy thumb, the finger
Figure 1 Three types of the included patients. A: Preservation of thumb body involving palmar skin defects of fingernails; B: Preservation of thumb body involving different lengths of fingernails; C: Preservation of thumb body narrow lateral deviation of fingernails.

Figure 2 Surgical procedure of transfer flap. A: The excision of finger and flap was designed and transferred locally; B: The excision of nail flap was designed and transferred locally; C: The excision of composite tissue flap was designed and transferred locally.

Figure 3 Operation process. A: Longitudinal ridge after nail fusion; B: The nail flap was pushed far away to maintain the length of the finger.

strength line, the stability and mobility of the MCPJ and IPJ, and the appearance of the nail were observed and recorded. These objective indexes were evaluated by the Horri Tata score system (Table 1) and the ALURRA score system[11] (Table 2). Meanwhile, the satisfaction of the parents of the children with the reconstruction of thumb appearance (aesthetic) and function was recorded.

Statistical analysis
All patients with thumb duplication were treated by pedicle complex tissue flap transfer. Sex distribution, weight, types of duplicated thumb, and nail deformity information were provided. Parametric data, including age, follow-up, range of motion and alignment deviation of the IPJ and MCPJ, aesthetic aspects including circumference, length, nail size, and nail deformities, ALURRA score, and Tata score are described as the mean ± SD.

RESULTS

Patient demographics
In total, 15 patients involving eight males and seven females, were included in this
Table 1 TATA criteria of postoperative evaluation

<table>
<thead>
<tr>
<th>Score</th>
<th>2</th>
<th>1</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range of motion(^1)</td>
<td>&gt; 70%</td>
<td>50%-70%</td>
<td>&lt; 50%</td>
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<tr>
<td>Instability</td>
<td>-</td>
<td>No instability</td>
<td>Instability</td>
</tr>
<tr>
<td>Deformity</td>
<td>&lt; 10°</td>
<td>10°-20°</td>
<td>&gt; 20°</td>
</tr>
<tr>
<td>Cosmetic</td>
<td>Acceptable</td>
<td>Moderate deformity</td>
<td>Substantial deformity</td>
</tr>
</tbody>
</table>

\(^1\)Compared with the opposite side.
Results over or equal to 5 were categorized as good, 3 and 4 as fair, and less than 3 as poor.

Table 2 ALURRA criteria

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Alignment</td>
<td>&lt; 10°</td>
</tr>
<tr>
<td>Ulnar instability</td>
<td>&lt; 5°</td>
</tr>
<tr>
<td>Radial instability</td>
<td>&lt; 5°</td>
</tr>
<tr>
<td>Range of motion</td>
<td>&lt; 70°</td>
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<tr>
<td>Aesthetical aspects</td>
<td>75-100</td>
</tr>
</tbody>
</table>

A total score above 20 is categorized as good, between 13 and 20 as moderate, and less than 13 as poor. IP: Interphalangeal; MCP: Metacarpophalangeal.

study, with an average age at surgery of 13 mo (range: 10 mo to 2 years old). All 15 patients were followed from 20 to 60 mo, with a mean of 42 mo (Table 3). Due to the absence of cooperation, outcomes were measured using appearance, parent satisfaction, and ROM.

**Efficacy evaluation**

All pedicle complex tissue flaps survived well after the operation with no arteriovenous crises. The reconstructed thumbs in 14 patients obtained a good longitudinal axis, with appropriate length and girth matching the healthy contralateral thumbs. The reconstructed thumb girth of one child was larger than the contralateral thumb, which was further improved upon treatment by plastic surgery during the surgery for removing the internal fixation. The appearance of the nail was good, though there were various degrees of ridging of the nail after operation of the two halves in some patients (Figure 3). All the MCPJs and IPJs except for one joint of one thumb remained stable after the primary surgery. One case required revision due to IPJ radial collateral instability. The active and passive mobility levels of the MCPJs were good, the
### Table 3 Demographic data of the included patients

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
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<th>Age (mo)</th>
<th>Weight (kg)</th>
<th>Wassel type</th>
<th>Follow-up</th>
<th>ALURRA criteria</th>
<th>TATA criteria</th>
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<tr>
<td></td>
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<td>Instability</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
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<td>MCPJ (radial)</td>
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<td>12</td>
<td>10</td>
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<td>11</td>
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<tr>
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<td>V</td>
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<td>9</td>
<td>V</td>
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<td>9</td>
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<td>15</td>
<td>V</td>
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<tr>
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<td>F</td>
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<td>12</td>
<td>10.5</td>
<td>VI</td>
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</tr>
</tbody>
</table>
mobility of the interphalangeal joints was diminished, and the active mobility was significantly diminished. Compared with the non-operated side, the length of the operated thumb was approximately 82.9%, the girth was 90.7%, and the nail width was 83.3%. The mean ROMs were 62.1% of the unaffected thumb in the IPJ and 78.3% in the MCPJ. MCPJ malalignment showed statistically significant negative correlations with the Tada, and ALURRA scores. Most of the parents were satisfied with the cosmetic and functional results of the reconstructed thumb. The mean ALURRA score was 21.8 (range: 20-24), and the Tada score was 6.9 (range: 5-8).

**DISCUSSION**

The basic goals of reconstruction surgery for thumb duplication are to obtain good appearance and function [12,13]. There are many important factors to be considered in the process of reconstruction surgery, including good finger line, sufficient circumference and length of finger, stable metacarpophalangeal and interphalangeal joints, adequate blood circulation, and keen sense function [14,15]. In the case of the poor development of the preserved thumb or even the poor development of both thumbs, it is necessary to cut a part of the tissue structure from the resected thumb to make up for the defects of the preserved thumb.

The Bilhaut-Cloquet procedure and its modified operation provided a sound solution to these situations involving symmetrical or essentially symmetrical compound thumbs, slender little finger bodies, joint deflection and instability, lateral deviation of the nail, and skin defects [16-19]. If the distance between the two thumbs is far or if they are different in length, BC and its modified operation have difficulty achieving good thumb results. Therefore, according to the condition of retaining the tissue deficit of the thumb, a tissue flap pedicled with the neurovascular bundle of the finger can be designed and cut from the resected finger for long-distance transfer, which can effectively solve the above problems. Our study included 15 cases with a long distance between or different lengths of the two thumbs. We used the above method for surgical treatment, and good clinical outcomes were achieved during the follow-up.
When the two thumbs had different lengths (Figure 1B), we usually used the shorter thumb with pedicle extension and then combined it with the other thumb to keep the thumb length as long as possible (Figure 3B). The case presented in this study demonstrated that the pedicle can effectively extend to the distal end up to 1 cm, which is enough to compensate for the difference in length between the two thumbs. The skin defect of the proximal pedicle caused by the extension of the thumb to the distal end can be effectively covered by local skin.

When the distance between the two thumbs was relatively far, especially when combined with a narrow mouth in the thumb web (Figure 4A), a tissue flap pedicled with the digital nerve and vascular bundle for a longer distance transfer was used to achieve the combination of the two thumbs (Figure 4B). To achieve the distant transfer of pedicled tissue flaps, the vascular pedicle often needs to be free to the proximal end to reach the level of the metacarpal base. If the tissue mass is large, it can be transferred with a piece of dorsal reflux vein. A transverse design should be avoided in the incision at the thumb web to prevent contracture scarring.

In the process of bone joint splicing, especially the IPJ, epiphyseal plate butt joint and joint face joint connections were often contradictory. To preserve the growth potential of the phalanges, the epiphyseal plate butt joint had priority in handling and subsequently repairing the surface of the joint. In the follow-up cases, although the active and passive ranges of motion of the interphalangeal joint decreased, the joint was stable with a good holding function.

Nail splicing is an important step in the process of correcting compound thumb deformities. Tien et al[20] and Wang et al[21] performed an in-depth follow-up investigation and formulated the evaluation criteria in detail. To achieve enough width and good radians of regenerated nails and to prevent the occurrence of longitudinal ridges in the middle of nails, longitudinal oblique osteotomy of the distal phalanx can achieve a good arc fit of the nail bed. If the original nail is too narrow, we usually butt sutures after removing the nail and peeling off the nail bed from the upper part of the phalanx on the basis of the abovementioned treatment. In the follow-up, the regenerated nails achieved a good appearance. In conclusion, distal transfer of pedicled composite tissue flaps from thumb resection can effectively compensate for a variety of tissue defects of the thumb to achieve good therapeutic effects.

CONCLUSION
Harvesting a pedicle flap from the severed thumb is a safe and reliable procedure. Defects of the preserved thumb, such as the skin, nail, and bone, can be effectively restored with the complex tissue flap.

ARTICLE HIGHLIGHTS
Research background
Thumb polydactyly is one of the most common congenital hand deformities, and the Bilhaut-Cloquet procedure or a modified one is often used. However, controversy
remains over the rare instances in which both thumbs are not of similar length or far apart in distance.

**Research motivation**

Bilhaut-Cloquet procedure or a modified one is often used for thumb polydactyly. However, controversy remains over the rare instances in which both thumbs are not of similar length or far apart in distance.

**Research objectives**

To evaluate the clinical outcomes of pedicle complex tissue flap transfer in the treatment of duplicated thumbs with unequal size.

**Research methods**

We performed a cross-sectional study of patients who underwent duplicated thumb reconstruction by pedicle complex tissue flap transfer from January 2014 to December 2020.

**Research results**

An appropriate volume with a stable joint and good appearance was obtained in 14 reconstructed thumbs. The mean ALURRA score was 21.8 (range: 20-24), and the Tada score was 6.9 (range: 5-8). Compared with the non-operated side, the length of the operated thumb was approximately 95%, the girth was 89%, and the nail width was 82.9%. The mean ranges of motion were 62.1% of that of the unaffected thumb in the interphalangeal joint and 78.3% in the metacarpophalangeal joint.

**Research conclusions**

Harvesting a pedicle flap from a severed thumb is a safe and reliable procedure. Defects of the preserved thumb, such as the skin, nail, and bone, can be effectively restored using the complex tissue flap.

**Research perspectives**

Pedicle complex tissue flap transfer should be the initial management strategy for patients with duplicated thumbs with unequal size. In the future, more controlled studies with multicenter samples will be needed to confirm this finding.

**REFERENCES**

Wang DH et al. Pedicle complex tissue flap transfer


Retrospective Study

Minimally invasive surgery vs laparotomy in patients with colon cancer residing in high-altitude areas

Duo-Ji Suo Lang, Yang-Zhen Ci Ren, Zha-Xi Bian Ba

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Author contributions: Suo Lang DJ and Ci Ren YZ designed this retrospective study; Suo Lang DJ wrote this paper; Suo Lang DJ, Ci Ren YZ and Bian Ba ZX were responsible for sorting the data.

Institutional review board statement: The study was reviewed and approved by the People’s Hospital of Tibet Autonomous Region Institutional Review Board (Approval No. ME-TBHP-21-KJ-025).

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: Nothing to disclose.

Data sharing statement: No additional data are available.

Country/Territory of origin: China

Specialty type: Gastroenterology and Hepatology

Provenance and peer review: Original Article

Abstract

BACKGROUND
Colon cancer is associated with a higher incidence among residents in high-altitude areas. Hypoxic environment at high altitudes inhibits the phagocytic and oxygen-dependent killing function of phagocytes, thereby increasing the inflammatory factors, inhibiting the body’s innate immunity and increasing the risk of colon cancer.

AIM
To examine the effect of minimally invasive surgery vs laparotomy in patients with colon cancer residing in high-altitude areas.

METHODS
Ninety-two patients with colon cancer in our hospital from January 2019 to February 2021 were selected and divided into the minimally invasive surgery and laparotomy groups using the random number table method, with 46 patients in each group. Minimally invasive surgery was performed in the minimally invasive group and laparotomy in the laparotomy group. Operative conditions, inflammatory index pre- and post-surgery, immune function index and complication probability were measured.

RESULTS
Operative duration was significantly longer and intraoperative blood loss and recovery time of gastrointestinal function were significantly less (all \( P < 0.05 \)) in the minimally invasive group than in the laparotomy group. The number of lymph nodes dissected was not significantly different. Before surgery, there were no significant differences in serum C-reactive protein, interleukin-6 and tumor necrosis factor-\( \alpha \) levels between the groups, whereas after surgery, the levels were
INTRODUCTION

Colon cancer is a multiple malignant tumor of the digestive system that is associated with a higher incidence among residents in high-altitude areas. People living in these areas like to eat dairy products and red meat but consume less fruits and vegetables, so the risk of colon cancer is greater, which poses a great threat to the physical and mental health of these patients and to their quality of life[1]. A study by Frisancho et al[2] found that the hypoxic environment at high altitudes inhibits the phagocytic and oxygen-dependent killing function of phagocytes, thereby increasing the number of inflammatory factors such as interleukin-6 (IL-6), inhibiting the body’s innate immunity and increasing the risk of colon cancer. In recent years, due to the increasing incidence of colon cancer, the safe and effective treatment have become a research hotspot[3,4].

If colon cancer is not treated timely and effectively, it results in lesion metastasis, making treatment more difficult, with worse prognosis[5,6]. Therefore, after the diagnosis of colon cancer, timely selection of the best surgical plan is vital in the treatment of these patients. Surgery is an important measure in the current clinical treatment of colon cancer, and laparotomy and laparoscopic minimally invasive surgery are commonly used[7,8]. Complete circumferential mesorectal excision is the standard treatment for colon cancer. Traditional laparotomy can be performed under direct vision and achieves certain results. However, the larger surgical trauma and higher complication probability are not conducive to the body's functional recovery[9-11]. With improvements in minimally invasive technology and the popularization of this concept, laparoscopic surgery has been applied as an important clinical minimally invasive surgery in colon cancer. This surgery can reduce surgical trauma and shorten recovery time, which play an important role in the treatment[12-14].

Here, we aimed to study the application of minimally invasive surgery and laparotomy in patients with colon cancer residing in high-altitude areas.
MATERIALS AND METHODS

General information
This study was approved by the ethics committee of our hospital. Ninety-two patients with colon cancer in our hospital from January 2019 to February 2021 were selected and divided into the minimally invasive and laparotomy groups using the random number table method, with 46 patients in each group.

In the minimally invasive group, there were 25 males and 21 females. The average age was 57.56 ± 10.91 (range: 44–71) years. In 22 patients, the Dukes stage was stage A, for 19 patients, stage B and for 5 patients, stage C. The tumor diameter was between 3.8 cm and 6.2 cm, with an average of 5.06 ± 1.10 cm. The tumor location was the cecum (in 27 patients), colon ascendens (14 patients), hepatic flexure of the colon (3 patients) and colon transversum (2 patients).

In the laparotomy group, there were 29 males and 17 females. The average age was 59.06 ± 12.11 (range: 42–76) years. In 24 patients, the Dukes stage was stage A, in 18 patients, stage B and in 4 patients, stage C. The tumor diameter ranged from 4.1 cm to 6.5 cm, with an average of 5.31 ± 1.05 cm. The tumor location was the cecum (in 24 patients), colon ascendens (15 patients), hepatic flexure of the colon (3 patients) and colon transversum (4 patients).

Selection criteria
Patients were included if: (1) The disease met the diagnostic criteria of colon cancer in surgery[15]; (2) The tumor had been confirmed via colonoscopy and other examinations; (3) The tumor had not been preoperatively treated; (4) The tumor could be resected after computed tomography and evaluation; (5) They lived in high-altitude areas; and (6) They provided informed consent to this study. Patients with: (1) Other benign and malignant tumors; (2) Metastatic lesions; (3) Cardiopulmonary dysfunction and inability to fully tolerate surgery; (4) Anemia and malnutrition; (5) Mental disorders; and (6) Poor compliance and inability to cooperate with investigators to complete the investigation were excluded.

Laparotomy group
In this group, laparotomy was performed. Patients were placed in the supine position for general anesthesia. The location of the tumor and surgical incision were determined. The incision was selected near the rectus abdominis, and the upper and lower intestinal tubes and vessels at the mesangial root of the tumor were ligated. The affected intestine was dissociated, the mesentery and intestine were dissected, and the intestine was sutured and fixed. The intestinal tube was clipped approximately 5 cm below the mass to check the blood supply. The enterocoelis was cleaned, a drainage tube was placed, and sutures were applied.

Minimally invasive group
In this group, minimally invasive surgery (laparoscopic radical operation) was performed. Patients were assisted to take the supine position for general anesthesia, and CO₂ artificial pneumoperitoneum was established to maintain the pneumoperitoneum pressure at 13–15 mmHg. The laparoscope and trocar were placed to investigate the internal conditions of the enterocoelis, including the lesion location, volume, metastasis and invasion. According to the treatment requirements, the colonic mesentery, peritoneum and omentum were dissociated, and the colonic mesentery was dissociated to the corresponding vascular root of the lesion. A small incision was made in the middle of the abdominal wall, and the mesangial membrane and blood vessels of the intestine were separated. If the patient had colonic convoluted tumor, the pancreatic head, gastric omentum vessels and lymph nodes under the pylorus were simultaneously removed to remove the affected tissue and tumor. The distal colon was anastomosed using a stapler and returned to the enterocoelis with intermittent suture between the peritoneum and mesentery. The incision was cleaned, and sutures were applied. Both groups were administered antibiotics for infection prevention and control after surgery.

Data analyze
The surgical conditions in the two groups, including duration, intraoperative blood loss, recovery time of gastrointestinal function and number of lymph nodes dissected were measured. The inflammatory factor [C-reactive protein (CRP), IL-6, tumor necrosis factor-α (TNF-α)] levels were measured before and after surgery in the groups. We extracted 4 mL of fasting venous blood and centrifuged it at 3000 r/min
for 15 min. The supernatant was taken and analyzed using enzyme-linked immunosorbent assay. The immune function index (CD3+, CD4+, CD4+/CD8+) before and after surgery was determined. Blood samples were taken and measured using the FACSCANTO II flow cytometry (BD Company, United States). The complication probability in the two groups was analyzed.

Statistical analysis
SPSS22.0 was used for data analysis. The measurement data were expressed as means ± SD and were compared using t test. The enumeration data were expressed as n (%) and were compared using the χ² test. P < 0.05 indicated a statistically significant difference.

RESULTS
Clinical data for gender, age, Dukes stage, tumor diameter and tumor location were comparable between the groups (P > 0.05).

Comparison of surgical conditions
The operative duration was longer in the minimally invasive group (189.39 ± 20.38 min) than in the laparotomy group (145.62 ± 16.37 min), whereas intraoperative blood loss and recovery time of gastrointestinal function were less in the minimally invasive group than in the laparotomy group (101.26 ± 18.64 mL and 2.55 ± 0.39 d vs 153.22 ± 23.39 mL and 3.37 ± 0.46 d, respectively, P < 0.05). The number of lymph nodes dissected was not significantly different between the minimally invasive (14.26 ± 3.15) and laparotomy (15.51 ± 3.49, P > 0.05) groups (Table 1).

Comparison of inflammatory factors before and after surgery
Before surgery, there were no significant differences in the serum CRP, IL-6 and TNF-α levels between the groups (9.18 ± 3.38 mg/L, 122.33 ± 16.19 ng/mL and 76.37 ± 11.25 pg/mL vs 8.97 ± 3.60 mg/L, 119.64 ± 18.02 ng/mL and 78.62 ± 13.18 pg/mL, respectively, P > 0.05); after surgery, these levels were significantly higher in the minimally invasive group than in the laparotomy group (26.98 ± 6.91 mg/L, 146.38 ± 11.23 ng/mL and 83.51 ± 8.69 pg/mL vs 41.15 ± 8.39 mg/L, 186.79 ± 15.36 ng/mL and 110.65 ± 12.84 pg/mL, respectively, P < 0.05) (Table 2).

Comparison of the immune function index before and after surgery
Before surgery, there were no significant differences in CD3+, CD4+ and CD4+/CD8+ counts between the groups (61.23% ± 6.45%, 40.26% ± 4.11% and 5.96% ± 3.94% vs 63.09% ± 5.89% and 39.64% ± 5.89% and 1.58 ± 0.50, respectively, P > 0.05); after surgery, the counts were lower in both groups, with CD3+, CD4+ and CD4+/CD8+ counts being significantly higher in the minimally invasive group than in the laparotomy group (55.61% ± 4.39%, 35.45 ± 3.67% and 1.30 ± 0.35 vs 49.68% ± 5.33%, 31.21% ± 3.25% and 1.13 ± 0.30, respectively, P < 0.05) (Table 3).

Comparison of complication probability
The complication probability was significantly lower in the minimally invasive group (4.35%) than in the laparotomy group (17.39%, P < 0.05, Table 4).

DISCUSSION
In this study, we performed minimally invasive surgery and laparotomy for the treatment of colon cancer in patients from our hospital who were residing in high-altitude areas. The operative duration was significantly longer in the minimally invasive group, but there was no significant difference in the number of lymph nodes dissected between the groups. The amount of intraoperative blood loss was less and recovery time of gastrointestinal function was shorter in the minimally invasive group. Biondo et al.[16] reported no significant difference between laparoscopic and laparotomy in lymph node dissection in patients with colon cancer. Although laparoscopic surgery takes longer, it is associated with less blood loss and shorter recovery time of gastrointestinal function. This is consistent with the findings from this study, suggesting that minimally invasive surgery can achieve the same effect on lymph node dissection as open surgery in patients with colorectal cancer residing in high-altitude areas.
Table 1 Surgical conditions in the two groups (mean ± SD)

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of cases</th>
<th>Surgery duration (min)</th>
<th>Intraoperative blood loss (mL)</th>
<th>Gastrointestinal function recovery time (d)</th>
<th>Number of lymph node dissection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimally invasive</td>
<td>46</td>
<td>189.39 ± 20.38</td>
<td>101.26 ± 18.64</td>
<td>2.55 ± 0.39</td>
<td>14.26 ± 3.15</td>
</tr>
<tr>
<td>Laparotomy group</td>
<td>46</td>
<td>145.62 ± 16.37</td>
<td>153.22 ± 23.39</td>
<td>3.37 ± 0.46</td>
<td>15.51 ± 3.49</td>
</tr>
<tr>
<td>t value</td>
<td>11.36</td>
<td>11.783</td>
<td>9.222</td>
<td>0.000</td>
<td>1.803</td>
</tr>
<tr>
<td>P value</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.075</td>
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</tr>
</tbody>
</table>

Table 2 Inflammatory factors before and after surgery in the two groups (mean ± SD)

<table>
<thead>
<tr>
<th>Time</th>
<th>Group</th>
<th>n</th>
<th>CRP (mg/L)</th>
<th>IL-6 (ng/mL)</th>
<th>TNF-α (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before Surgery</td>
<td>Minimally invasive</td>
<td>46</td>
<td>9.18 ± 3.38</td>
<td>122.33 ± 16.19</td>
<td>76.37 ± 11.25</td>
</tr>
<tr>
<td>Laparotomy group</td>
<td>46</td>
<td>8.97 ± 3.60</td>
<td>119.64 ± 18.02</td>
<td>78.62 ± 13.18</td>
<td></td>
</tr>
<tr>
<td>t value</td>
<td>0.288</td>
<td>0.753</td>
<td>0.881</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>0.774</td>
<td>0.453</td>
<td>0.381</td>
<td></td>
<td></td>
</tr>
<tr>
<td>After Surgery</td>
<td>Minimally invasive</td>
<td>46</td>
<td>26.98 ± 6.91</td>
<td>146.38 ± 11.23</td>
<td>83.51 ± 8.69</td>
</tr>
<tr>
<td>Laparotomy group</td>
<td>46</td>
<td>41.15 ± 8.39</td>
<td>186.79 ± 15.36</td>
<td>110.65 ± 12.84</td>
<td></td>
</tr>
<tr>
<td>t value</td>
<td>8.842</td>
<td>14.404</td>
<td>11.872</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CRP: C-reactive protein; IL-6: Interleukin-6; TNF-α: Tumor necrosis factor-α.

Table 3 Immune function indexes in the two groups before and after surgery (mean ± SD)

<table>
<thead>
<tr>
<th>Time</th>
<th>Group</th>
<th>n</th>
<th>CD3⁺ (%)</th>
<th>CD4⁺ (%)</th>
<th>CD4⁺/CD8⁺ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before Surgery</td>
<td>Minimally invasive</td>
<td>46</td>
<td>61.23 ± 6.45</td>
<td>40.26 ± 4.11</td>
<td>1.58 ± 0.50</td>
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<tr>
<td>Laparotomy group</td>
<td>46</td>
<td>63.09 ± 5.96</td>
<td>39.64 ± 3.89</td>
<td>1.62 ± 0.44</td>
<td></td>
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<tr>
<td>t value</td>
<td>1.436</td>
<td>0.743</td>
<td>0.407</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>0.154</td>
<td>0.459</td>
<td>0.685</td>
<td></td>
<td></td>
</tr>
<tr>
<td>After Surgery</td>
<td>Minimally invasive</td>
<td>46</td>
<td>55.61 ± 4.39</td>
<td>35.45 ± 3.67</td>
<td>1.30 ± 0.35</td>
</tr>
<tr>
<td>Laparotomy group</td>
<td>46</td>
<td>49.68 ± 5.33</td>
<td>31.21 ± 3.25</td>
<td>1.13 ± 0.30</td>
<td></td>
</tr>
<tr>
<td>t value</td>
<td>5.825</td>
<td>5.866</td>
<td>2.501</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>0.000</td>
<td>0.000</td>
<td>0.014</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

regions and can reduce surgical trauma and shorten the time for functional rehabilitation. Because laparotomy is mature and can be performed under direct vision, the effect of lymph node dissection is ideal. However, laparoscopic minimally invasive surgery can be performed with the help of endoscopic amplification function, providing surgeons with a clear surgical field. It is beneficial to ensure the precision of anatomical separation, obtain sufficient tumor incisional margin and reduce trauma, which promote body function and recovery time shortening. However, laparoscopic surgery has high requirements for the operator’s skills, and the uterus, small intestine and other adjacent organs during the operation will affect the operation, which prolongs the operation time to a certain extent[17,18].

Invasive surgery can activate the hypothalamic-pituitary-adrenal cortical system and promote the production of TNF-α, IL-6, cortisol and norepinephrine. CRP is also an important indicator for clinical evaluation of the degree of trauma in the body, which can reflect the degree of inflammation in vivo. Our results showed that CRP, IL-6 and TNF-α levels in the minimally invasive group were lower than those in the open
group, which is consistent with the findings from Takemasa et al.[19].

From the microscopic perspective of serum factors, it has been proven that laparoscopic surgery has a higher application value in cases of colon cancer in patients residing in high-altitude regions than open surgery, which can reduce the degree of inflammatory stress response caused by surgical invasive trauma and ensure safe treatment. CD3+, CD4+ and CD4+/CD8+ are important immune cells in the body. CD3+ cells are active cells that can reflect the expression of mature lymphocytes in the peripheral blood. CD4+ cells are helper T cells, whereas CD8+ cells are cytotoxic T cells. CD4+/CD8+ can reflect the immune function of the body. Studies have shown that T cells can mediate cellular immunity \textit{in vivo}, and changes in the function and quantity of T cells are key indicators to evaluate cellular immunity. The stronger the function of T cells after colon cancer surgery, the better it can help patients eliminate residual tumor cells in the body and maintain the body’s immune function[20].

The results of this study showed that CD3+, CD4+ and CD4+/CD8+ levels in the two groups after the surgery were lower than those before surgery, but the levels of all the indicators were higher in the minimally invasive group than in the open group, indicating that laparoscopic surgery imparts less damage to the immune system of patients with colon cancer residing in high-altitude areas than open surgery and is of great significance in the postoperative recovery of these patients’ body functions. This is probably because laparoscopic surgery requires a small incision, which causes less damage to the body, and the inflammatory stress response caused by the invasive operation during the operation is less, which has less impact on the immune system function[21].

In addition, our findings also showed that the incidence of complications was significantly lower in the minimally invasive group than in the laparotomy group. Thus, laparoscopic surgery also has significant advantages in reducing the risk of complication probability in patients with colon cancer residing in high-altitude areas, which can ensure the effectiveness and safety of treatment of colon cancer in these patients.

**CONCLUSION**

Laparoscopic surgery for colon cancer in patients residing in high-altitude areas can reduce surgical trauma, alleviate inflammatory response and immune dysfunction caused by invasive surgery and thereby shorten the recovery time of body functions and reduce the risk of complications in these patients.

**ARTICLE HIGHLIGHTS**

**Research background**

Hypoxic environment at high altitudes increases the risk of colon cancer.

**Research motivation**

This study investigated the advantages of laparoscopic surgery in the treatment of colon cancer in the plateau area.

**Research objectives**

The authors aimed to examine the effect of minimally invasive surgery \textit{vs} laparotomy in patients with colon cancer residing in high-altitude areas.
Research methods

Ninety-two patients with colon cancer were included. The surgical conditions in the two groups, including duration, intraoperative blood loss, recovery time of gastrointestinal function and number of lymph nodes dissected, were measured. The inflammatory factor levels were measured before and after surgery in the groups. The immune function index before and after surgery was determined.

Research results

The operative duration was longer in the minimally invasive group than in the laparotomy group, whereas intraoperative blood loss and recovery time of gastrointestinal function were less in the minimally invasive group than in the laparotomy group. After surgery, these levels were significantly higher in the minimally invasive group than in the laparotomy group. The counts were lower in both groups, with CD3+, CD4+, and CD4+/CD8+ counts being significantly higher in the minimally invasive group than in the laparotomy group.

Research conclusions

The results suggest that the laparoscopic surgery for colon cancer in patients residing in high-altitude areas can reduce surgical trauma, alleviate inflammatory response and immune dysfunction caused by invasive surgery and thereby shorten the recovery time of body functions and reduce the risk of complications in these patients.

Research perspectives

The advantages of laparoscopic surgery for patients with other diseases can be explored in the future.

REFERENCES

12. Hirano Y, Hiranuma C, Hattori M, Douden K, Yamaguchi S. Long-term oncological outcomes of


Observational Study

Surgery for chronic pancreatitis in Finland is rare but seems to produce good long-term results

Mikael Parhiala, Juhani Sand, Johanna Laukkarinen

Abstract

BACKGROUND
Abdominal pain in chronic pancreatitis (CP) may require invasive interventions. Surgical procedures are rare, and little is known about the long-term results.

AIM
To study the nationwide frequency of pancreatic surgery for CP in Finland, and postoperative symptoms and quality of life (QoL).

METHODS
All patients in Finland with a diagnosis of CP who had undergone pancreatic surgery during 2000-2008 were selected from a national register. Only patients with CP as an indication for pancreatic surgery were included. Medical records were studied and questionnaires QLQ-C30, PAN26 and AUDIT, and symptom questionnaires were sent out.

RESULTS
During the 9-year period, pancreatic surgery for CP was performed on 30 patients [77% men, median age 45 (21-62) years]. Eighty-three percent underwent endoscopic procedures before surgery. Surgery was performed a median 2 (0-10) years after the original CP diagnosis, and 17% developed postoperative complications. Primary pain relief after surgery was reported in 70% of cases. Need for strong pain medication was lower after surgery. Eight of 21 (38%) returned the questionnaires and 88% reported that surgery had reduced their pain and 63% were almost or entirely pain-free at a median 14 (10-18) years after surgery. QoL results did not differ from those in our control Finnish CP group.

CONCLUSION
Surgery for CP is rare in Finland and most patients had prior endoscopic procedures. Patients who returned the questionnaires reported less pain and good QoL during the 14-year follow-up.

**Key Words:** Surgery; Pain; Chronic pancreatitis; Quality of life; Complication

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**Core Tip:** Our study provides valuable insight on the current state of chronic pancreatitis (CP) surgery for chronic pain in Finland. We included all the CP patients who underwent surgery for CP symptoms during 2000-2008 in Finland. We found that surgery is rare. We estimate that 0.6%-0.8% of CP patients undergo surgery for CP pain, which produces good long-term effects. Opiate usage was reduced after surgery. Most of the patients had undergone endoscopic procedures before surgery. Complications after CP surgery were rare.

**INTRODUCTION**

Chronic pancreatitis (CP) leads to permanent morphological changes in the pancreatic tissue such as ductal lesions and calcifications. Persistent inflammation may cause abdominal pain and also lead to pancreatic insufficiency, seen as secondary diabetes and malnutrition as well as various complications[1-4].

There are several mechanisms behind CP pain. High pressure in the pancreatic ducts due to pseudocysts or strictures may cause pain. High alcohol consumption and smoking may lead to oxidative stress, increasing pain. Exocrine insufficiency may result in low vitamin and antioxidant levels, causing pain. Even pancreatic ischemia may be behind the development and pain of CP[5-9].

Conservative pain treatment is often not enough and invasive treatments such as endoscopic stenting and surgery are needed. Endoscopic treatments, such as pancreatic stenting and celiac plexus interventions, are less invasive than surgery, but the long-term results may be of limited benefit[10-13].

Surgery for CP is planned individually depending on the pancreatic findings. Surgical methods can be classified as pancreatic drainage, pancreatic resection or a combination of these. The earliest surgery for CP was pancreaticoduodenectomy (PD) [14-17]. Duodenum-preserving surgery for CP includes the Frey, Puestow, Berger and Berne modifications, where pancreatic tissue is resected and/or drained and a pancreatojejunostomy is performed using a Roux-Y jejunal loop[18-23].

Surgery for CP is rare and no universal recommendations exist. Some evidence suggests that earlier surgery for CP may improve results. To the best of our knowledge, there are no nationwide data in Finland on the frequency of the various surgical procedures, or on the effect on pain and quality of life (QoL) during long-term follow-up after surgery.

The aim of this study was to investigate the variety of surgical procedures used and their impact during a long-term follow-up on symptoms and QoL in patients operated on for CP nationwide in Finland in 2000-2008.

**MATERIALS AND METHODS**

**Study design and patients**

All the pancreatic resections [Nordic Classification of Surgical Procedures codes JLC* (resection of the pancreas) or JLW96 (other operations on pancreas)] performed in Finland during 2000-2008 for a diagnosis of CP (ICD-10 code: K86.01, K86.1, K86.08,
k86.8 and K86.9) were selected from the Finnish National Institute for Health and Welfare HILMO register. There were 97 patients. After reviewing their medical records, only 30 patients with CP as an indication for pancreatic surgery were included in the final database (Figure 1).

From the patient archives, information was gathered about medical history, time of CP diagnosis, etiology of CP, previous CP treatments, type of current surgical therapy, postoperative complications, possible reoperations, and exocrine and endocrine pancreatic insufficiency. The date of death was recorded on September 22, 2017.

QLQ-C30, PAN-26[24] and AUDIT questionnaires and a nonstandardized questionnaire about pain before and after surgery were sent to the patients.

A previously reported Finnish general CP cohort from 2014-2015 was used as a control for the AUDIT, QLQ-C30 and PAN26 questionnaires[25]. In the control cohort, the median age was 58 (26-95) years, 67% were male and median time after diagnosis was 4 (1-42) years. Around 68% and 58% of patients had alcohol and smoking, respectively, as a risk factor for CP. Calcifications were found in 66% of the patients and ductal lesions were present in half of the patients. Endoscopic procedures were performed on 27% of patients and 9% underwent surgery.

Ethical aspects
The study was approved by the Ethics Committee of Tampere University Hospital, Finland (ETL code R16153). The data from the HILMO register was provided by the Finnish National Institute for Health and Welfare with a license/permission (THL/1854/5.05.00/2012)

Statistical analysis
Data are presented as median (range). The statistical analyses were performed using Pearson’s χ² or Fisher’s exact test. For analysis of the QLQ-C30 and PAN26 questionnaires, the Mann-Whitney U test was used. The EORTEC scoring manual was used for the QLQ-C30 and PAN26 questionnaires, and the responses were scored as 0-100. A higher score on QoL/functioning indicated better QoL and a lower score on symptoms (e.g., pain or insomnia) represented better QoL. P < 0.05 was considered statistically significant.

RESULTS
Thirty patients underwent pancreatic surgery for CP in Finland during the period 2000-2008 and formed the final study cohort.

Surgery was performed in 13 different hospitals; median two (range 1-7) per hospital. Of the patients 77% were men and the median age was 45 (21-62) years. Surgery was performed a median 2 (0-10) years after diagnosis of CP. During the 16 (10-26) years of follow-up, eight patients died, a median 4.5 (0-16) years after surgery. The etiology of CP was alcohol in 60%, while 47% had idiopathic disease. Eighty-seven percent had recurrent episodes of acute pancreatitis (AP).

Half of the patients smoked. All of the smoking patients were on opioids before surgery, compared to 42% in the non-smoking group (P = 0.0004).

Out of the 30 operations performed in the course of 9 years, one was a drainage procedure (Puestow), nine combined resection and drainage, and there were 20 pancreatic resections (16 distal and 4 pylorus-preserving PD/PDs). Fifteen included splenectomies (Figure 2). Out of the combined pancreatic resection and drainages, four were Frey´s procedure, two were Beger´s procedure and three were Puestow´s drainage combined with caudal resection (Figure 3).

Eighty-three percent (n = 25) of the patients had no postoperative complications, 17% (n = 5) developed complications: two had Clavien-Dindo (CD) grade 1 complications; two had CD grade 2 complications and one had CD grade 3b complications. One patient died within 3 wk of surgery; this patient had undergone four prior laparotomies and had intraoperative hemorrhage during surgery for CP.

Seventy percent of the patients had reported primary pain relief after the surgery and 64% of those who had undergone previous endoscopic procedures had experienced primary pain relief and all those with no previous endoscopic procedures had experienced primary pain relief, but the nonendoscopic group was so small that the difference was not significant (P = 0.10). No correlation was seen in time after diagnosis and primary pain relief (P = 0.43) (Figure 2).
Figure 1 Flowchart of patients. The study included all patients who underwent pancreatic surgery for chronic pancreatitis in the whole of Finland in 2000-2008. CP: Chronic pancreatitis.

### Table A

<table>
<thead>
<tr>
<th>Category</th>
<th>Total</th>
<th>Male</th>
<th>Female</th>
<th>Time from diagnosis to surgery median (range)</th>
<th>Follow-up time median (range)</th>
<th>Age when surgery median (range)</th>
</tr>
</thead>
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<td>Calculations</td>
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<td>Ductal lesion</td>
<td>67%</td>
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<tr>
<td>Pseudocysts</td>
<td>57%</td>
<td></td>
<td></td>
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<tr>
<td>Recurrent AP</td>
<td>87%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEI (pre-op vs post-op)</td>
<td>34% vs 67%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Diabetes (pre-op vs post-op)</td>
<td>32% vs 56%</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Opiate use (pre-op vs post-op)</td>
<td>73% vs 37%</td>
<td></td>
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<tr>
<td>Primary benefit from surgery</td>
<td>70%</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Death</td>
<td>27%</td>
<td></td>
<td></td>
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<td>Age after surgery</td>
<td>5.5 (0-16)</td>
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</tr>
<tr>
<td>Age of death</td>
<td>51 (42-63)</td>
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</table>

Figure 2 Demographics and outcome of chronic pancreatitis surgery. A: Demographics of the surgical chronic pancreatitis patients; B: Surgical chronic pancreatitis patients grouped based on pain relief approximately one year after surgery. AP: Acute pancreatitis; PEI: Pancreatic exocrine insufficiency; DM: Diabetes mellitus.

Pancreatic exocrine insufficiency (PEI) was present in 34% of the patients preoperatively and in 67% postoperatively. Diabetes was seen in 32% of the patients preoperatively and in 56% postoperatively. When comparing CP patients who had surgery (n = 25) to the Finnish general CP cohort who did not have pancreatic surgery (n = 195) and had a median time after diagnosis of 5-43 years, the frequency of PEI was similar (surgery group 67% vs nonsurgical group 63%, P = 0.679). Also, the frequency of diabetes was the same in CP patients not undergoing pancreatic surgery (61%) as in patients undergoing surgery (56%; P = 0.586). Seventy-three percent of the patients were on opioids before surgery and 37% after surgery (P = 0.004). Opioid use for the control group was not recorded (Figure 4).

Endoscopic retrograde cholangiopancreatography was performed on 83% of the patients prior to surgery. Twenty percent had already undergone prior pancreatic surgery for pancreatic pseudocyst complications. When comparing these parameters to the Finnish general CP cohort, significantly more endoscopic procedures (83% vs 27%, P < 0.0001) and recurrent AP (87% vs 67%, P = 0.007) were seen in these surgically treated CP patients than in the overall CP patients in the control group (Figure 4).
Figure 3 Distribution of chronic pancreatitis surgery in Finland. A: Type of surgery for chronic pancreatitis. Most operations involved a pancreatic resection (pancreaticoduodenectomy or a distal resection); B: Type of surgical operations in detail. CP: Chronic pancreatitis.

Figure 4 Surgical chronic pancreatitis patients compared to control population, which included nonsurgical chronic pancreatitis patients from the Finnish chronic pancreatitis cohort from 2014 to 2015 (n = 233). There was more recurrent acute pancreatitis and prior endoscopic procedures in the chronic pancreatitis patients who underwent surgery. Pancreatic insufficiency and diabetes were similar between the groups. CP: Chronic pancreatitis; AP: Acute pancreatitis; PEI: Pancreatic exocrine insufficiency; DM: Diabetes mellitus.

Out of the 21 patients asked to complete the questionnaires, eight (38%) returned the QoL questionnaires (QLQ-C30 and Pan-26) and the AUDIT questionnaire. There was no significant difference between the responders and nonresponders in gender, pancreatic calcifications, PEI, recurrent AP or alcohol-related etiology. All the patients who responded had a history of smoking and 63% continued smoking compared to 35% among the nonrespondent patients (P = 0.003).

Of the CP patients who responded, 88% reported that the surgery helped their pain and 63% were almost or entirely pain-free 14 (10-18) years after surgery. The AUDIT questionnaire median was 4 (0-28) points, and in the control CP population, the AUDIT score median was 3 (0-39) points (P = 0.764).

When comparing the QLQ-C30 and PAN26 responses to the Finnish general CP cohort (Figure 5) the nonsurgery group had more pain, pancreatic pain and hepatic symptoms but this was not significant (P = 0.869, P = 0.970 and P = 0.379). Since all the responding CP patients undergoing surgery were smokers, we compared them to those in the Finnish general CP cohort who had been smoking.

DISCUSSION

Surgery for CP is rare and no nationwide data with long-term follow-up after surgery are available. Our aim was to find out how common CP surgery is and what the long-term effects on CP patients are. We found that surgery for CP is rare but seems to give long-term pain relief in CP and reduces opiate use.

Approximately three operations for CP pain were performed per year in the whole of Finland. We estimate that 0.6%-0.8% of CP patients undergo surgery for CP pain.
Most of the surgical interventions in CP are for treatment of complications (such as pseudocyst infections, hemorrhage and bowel obstruction), or due to suspicion of malignancy. Overall, pancreatic surgery for CP is rare in Northern Europe: < 10%, compared to studies from North America and Hungary, reporting 20% pancreatic surgery in the CP population[26-28]. Most patients had already undergone endoscopic procedures; some of them multiple times. In our study, patients with no previous endoscopic procedures had better pain relief (64% vs 100%) even though the difference was not significant due to the number patients with no previous endoscopies. It seems that in Finland surgical procedures are only considered after endoscopic means have been already tried. Thirty-four percent percent already had preoperative PEI, indicating advanced CP. Retrospective studies have shown that pancreatic surgery for pancreatic duct decompression is more cost-effective than endoscopy[29,30].

During the time of the study, CP pancreatic surgery was spread over many hospitals in Finland, 13 in total — compared to five centers at present. Most of the patients underwent endoscopic procedures before the operation. The procedures performed were also heterogeneous. In our study there was no correlation in the timing of the surgery and primary pain relief but most of the operations were performed within 3 years of diagnosis (74%). A few retrospective studies have reported that earlier CP surgery (< 3 years after diagnosis) improves the outcome and is also safe. In a prospective, multicenter randomized controlled trial (ESCAPE trial), surgery was reported to produce better outcomes when performed early enough before endoscopic procedures. In CP, the pancreas tends to be harder due to fibrosis, which can lead to fewer postoperative pancreatic fistulas than in a soft normal pancreas. Compared to reports in Europe and North America, the low percentage of CP surgery in Finland suggests that CP patients are operated on too seldom in Finland, which could be due to advances in endoscopic procedures or to a high threshold for performing pancreatic surgery on a benign disease[31-35].

Most of the patients in our study used opioids before surgery, and surgery reduced the need for opioids. Perhaps when opioids are needed surgery should be considered. Thirty-six percent of the patients had opioids after surgery and this could be due to opioid tolerance and addiction. Preoperative opioid use, persistent pain (3 mo) and previous surgery have been shown to be risk factors for postoperative pain in abdominal surgery. Chronic use of opioids in abdominal pain such as in CP can cause hyperalgesia in which abdominal pain paradoxically may become more severe[36-39].

Half of the CP patients undergoing surgery were smokers and they took significantly more opioids before surgery. Smoking has been reported to impair the outcome of pancreatic surgery and QoL[40]. Cessation of smoking and opioid use should be considered before pancreatic surgery for CP.

There was no significant difference in PEI, diabetes or QLQ responses between CP patients undergoing surgery and a Finnish control CP group, even though it seems that the CP patients who underwent pancreatic surgery were a selected patient group with more severe pancreatitis, since they had significantly more endoscopic procedures (83% vs 27%, $P < 0.0001$) and recurrent AP (87% vs 67%, $P = 0.023$) than the
control CP group. Nonoperated and operated CP patients had approximately the same amount of PEI. Surprisingly, diabetes is more common in CP patients without pancreatic surgery. This could be due the decompressing surgery influencing the progression of pancreatitis and slowing pancreatic insufficiency[41,42].

The rate of idiopathic pancreatitis is high in patients who have surgery. In some cases, it could be due to the difficulty in differencing benign pancreatic masses and malignant tumors, which could affect the decision for surgery[43-45].

The strength of our study is that it involved all the CP patients in Finland. We made a broad selection and only included patients with CP diagnosis and surgery performed for CP pain. To the best of our knowledge, no national study on CP surgery had been published earlier. In spite of the small population, our study provides a valuable description of CP patients who undergo surgery for CP.

The limitations of this study were the small patient number and low response rate of 38%, which is approximately the same as in an earlier study[25]. We gathered the medical histories retrospectively, and one was lost because the patient was deceased, and the record had been deleted. Smoking and alcohol consumption were not always recorded accurately, so presumably these may have been more common.

**CONCLUSION**

Surgery for CP is rare in Finland, but seems to produce good long-term results. Opiate usage was reduced after surgery. Most of the patients had undergone endoscopic procedures before surgery. Complications after CP surgery were rare. More studies are needed on the timing of CP surgery to ensure maximum benefit for patients.

**ARTICLE HIGHLIGHTS**

**Research background**

Chronic pancreatitis (CP) may need invasive surgical interventions. There is no current knowledge of long-term outcomes and prevalence of surgery for CP.

**Research motivation**

We wanted to investigate the current state of pancreatic surgery in Finland for CP.

**Research objectives**

Our objective was to find long-term outcomes of patients who have pancreatic surgery for CP pain in Finland.

**Research methods**

We gathered all CP patients who had pancreatic surgery in Finland in 2000-2008 via the Finnish National Institute for Health and Welfare registry. We gathered information about the time of CP diagnosis, etiology of CP, previous CP treatments, type of current surgical therapy, postoperative complications, possible reoperations, and exocrine and endocrine pancreatic insufficiency.

**Research results**

We found that surgery for CP is rare in Finland but most patients (70%) are pain free after surgery. Opiate usage was less after surgery.

**Research conclusions**

CP surgery is rare and produces good long-term results in CP patients.

**Research perspectives**

Our study was limited because of the small number of patients but we provide a long 16-year follow-up and our study contains all of CP patients in Finland who had pancreatic surgery.


Observational Study

Association of overtime work and obesity with needle stick and sharp injuries in medical practice

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Author contributions: Chen YH and Yeh CJ conceived and designed this manuscript; Jong GP and Yeh CJ analyzed and interpreted the data of this study; Chen YH wrote the original draft; Jong GP and Yeh CJ reviewed and edited the manuscript; Jong GP and Yeh CJ also share equal contribution; all authors were contributed to drafting and/or revising the article, and all authors approved the final version to be published.

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STROBE statement: The authors have read the STROBE statement, and the manuscript was prepared.

Abstract

BACKGROUND
Needle stick and sharps injuries (NSIs) may cause infections among medical personnel. Obesity and overtime work among medical personnel increase the incidence of work injuries.

AIM
To investigate whether overtime work and obesity increase the risk of NSIs.

METHODS
This cross-sectional study used the data of 847 hospital personnel, including 104 doctors, 613 nurses, 67 medical laboratory scientists, 54 specialist technicians, and nine surgical assistants. Of them, 29 participants notified the hospital of having at least one NSI in 2017. The data collected included age, overtime work, body mass index, medical specialty such as doctor or nurse, and professional grade such as attending physician or resident. The $\chi^2$ and Fisher’s exact tests were used to compare categorical variables. Multiple logistic regression analysis and the Sobel test were used to assess the risk of NSIs.

RESULTS
Overtime work, body weight, and medical specialty were significantly associated with NSIs ($P < 0.05$). After adjustment for risk factors, heavy overtime work was an independent risk factor for NSIs, and healthy body weight and nursing specialty were independent protective factors against NSIs. After adjustment for risk factors, medical personnel with healthy body weight has half as many NSIs as
INTRODUCTION

Needlestick and sharp injuries (NSIs) carry the risk of various infections, such as hepatitis B, hepatitis C, and human immunodeficiency virus (HIV) infections[1,2]. In 2000, occupational exposure to percutaneous injuries caused by medical personnel resulted in 16000 cases of hepatitis C, 66000 cases of hepatitis B, and 1000 cases of HIV worldwide[3]. The mean number of NSIs per 100 occupied beds per year was 4.8–7.6 from 2009 to 2011 in Japan[4]. Poor organizational climate and high workloads are associated with NSIs and near-misses in nurses[5]; however, the incidence of NSIs remains higher among doctors, commonly due to stress or overwork, followed by careless attitude[6]. This careless attitude can be effectively reduced by providing preventive education[7-10] and supplying protective equipment for procedures such as intravenous access or blood draws[5]. Some occupational factors, such as long working hours and overtime, can increase the risk of NSIs among medical personnel[11,12]; the risk of work-related injuries due to overtime has also been observed in other occupations[13]. According to the Survey of Occupational Injuries and Illnesses compiled by the United States Department of Labor, overtime work increased the injury hazard rate by 61%. In particular, the injury hazard rate was increased by 37% and 23% for work that lasted more than 12 h daily and 60 h, respectively, per week[13]. To ensure that medical services are promptly delivered, medical personnel routinely extend their working hours in cases of personnel shortage or sudden spikes in demand at the medical site. In Taiwanese hospitals, medical personnel working overtime mainly comprise doctors, 40% of whom work more than 60 h per week. In particular, 97% and 83% of doctors in medical centers and regional hospitals, respectively, work overtime[14].

and revised according to the Strobe statement.

Country/Territory of origin: Taiwan

Specialty type: Public, environmental and occupational health

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review report’s scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): 5
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

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Core tip: Needle stick and sharp injuries (NSIs) are complex multifactorial processes that are commonly observed in physical, psychological, and environmental fields. Therefore, preventing NSIs in medical personnel remains a critical health issue. To reduce the risk of NSIs, other factors affecting their incidence, such as medical specialty and body weight, should be analyzed. We investigated whether overtime and obesity increase the risk of NSIs. We also aimed to provide insights into the development of more effective prevention plans for NSIs. To the best of our knowledge, these findings have never been reported.

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DOI: https://dx.doi.org/10.12998/wjcc.v9.i35.10937

CONCLUSION

In addition to promoting the use of safety needles and providing infection control education, managers should review overtime schedules, and medical personnel should be encouraged to maintain a healthy weight.

Key Words: Medical staff; Needle stick and sharps injuries; Overtime work; Healthy body weight; Obesity
Obesity has been significantly associated with diseases such as type 2 diabetes, cardiovascular diseases, and several forms of cancer\cite{15} and occupational injuries\cite{16}. Occupational injuries caused by obesity generally comprise sprains, strains, lower limb injuries, and falls\cite{17}. However, a study found no significant relationship between obesity and contact with sharp material agents without adjusting for medical specialty and overtime work\cite{16}. Male health workers were found to be 10 times more likely than female health workers to encounter NSIs\cite{18}. Furthermore, low work experience was associated with high NSI incidence among nurses\cite{9}, and resident doctors (RDs) have a higher incidence of NSIs than do attending physicians (APs)\cite{19}. NSI incidence among doctors differed from that among nurses\cite{7}, and RDs had a higher incidence than APs and nurses\cite{19}.

NSIs are complex multifactorial processes that are related to physical, psychological and environmental fields. Therefore, preventing NSIs in medical personnel remains a critical health issue. To further reduce the risk of NSIs, other factors affecting NSI incidence should be analyzed, such as medical specialty and body weight (BW), and an effective prevention plan should be developed accordingly.

**MATERIALS AND METHODS**

This cross-sectional study used data regarding doctors, nurses, and medical laboratory scientists working in Chung Shan Medical University Hospital, Taichung, Taiwan, recorded during 2017. The following data were collected: sex, age, height, weight, intensity of overtime work, medical specialty (doctor, nurse, medical laboratory scientist, specialist, or surgical assistant), professional level (AP or RD for doctors and N, N1, N2, N3 or N4 for nurses based on The Guidelines of Nursing Clinical Ladder System Program in Hospital). In this study, nurses with the professional level of N, which represents < 1 year of clinical work, were categorized as junior nurses (JNs) and nurses with higher levels were categorized as experienced nurses. We defined a medical laboratory scientist as a professional technician (excluding pathology laboratory personnel), a specialized technician as a specialist nurse in some medical specialty, and a surgical assistant as a person who assists a doctor in performing a surgical operation.

This study included 847 participants (104 doctors, 613 nurses, 67 medical laboratory scientists, 54 specialist technicians, and nine surgical assistants). Among them, 29 notified the hospital of having at least one NSI in 2017; NSIs were recorded by the hospital’s occupational safety and health department. In this study, the aforementioned data were analyzed after depersonalization. Body weight was classified according to the definition of overweight or obesity by the Health Promotion Administration, Ministry of Health and Welfare. Specifically, body mass index (BMI) between 18.5 and 24.0 was considered a healthy BW (HBW), and any other BMI outside this range was considered an unhealthy BW (UHBW). Overtime work was classified according to the workload levels in the Guidelines for Prevention of Diseases Caused by Abnormal Workloads (Second Edition) from the Occupational Safety and Health Administration, Ministry of Labor. Specifically, extra work (both overtime and non-overtime) was categorized as slight (< 45 h/mo), moderate (45–80 h/mo), and heavy (> 80 h/mo) overtime work, respectively.

All statistical analyses were conducted using SAS v6.1 (SAS Institute, Cary, NC, United States). In addition, the χ² and Fisher’s exact tests were used to compare categorical variables. Multiple logistic regression analysis was used to analyze the correlation of NSI with the study’s main variables. The mediation effect was determined using the following approach proposed by Baron and Kenny (1986)\cite{20}:

(1) The independent variable (IV) significantly affects the mediator (first-stage effect);
(2) The IV significantly affects the dependent variable (DV) in the absence of the mediator;
(3) The mediator has a significant unique effect on the DV (second-stage effect); and
(4) The effect of the IV on the DV decreases upon the addition of the mediator to the model. Finally, the Sobel test\cite{21} was conducted to determine the significance of this mediation effect, for which the sample size was required to be at least 200\cite{22}. Before performing the Sobel test, if the IV, mediator, or DV was not continuous, the logistic regression coefficient was standardized: X is an independent variable, Y is a dependent variable and M is an adjusting variable (mediating factor) in a simple mediating model. a is the unary logistic regression coefficient of X against M when M is the dependent variable and X is the independent variable. b is the logistic regression coefficient of M against Y in a simple mediating model. c is the unary logistic regression coefficient of X against Y, and c’ is the logistic regression coefficient...
of X against Y with M as the adjusting variable. Moreover, \( S_a \) and \( S_b \) were the standard errors of a and b, respectively. Mediation analysis for categorical variables was conducted following the method recommended by Iacobucci (2012)\[23\].

\[
\hat{Y} = b_{01} + cX
\]

\[
\hat{M} = b_{02} + aX
\]

\[
\hat{Y} = b_{03} + c'X + bM
\]

\[
Z_a = \frac{a}{S_a}
\]

\[
Z_b = \frac{b}{S_b}
\]

The original Sobel test formula was modified as follows:

\[
Z_{\text{meditation}} = \frac{\frac{a \times \frac{b}{S_a}}{\sqrt{Z_a^2 + Z_b^2 + 1}}}{\sqrt{Z_a^2 + Z_b^2}}
\]

It was considered significant at the \( \alpha = 0.05 \) Level if its value exceeded \(|1.96|\) (for a two-tailed test with \( \alpha = 0.05 \)). In this study, statistical significance was indicated by \( P < 0.05 \).

This study was approved by Institutional Review Board of Chung Shan Medical University Hospital on December 2, 2019 (CSMUH No: CS19137).

**RESULTS**

Table 1 presents the participant characteristics, including sex, body weight, and level of overtime work. If the \( \chi^2 \) test’s assumptions were violated, Fisher’s exact test was performed. Medical personnel were classified as doctors, nurses, and others (which included medical laboratory scientists, specialist nurses, and surgical assistants). Different types of medical personnel differed significantly in terms of NSI, sex, age, and moderate or heavy overtime (Table 1). Among them, the proportion of NSIs was the highest among doctors (7.7%). Furthermore, our cohort had an exceptionally low proportion of male nurses, with 95.9% of nurses being female; by contrast, the proportion of female doctors was lower (26.9%). Among the medical specialties, nurses were the youngest, with a mean age of 33.6 years. Moreover, no significant differences were observed in HBW between the three groups. The proportions of moderate and heavy overtime work among doctors (29.8% and 16.3%, respectively) were significantly higher than those among nurses and others.

Among doctors, APs and RDs differed significantly in terms of NSIs, sex, age, and moderate and heavy overtime, but not in terms of HBW. The proportion of NSIs among RDs (21.2%) was considerably higher than that among APs (21.2% vs 1.4%, \( P < 0.01 \)). The significant difference in age between RDs and APs was expected due to the training system (45.5 vs 31.0, \( P < 0.0001 \)). The proportion of moderate overtime was higher among APs than RDs (31.0% vs 27.3%, \( P < 0.01 \) but that of heavy overtime was considerably higher among RDs than APs (33.3% vs 8.5%, \( P < 0.01 \)).

Nurses of different professional grades (N1–N4) differed significantly in terms of age (\( P < 0.0001 \)) and moderate overtime (\( P < 0.05 \)). Nurses with the professional level of N had the highest proportion of NSIs (6.2%). Age increased with the professional grade, which was expected due to the nursing clinical ladder system. Among nurses, nurses with the professional level of N had the highest proportion of moderate overtime work (32.6%), but the proportion of heavy overtime work was not the highest in this group (4.7%).

As presented in Table 2, the proportion of NSIs in participants with HBW was 0.5 times [odds ratio (OR) = 0.5, \( P < 0.05 \)] that in participants with UHBW in the \( M_1 \) model of all participants. The proportion of NSIs in doctors with HBW was 0.2 times (OR = 0.2, \( P < 0.05 \)) that in doctors with UHBW in the \( M_2 \) model of doctors. In addition, the proportion of NSIs in nurses with HBW was 0.5 times that in nurses with UHBW, but the difference was not significant.

Table 2 presents a clear effect of heavy overtime work on NSIs: medical personnel with heavy overtime work were 4.3–5.7 times more likely to experience an NSI than those with mild overtime work, and the difference was significant. Similarly, NSIs occurred 5.4 times more proportion in doctors with heavy overtime work (OR = 5.4, \( P < 0.05 \)) than in those with slight overtime work; however, this effect could be
explained by the other effects such as HBW (OR = 0.2, P < 0.05) and RDs (OR = 17.3, P < 0.05). Although nurses with heavy overtime work experienced more NSIs (OR = 3.7 and 3.8) than others, the difference was not significant.

Doctors experienced more NSIs incidence than other types of medical personnel, but the difference was nonsignificant (OR = 1.3–2.1, P > 0.05). After adjustment for other variables (M1 model), the nurse specialty was identified as an independent protective factor for NSIs (OR = 0.3, P < 0.05). Among doctors, regardless of whether adjustments were made for other variables, being an RD was an independent risk factor for NSIs (OR = 18.9, P < 0.01 and OR = 17.3, P < 0.05). Similarly, among nurses, being a JN was also an independent risk factor for NSIs regardless of whether adjustments were made for variables (both OR = 3.9, P < 0.01).

Consequently, RDs and JNs were added to the logistic regression model in Table 3 for further exploring the relationships of BW and overtime work with NSI in professional experience. HBW was a protective factor against NSI occurred regardless of whether adjustments were made for variables (M0, M1, and M2). However, after adjustment for HBW and RD effects, the effect of heavy overtime work was no longer significant (M2, OR = 1.9, P > 0.05). The proportion of NSIs among RDs was 4.1 times (M1, OR = 4.1, P < 0.05) higher than that among JNs without adjustment for variables; this increased to 19.5 times (M2, OR = 19.5, P < 0.05) after adjustment for sex, age, overtime work, and body weight. Therefore, UHBW was determined to be an independent risk factor for NSIs in RDs and JNs.

Table 4 presents the results of multiple logistic regressions after adjusting for age for NSI because experienced nurses have a wider age distribution. The results indicated that the proportion of NSIs among nurses with heavy overtime work was 6.6 times (OR = 6.6, P < 0.05) higher than that among nurses with mild overtime work, and the difference was significant. However, the proportion of NSIs in nurses with HBW was 1.2 times (M2, OR = 1.2, P > 0.05) that of nurses with UHBW, but the difference was not significant.

Table 5 illustrates the significant mediation effects (Zm = 2.5, P < 0.05) of heavy overtime work on the relationship between NSIs and doctors. No mediation effects were noted for the other five combinations.
### Table 2 Main effects on needle stick and sharps injuries in different models for all participants

<table>
<thead>
<tr>
<th>Main effect</th>
<th>ORs of NSIs for All participants</th>
<th>ORs of NSIs for doctors</th>
<th>ORs of NSIs for nurses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$N$</td>
<td>$n$</td>
<td>$M_0$</td>
</tr>
<tr>
<td>Body weight level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy body weight (HBW)</td>
<td>471</td>
<td>11</td>
<td>0.8*</td>
</tr>
<tr>
<td>Unhealthy body weight (UHBW)</td>
<td>376</td>
<td>18</td>
<td>1.0</td>
</tr>
<tr>
<td>OT work</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heavy</td>
<td>45</td>
<td>6</td>
<td>5.7*</td>
</tr>
<tr>
<td>Moderate</td>
<td>193</td>
<td>7</td>
<td>1.4</td>
</tr>
<tr>
<td>Mild</td>
<td>609</td>
<td>16</td>
<td>1.0</td>
</tr>
<tr>
<td>Type of medical personnel</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doctors</td>
<td>104</td>
<td>8</td>
<td>2.1</td>
</tr>
<tr>
<td>Nurses</td>
<td>613</td>
<td>16</td>
<td>0.7</td>
</tr>
<tr>
<td>Others</td>
<td>130</td>
<td>5</td>
<td>1.0</td>
</tr>
<tr>
<td>Professional grade (Doctors)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resident doctor (RD)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Associate (AP)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Professional grade (Nurses)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Junior (experiencing)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

| $^aP < 0.05.$                  |      |     |       |       |       |      |     |       |       |       |      |     |       |       |       |
| $^bP < 0.01.$                  |      |     |       |       |       |      |     |       |       |       |      |     |       |       |       |
| $^cP < 0.0001.$                |      |     |       |       |       |      |     |       |       |       |      |     |       |       |       |

NS: Not significant.

Odds ratio = 1.0 indicates the reference; ORs: Odds ratios; $N$: Participants; $n$: Participants for needle stick and sharps injuries; $M_0$: Model only including main effect; $M_1$: Model adjusted for sex, age, overtime work, and medical specialty; $M_2$: Model adjusted for sex (only doctors), overtime work, professional grade, and body weight; HBW: Healthy body weight; UHBW: Unhealthy body weight; OT: Overtime; NSIs: Needle stick and sharps injuries.

### Table 3 Main effects on needle stick and sharps injuries in various models for resident doctors and junior nurses

<table>
<thead>
<tr>
<th>Main effect</th>
<th>ORs for NSIs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$N$</td>
</tr>
<tr>
<td>Body weight level</td>
<td></td>
</tr>
<tr>
<td>Healthy body weight (HBW)</td>
<td>95</td>
</tr>
<tr>
<td>Unhealthy body weight (UHBW)</td>
<td>52</td>
</tr>
<tr>
<td>OT work</td>
<td></td>
</tr>
<tr>
<td>Heavy</td>
<td>13</td>
</tr>
<tr>
<td>Moderate</td>
<td>46</td>
</tr>
<tr>
<td>Mild</td>
<td>88</td>
</tr>
<tr>
<td>Professional subfield</td>
<td></td>
</tr>
<tr>
<td>Resident doctor (RD)</td>
<td>26</td>
</tr>
<tr>
<td>Junior (JN)</td>
<td>121</td>
</tr>
</tbody>
</table>

| $^aP < 0.05.$                  |      |     |       |       |
| $^bP < 0.001.$                 |      |     |       |       |

Odds ratio = 1.0 indicates the reference; ORs: Odds ratios; $N$: Participants; $n$: Participants for needle stick and sharps injuries; $M_0$: Model only including main effect; $M_1$: Model adjusted for sex and age; $M_2$: Model adjusted for sex, age, and main effects; RD: Resident doctor; JN: Junior nurse; HBW: Healthy body weight; UHBW: Unhealthy body weight; OT: Overtime; NSIs: Needle stick and sharps injuries.

### DISCUSSION

A cross-sectional study evaluating NSI incidence among 29 doctors and 51 nurses demonstrated that the proportion of NSIs among nurses was 0.2 times that among doctors[6]. A study including NSI data from 2002 to 2007 in a university hospital in Pakistan demonstrated that the number of NSIs has higher in junior doctors than in nurses[7]. The differences between doctors and nurses may stem from differences in their work patterns or attitudes. For example, doctors often experience NSIs during wound irrigation, sutures, incisions, handling body fluids, and tissue sample...
Table 4 Main effects on needle stick and sharps injuries for experienced nurses

<table>
<thead>
<tr>
<th>Main effect</th>
<th>Participants</th>
<th>ORs for NSIs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>M₀</td>
</tr>
<tr>
<td>Body weight level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBW</td>
<td>276</td>
<td>5</td>
</tr>
<tr>
<td>UHBW</td>
<td>208</td>
<td>3</td>
</tr>
<tr>
<td>OT work</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heavy</td>
<td>22</td>
<td>2</td>
</tr>
<tr>
<td>Moderate</td>
<td>105</td>
<td>1</td>
</tr>
<tr>
<td>Mild</td>
<td>357</td>
<td>5</td>
</tr>
</tbody>
</table>

*a P < 0.05.
Odds ratio = 1.0 indicates the reference. ORs: Odds ratios; HBW: Healthy body weight; OT: Overtime; NSIs: Needle stick and sharps injuries; n: Participants for needle stick and sharps injuries; M₀: Model only including the main effect; M₁: Model adjusted for age, sex, body weight, and overtime work.

Table 5 Mediation effect of heavy overtime work and healthy body weight for needle stick and sharps injuries and the main effect

<table>
<thead>
<tr>
<th>IV</th>
<th>Mediator factor</th>
<th>Heavy OT work⁴</th>
<th>HBW⁵</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>c</td>
<td>c'</td>
<td>a</td>
</tr>
<tr>
<td>All participants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doctors¹</td>
<td></td>
<td>1.1</td>
<td>0.8</td>
</tr>
<tr>
<td>Doctors effect</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RD²</td>
<td></td>
<td>2.9</td>
<td>2.6</td>
</tr>
<tr>
<td>Nurse effect</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>JN³</td>
<td></td>
<td>1.4</td>
<td>1.4</td>
</tr>
</tbody>
</table>

*P < 0.05.
*b P < 0.01.
*c P < 0.0001.
NS: Not significant.
¹Reference variable includes nurses and others.
²Reference variable is Aps.
³Reference variable is experienced nurses.
⁴Reference variable includes moderate overtime and slight overtime.
⁵Reference variable is unhealthy body weight.
IV: Independent variable; RD: Resident doctor; JN: Junior nurse; HBW: Healthy body weight.

collection. By contrast, for nurses, injuries often occur during injections, intravenous infusions, heparin cap sealing, intravenous connections, and venous or arterial blood collection[24]. In addition, some studies have determined that the NSI risk is affected by education and work experience[9,10,25] among nurses and by stress and carelessness[6] among doctors. Consistent with this finding, our study indicated that doctors experienced more NSIs than nurses did (7.7% vs 2.6%). In addition, nurses who intensively contact patients were the protective factor of NSIs (OR = 0.3, P < 0.05). Our analysis revealed that the proportion of NSIs 4.1 times (OR = 4.1, P < 0.05) higher among RDs than among JNs; this increased to 19.5 times after adjusting for age and overtime work. Therefore, the NSI risk among RDs may be more serious than expected and has often been ignored in the past.

A cross-sectional survey of staff physicians, RDs, staff dentists, nurses, and laboratory technicians illustrated that RDs were significantly associated with NSIs; NSIs were three times more common among RDs than among Aps[19]. The present data indicate a difference of 17.3 times between RDs and Aps (21.2% vs 1.4%), which was markedly higher than in past studies. This may be because the numbers of NSIs among Aps were low (n = 1), which may have led to the overestimation of this result. Nevertheless, the risk of NSIs among RDs was higher than that among other types of...
medical personnel; for example this risk was 19.5 times higher in RDs than that in JNs. 

Nurses with less work experience have a higher risk of NSIs[5,9]; in particular, nursing work experience of < 5 years was associated with significantly more NSIs than nursing work experience of > 5 years[3,11]. Consistent with these results, our study demonstrated that JNs have a higher risk of NSIs (OR = 3.9, P < 0.001) than experienced nurses after adjustment for other variables. 

A cohort study including 11,728 employees revealed that claims costs were 7–11 times higher among those with BMI ≥ 40 compared with those within the recommended weight range[26]. A prospective cohort study of nearly 70,000 public sector employees demonstrated that, compared with employees whose BMI was in the healthy range, overweight or obese employees had an 11%–62% excess risk of occupational injury[16]. In addition, a study involving 7,690 employees aged 18–65 years of an aluminum manufacturing company in the USA revealed that the proportion of injuries of participants with overweight or obesity was 1.3–2.2 times higher than those with normal weight[27]. The present results were in agreement with these findings and revealed that the proportion of NSIs among medical personnel with HBW was 0.5 times (OR = 0.5, P < 0.05) that among medical personnel with UHBW. Although we observed a relationship between NSIs and BW, the present study structure and data collected was insufficient to illustrate how BW affects NSIs. However, studies have demonstrated that fatigue increases the risk of NSIs among nurses and medical interns [28,29], and studies on grip strength have identified that, all things being equal, young people with obesity use more energy, have reduced endurance, and have accelerated power loss compared with nonobese young people. However, these obesity-related differences were not observed in the older age group[30]. These studies may explain the positive correlation between obesity and NSIs; obese people are more likely to use their poorer muscle strength improperly and be more prone to fatigue when performing clinical tasks, thus increasing their risk of NSIs. 

A strong dose–response effect was noted between work hours and hazard rate[13], and working hours before injury will increase significantly compared to the past[31]. The positive trend between work hours and NSIs was observed in medical personnel: nurses with work hours of > 8 h/d[11] or > 40 h/wk[8] had higher risk of NSIs than those working < 8 h/d or < 40 h/wk. Our study found that the proportion of NSIs in participants with heavy overtime work was 4.3 times (OR = 4.3, P < 0.05) that in those with mild overtime work, but moderate overtime work effect (OR = 1.2, P > 0.05) was not significant; therefore, only heavy overtime work increased the risk of NSIs. Heavy overtime work was a risk factor for NSIs among doctors (OR = 5.4, P < 0.05) without adjustment for any variable, but this relationship was not significant when adjustments were made for sex, overtime work, professional grade, and BW; this was probably due to the higher proportion of heavy overtime work in RDs (33.3%) than in APs (8.5%). A dose–response effect was also noted between overtime work and NSIs for nurses, but it was not significant. However, experienced nurses engaged in heavy overtime work had 6.6 times (OR = 6.6, P < 0.05) more NSIs than those engaged in mild overtime work (Table 4); the effect of moderate overtime work on NSIs was not significant. Therefore, even among experienced nurses, only heavy overtime work affected the risk of NSIs. The proportion of NSIs was related to overtime work, but this relationship was not significant among nurses (Table 2); however, the association between NSIs and overtime work (OR = 6.6–7.0, P < 0.05) was significant among experienced nurses (Table 4). In addition, the mediation analysis (Table 5) demonstrated that heavy overtime work mediated (Zm = 2.5, P < 0.05) the relationship between NSIs and medical specialty, confirming the impact of heavy overtime work on NSI. However, heavy overtime work and HBW were not mediation factors for the relationship between NSIs and experience level for doctors or nurses, indicating that low experience among medical personnel might itself be the cause of NSIs. A study indicated that the incidence of NSIs among first-year RDs was higher than expected—more than 60% during the first 6 mo[32]—implying that education and training may influence the risk of NSIs. Burnout also increases the risk of occupational accidents and its sequelae[33], and it was also a factor influencing NSIs among nurses [34]. Burnout decreases with an increase in professional experience[35]; this may also explain by burnout why RDs experience higher NSIs incidence than Aps. Future studies should comprehensively assess the burnout level of participants. 

Because this study only collected data from one hospital, its findings are limited by the data collection method, sample size, as well as the hospital’s environmental facilities, education, and training systems. In addition, because the number of reported NSIs was low, slight variations in the sample could have considerable influence on the conclusions. Moreover, factors such as hospital employees’ work patterns, workload, burnout level, work stress, and willingness to report occupational injuries were not
considered in this study. These factors should be incorporated in the questionnaire design of future studies to further control for and discuss these effects on NSI risk. Although our results regarding NSI risk were consistent with those of past studies, this study compared the NSI risk between doctors and nurses, which has been rarely discussed in the literature. The findings can guide NSI prevention strategies in the medical practice.

CONCLUSION

This study revealed that heavy overtime work and low professional experience were associated with an increased NSI risk, particularly among RDs. Moreover, the present data indicated that HBW may reduce the risk of NSIs, which has rarely been evaluated in other studies. Maintaining an HBW had a protective effect against NSI for RDs and JNs. Therefore, in addition to promoting the use of safety needles and strengthening education and training related to infection control, the overtime schedule of medical personnel should be regularly reviewed; long work hours and excessive overtime should be avoided. Furthermore, strategies aimed at promoting the maintenance of HBW among employees should be implemented, which could further reduce NSI incidence.

ARTICLE HIGHLIGHTS

Research background
Needle stick and sharp injuries (NSIs) may cause infections among medical personnel. Obesity and overtime work among medical personnel increase the incidence of work injuries.

Research motivation
The associations of overtime work and obesity with NSIs are unclear.

Research objectives
The study aimed to investigate whether overtime work and obesity increase the risk of NSIs.

Research methods
This cross-sectional study used the data of 847 hospital personnel, including 104 doctors, 613 nurses, 67 medical laboratory scientists, 54 specialist technicians, and nine surgical assistants. Of them, 29 participants notified the hospital of having at least one NSI in 2017. The χ² and Fisher’s exact tests were used to compare categorical variables. Multiple logistic regression analysis and the Sobel test were used to assess the risk of NSIs.

Research results
Overtime work, body weight (BW), and medical specialty were significantly associated with NSIs. After adjustment for risk factors, heavy overtime work was an independent risk factor for NSIs, and healthy BW (HBW) and nursing specialty were independent protective factors against NSIs. Also, after adjustment for risk factors, medical personnel with HBW had half as many NSIs as those with unhealthy BW (UHBW); the proportion of NSIs in doctors with HBW was 0.2 times that in doctors with UHBW; the proportion of injuries among residents was 17.3 times higher than that among attending physicians; the proportion of injuries among junior nurses was 3.9 times higher than that among experienced nurses; the proportion of injuries among nurses with heavy overtime work was 6.6 times higher than that among nurses with mild overtime work; and the proportion of injuries among residents was 19.5 times higher than that among junior nurses. Heavy overtime work mediated the association of medical specialty with NSIs.

Research conclusions
Heavy overtime work and low professional experience were associated with an increased NSI risk, particularly among resident doctors. Maintaining HBW had a protective effect against NSI for resident doctors and junior nurses.
Research perspectives

In addition to promoting the use of safety needles and providing infection control education, managers should review overtime schedules, and medical personnel should be encouraged to maintain an HBW.

REFERENCES


Stone CA, Sobel ME. The robustness of estimates of total indirect effects in covariance structure models estimated by maximum. Psychometrika 1990; 55: 337-352


Fisman DN, Harris AD, Rubin M, Sorock GS, Mittleman MA. Fatigue increases the risk of injury from sharp devices in medical trainees: results from a case-crossover study. Infect Control Hosp Epidemiol 2007; 28: 10-17 [PMID: 17230382 DOI: 10.1086/510569]

Mehta RK, Cavuoto LA. The effects of obesity, age, and relative workload levels on handgrip endurance. Appl Ergon 2015; 46 Pt A: 91-95 [PMID: 25088026 DOI: 10.1016/j.apergo.2014.07.007]


Observational Study

Serum gastrin-17 concentration for prediction of upper gastrointestinal tract bleeding risk among peptic ulcer patients

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Author contributions: Wang JX and Su P contributed study concept, design, analysis and interpretation of data; Cao YP, Su P, He W, Li XP and Zhu YM contributed acquisition of data; Wang JX, Cao YP and Su P wrote the manuscript; all authors wrote, read and approved the final manuscript.

Institutional review board statement: The study was reviewed and approved by the Second People’s Hospital of Anhui Province, Institutional Review Board (Approval No. 2015-036).

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

Conflict-of-interest statement: The authors have no potential competing interests to declare.

Data sharing statement: No additional data are available.

STROBE statement: The authors

Abstract

BACKGROUND

Serum gastrin-17 (G-17), pepsinogen I (PGI), and pepsinogen II (PGII) concentrations regulate gastric acid secretion, and hypersecretion of gastric acid increases the risks of peptic ulcer and upper gastrointestinal bleeding. These associations suggest that serum G-17, PGI, and (or) PGII may predict gastrointestinal bleeding risk among peptic ulcer patients.

AIM

To evaluate the efficacies of serum G-17, PGI, PGII, and PGI/PGII ratio (PGR) for predicting upper gastrointestinal bleeding among peptic ulcer patients.

METHODS

A total of 199 patients diagnosed with peptic ulcer confirmed by gastroscopy and positivity for Helicobacter pylori by the 13C-urea breath test were recruited, including 107 patients with simple peptic ulcer and 92 cases complicated by upper gastrointestinal bleeding. Serum PGI, PGII, G-17, and PGR were measured by immune methods and compared between bleeding and non-bleeding groups by univariate analysis. The specificity and sensitivity of PGs and G-17 for evaluating upper gastrointestinal bleeding risk were then assessed by constructing receiver operating characteristic (ROC) curves.

RESULTS

Serum G-17 was significantly higher among peptic ulcer patients with upper gastrointestinal bleeding compared to simple peptic ulcer patients (25.34 ± 14.29 vs 8.84 ± 8.03 pmol/L, t = 9.822, P < 0.01), whereas serum PGI, PGII, and PGR did not differ significantly between bleeding and non-bleeding groups (all P > 0.05). The risk of bleeding was significantly higher among peptic ulcer patients with elevated serum G-17 (> 15 pmol/L) compared to patients with normal or low serum G-17 (73.2% vs 27.4%, χ² = 40.72, P < 0.01).
Peptic ulcer is among the most common digestive system diseases, and upper gastrointestinal bleeding is the most prevalent complication. Hypersecretion of gastric acid is a critical risk factor for peptic ulcer bleeding, and secretion level is strongly correlated with serum concentration of the gut-derived peptide hormone gastrin-17 (G-17) [1,2]. High serum levels of pepsinogen I (PGI) and PGII are also associated with gastric acid secretion rate by the gastric mucosa and with the incidence of peptic ulcer [3]. Conversely, low serum PGI and PGI/PGII ratio are associated with gastric atrophy. Thus, modulation of G-17, PGI, and PGII secretion levels can be utilized to treat dyspepsia and other gastric diseases [4]. High serum gastrin or PGI/PGII ratio (PGR) will lead to excessive secretion of gastric acid, overcoming the protective capacity of the gastric mucosa and increasing the incidence of peptic ulcer and digestive tract tumors [5]. Indeed, combined detection of serum G-17 and PG is a fundamental screening method for early gastric cancer detection [6]. However, serum PGI, PGII, and G-17 levels among peptic ulcer patients with and without bleeding have not been examined in detail. In the present study, these levels were measured and their predictive values for assessing the risk of peptic ulcer complicated by upper gastrointestinal bleeding tested by univariate and receiver operating characteristic (ROC) curve analyses.

**MATERIALS AND METHODS**

**Baseline data**

Patients diagnosed with peptic ulcer or peptic ulcer complicated by upper gastrointestinal bleeding admitted to the Department of Gastroenterology of Anhui No.2 Provincial People’s Hospital from July 2015 to November 2019, were recruited. Serum for serum G-17 was 0.866 ± 0.024, and a cut-off of 9.86 pmol/L yielded 90.2% sensitivity and 68.2% specificity for distinguishing peptic ulcer with and without upper gastrointestinal bleeding.

**CONCLUSION**

Serum G-17 is significantly upregulated in peptic ulcer patients and higher levels are predictive of upper gastrointestinal bleeding. Conversely, serum PGI, PGII, and PGR have no predictive value. Further prospective studies are warranted to examine if high G-17 can be used to assess risk of bleeding prior to onset.

**Key Words:** Peptic ulcer; Upper gastrointestinal bleeding; Gastrin; Pepsinogen; Receiver operating characteristic curve

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levels of G-17, PGI, and PGII were measured and the PGR was calculated. Candidates were excluded due to the following conditions: (1) Malignant tumors or severe atypical hyperplasia as indicated by endoscopic pathology; (2) Negative for Helicobacter pylori (HP) or not tested for HP; (3) History of stomach, esophagus or duodenum surgery; (4) Serious cardiopulmonary diseases that may independently influence gastrin or PG secretion; (5) Long-term use of aspirin or clopidogrel, or recent administration of antiplatelet/anticoagulant drugs such as heparin; (6) History of long-term non-steroidal anti-inflammatory analgesic or glucocorticoid administration; (7) Peptic ulcer complicated by other severe digestive system diseases; (8) Stress ulcer or stress ulcer complicated by bleeding; (9) Non-ulcerative upper gastrointestinal bleeding due to other causes; (10) Long-term history of proton pump inhibitor administration; and (11) Diagnosis of gastrinoma. A total of 199 patients were enrolled meeting the inclusion and exclusion criteria, including 138 males and 61 females with a mean age of 50.43 ± 16.16 years. Among these patients, 107 had peptic ulcer without bleeding [75 males and 32 females, mean age 52.6 ± 14.7 years], including 49 cases of duodenal ulcer, 45 of gastric ulcer, and 13 cases of complex ulcer. The other 92 patients were diagnosed with peptic ulcer complicated by upper gastrointestinal bleeding [63 males and 29 females, mean age 47.9 ± 17.4 years], including 64 cases of duodenal ulcer, 20 cases of gastric ulcer, and 8 cases of complex ulcer. Patients with gastric ulcer or complex ulcer received routine pathological examination to exclude the possibility of high-grade neoplasia or malignancy, whereas those with duodenal ulcer with or without bleeding did not undergo routine pathological examination. All patients were confirmed to be HP-positive by the 14C-urea breath test. Patients with peptic ulcer complicated by bleeding were significantly younger than patients with peptic ulcer alone (47.9 ± 17.4 vs 52.6 ± 14.74, \( P = 0.040 \)), whereas the sex ratio did not significantly differ between the groups (Table 1).

Blood sample collection, processing, and hormone detection
Approximately 5 mL of fasting (for about 6 h) blood was collected, and the serum was separated for subsequent immunofluorescence measurements of PGI, PGII, and G-17. A serum pepsinogen and G-17 kit was purchased from BIOHIT Healthcare (Hefei) and a microplate reader from Anthos Labtec Instruments (Austria).

Reference ranges of PGI, PGII, PGR and G-17
The reference ranges of these concentrations are as follows: PGI, 70–165 μg/L; PGII, 3–15 μg/L; PGR, 7%-20%; G-17, 1-15 pmol/L. Serum PGI > 165 μg/L, serum PGII >15 μg/L, PGR > 20, and G17 > 15 pmol/L were regarded as elevated.

Statistical analysis
All statistical analyses were conducted using SPSS16.0 (SPSS Inc., Chicago, IL, United States). The serum levels of PGI, PGII, G-17, and PGR were compared between bleeding and non-bleeding groups by independent samples t-test. The proportions of peptic ulcer cases complicated by bleeding were compared between patient subgroups stratified according to upper-range cut-offs (e.g., greater or less than 15 pmol/L for G-17) by the Chi-square test. The efficacy of G-17 for predicting bleeding complication was assessed by ROC curve analysis. A \( P < 0.05 \) (two-tailed) was considered statistically significant for all tests.

RESULTS
Elevated serum G-17 in peptic ulcer patients with bleeding
Serum G-17 concentration was significantly higher in peptic ulcer patients with upper gastrointestinal bleeding compared to non-bleeding patients (\( t = 9.822, P < 0.01 \)) (Table 2). Furthermore, serum G-17 was also significantly higher in gastric ulcer (GU) patients with bleeding and duodenal ulcer (DU) patients with bleeding compared to corresponding non-bleeding subgroups (both \( P < 0.01 \)). Serum G-17 was slightly higher in DU patients without bleeding compared to GU patients without bleeding (\( P = 0.209 \)), but did not differ between GU patients with bleeding and DU patients with bleeding (\( P = 0.940 \)). Serum G-17 was also higher among patients with complex ulcer (CU) complicated by bleeding compared to patients with CU alone, but again the difference did not reach significance (\( P > 0.05 \)). In contrast to G-17, there were no significant differences in serum PGI, PGII, and PGR between the bleeding and non-bleeding subgroups (all \( P > 0.05 \), Table 2). Thus, serum G-17 (but not PGI, PGII, or
Table 1 Demographic distributions of peptic ulcer patients with and without bleeding

<table>
<thead>
<tr>
<th>Group</th>
<th>Sex</th>
<th>Number of Cases</th>
<th>Male</th>
<th>Female</th>
<th>Age (yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peptic ulcer without bleeding</td>
<td></td>
<td></td>
<td>75</td>
<td>32</td>
<td>52.6 ± 14.7</td>
</tr>
<tr>
<td>Peptic ulcer complicated by bleeding</td>
<td></td>
<td></td>
<td>63</td>
<td>29</td>
<td>47.9 ± 17.4*</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>138</td>
<td>61</td>
<td>50.4 ± 16.16</td>
</tr>
</tbody>
</table>

*Mean ± SD.

*P < 0.05 compared to the non-bleeding group.

Table 2 Serum pepsinogen I, pepsinogen II, pepsinogen ratio, and gastrin-17 values for patient subgroups stratified by bleeding complication and ulcer type

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of cases (n)</th>
<th>G-17 (pmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GU</td>
<td>45</td>
<td>197.90 ± 89.97</td>
</tr>
<tr>
<td>DU</td>
<td>49</td>
<td>204.43 ± 80.60</td>
</tr>
<tr>
<td>CU</td>
<td>13</td>
<td>220.48 ± 107.82</td>
</tr>
<tr>
<td>Total</td>
<td>107</td>
<td>225.86 ± 91.10</td>
</tr>
<tr>
<td>Peptic ulcer group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GU</td>
<td>20</td>
<td>240.52 ± 83.47</td>
</tr>
<tr>
<td>DU</td>
<td>64</td>
<td>250.64 ± 85.70</td>
</tr>
<tr>
<td>CU</td>
<td>8</td>
<td>238.55 ± 95.15</td>
</tr>
<tr>
<td>Total</td>
<td>92</td>
<td>234.98 ± 90.67</td>
</tr>
</tbody>
</table>

*P < 0.01 compared to the corresponding non-bleeding group.

PGI: Pepsinogen I; PGII: Pepsinogen II; PGR: PGI/PGII ratio; G-17: Gastrin-17; GU: Gastric ulcer; DU: Duodenal ulcer; CU: Complex ulcer.

PGR) may be useful for distinguishing bleeding from non-bleeding peptic ulcer patients.

**Association between serum G-17 level and bleeding risk**

Serum G-17 ranging from 1 to 15 pmol/L is considered normal. Therefore, we first compared bleeding incidence between peptic ulcer patients stratified by a serum G-17 cut-off of 15 pmol/L. Among peptic ulcer patients with serum G-17 > 15 pmol/L, approximately 73.2% exhibited bleeding compared to only 27.4% of patients with serum G-17 < 15 pmol/L (χ² = 40.72, P < 0.01) (Table 3). In contrast, the proportions of bleeding cases did not differ between groups stratified by similar upper limits in serum PGI, PGII, and PGR (χ² = 0.395, P = 0.009, and χ² = 2.242, respectively, all P > 0.05).

**Efficacies of serum G-17, PGI, PGII, and PGR for predicting bleeding complication among peptic ulcer patients**

The area under the ROC curve (AUC) of serum G-17 for peptic ulcer patients with or without upper gastrointestinal bleeding was 0.886 ± 0.024. According to the Youden index, the optimal serum G-17 cut-off value for distinguishing bleeding from non-bleeding patients was 9.86 pmol/L, yielding 90.2% sensitivity and 68.2% specificity (Figure 1). In contrast, the AUC values for serum PGI, PGII, and PGR were only 0.599, 0.496, and 0.598, respectively, indicating low efficacy for distinguishing bleeding from non-bleeding peptic ulcer (Figure 2).
Table 3 Association between serum gastrin-17 and upper gastrointestinal bleeding

<table>
<thead>
<tr>
<th>Serum G-17 level</th>
<th>Peptic ulcer, n (%)</th>
<th>Peptic ulcer complicated by bleeding, n (%)</th>
<th>Total, n</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (≤ 15 pmol/L)</td>
<td>85 (72.6)</td>
<td>32 (27.4)</td>
<td>117</td>
<td></td>
</tr>
<tr>
<td>Elevated (&gt; 15 pmol/L)</td>
<td>22 (26.8)</td>
<td>60 (73.2)</td>
<td>82</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>107</td>
<td>92</td>
<td>199</td>
<td>0.000</td>
</tr>
</tbody>
</table>

G-17: Gastrin-17.

DISCUSSION

We report that serum gastrin concentration is significantly elevated above normal reference ranges in patients with gastric or duodenal ulcer, and is even higher among patients with peptic ulcer complicated by upper gastrointestinal bleeding. Indeed, the proportion of peptic ulcer patients with serum G-17 concentrations above the upper limit of normal (approximately 15 pmol/L) was significantly greater among those with bleeding compared to patients without bleeding (simple GU). Furthermore, ROC curve analysis revealed that G-17 > 9.86 pmol/L distinguished bleeding from non-bleeding GU patients with high sensitivity and moderate specificity, suggesting that G-17 evaluation prior to endoscopic examination could be employed to assess bleeding risk, thereby facilitating timely intervention, such as a higher proton pump inhibitor dose[7], and improving overall prognosis. Serum G-17 was also higher among complex ulcer (CU) patients with bleeding compared to CU patients without bleeding, although the difference did not reach statistical significance due to the small sample size. Hence, larger-scale studies are warranted to fully assess the efficacy of high G-17 for prediction of bleeding among GU patient subgroups, including prospective studies directly evaluating the association between baseline G-17 and future bleeding.

Approximately 10% of individuals will develop gastric or duodenal ulcer over a lifetime, but the majority can be completely cured with treatment. However, GU complicated by acute upper gastrointestinal bleeding increases treatment difficulty and can be life-threatening if uncontrolled[8]. Therefore, identifying predictive indices for upper gastrointestinal bleeding is critical for improving prognosis among more severely afflicted GU patients.

The incidence and severity of peptic ulcer are significantly associated with the production rates of gastric acid, gastrin, and pepsin[9]. Gastrin is a pre-hormone secreted by G-cells in the gastric antrum that is then converted to active molecules,
mainly G-34 and G-17, of which G-17 accounts for approximately 80%-90% of the total bioactivity. The main physiological functions of gastrin are to stimulate gastric acid and PG secretion, regulate gastrointestinal motility, increase gastric mucosal blood flow, and promote gastric mucosal growth and nutrition[10]. However, excessive gastric acid secretion by high serum G-17 may destroy the gastric mucosa, leading to ulcer formation and possibly bleeding. In the presence of gastric acid, PG is rapidly converted into active pepsin, which can cause the dissolution of blood clots and thus impair the control of bleeding. Consequently, it is rational to speculate that high G-17 and high PG may predict the risk of bleeding among peptic ulcer patients. However, serum PG was unrelated to bleeding incidence, possibly because many factors can influence PG production aside from gastric acid secretion rate. In fact, the secretion of gastric acid, gastrin, and PG can be affected by multiple factors. For instance, HP infection increases gastrin secretion[11]. Hence, all patients enrolled in the present study were HP-positive to eliminate the effects of HP and related factors. In addition, long-term use of proton pump inhibitors may cause a compensatory increase in gastrin secretion[12], so patients receiving proton pump inhibitors were also excluded from the present study. Furthermore, peptic ulcer patients with other conditions associated with bleeding risk were eliminated, so the difference between groups likely reflects disease severity, further underscoring the importance of serum G-17 for evaluation of patient condition and prognosis. On the other hand, as yet unidentified factors influencing PG may have obscured differences between bleeding and non-bleeding patients.

Such PG measurements may still have clinical value. Pepsinogen can be classified as PGI or PGII according to immunogenicity, and these isoforms are generated by different regions of the gastric mucosa. Therefore, separate detection of serum PGI and PGII can provide an estimate of region-specific gastric acid secretion rate[13]. Activated pepsin can both enhance the risk of peptic ulcer and impair coagulation, potentially enhancing bleeding risk and diminishing treatment efficacy. In this study, however, serum PGI, PGII, and PGR were not associated with bleeding, possibly because PG secretion is affected to a greater extent by gastric mucosal atrophy, dysplasia, and other diseases than by ulcer (with or without bleeding)[14].

Although we controlled for multiple factors potentially influencing the secretion rates of G-17 and PG, factors such as drinking[15], smoking[16], age[17], and gastric mucosal lesions[18] may have differed between the groups. Thus, larger-scale studies allowing for more extensive subgroup analyses are required to validate the current finding that serum G-17 is a major predictive factor for bleeding among peptic ulcer patients.

Figure 2 Efficacies of serum pepsinogen I, pepsinogen II and pepsinogen ratio for distinguishing peptic ulcer with or without upper gastrointestinal bleeding. PGI: Pepsinogen I; PGII: Pepsinogen II; PGR: PGI/PGII ratio.
CONCLUSION

In summary, serum G-17 is significantly elevated in peptic ulcer complicated by bleeding. Serum G-17 > 9.86 pmol/L distinguishes bleeding from non-bleeding cases with high sensitivity, suggesting its clinical utility for predicting bleeding risk.

ARTICLE HIGHLIGHTS

Research background

Peptic ulcer is a relatively common chronic gastrointestinal disorder most frequently caused by Helicobacter pylori infection or long-term non-steroid anti-inflammatory drug administration. Severe cases are often complicated by bleeding, which can exacerbate symptoms, cause anemia, and lead to life-threatening hemorrhage. Hypersecretion of gastric acid increases the risk and severity of peptic ulcer. Gastric acid secretion is controlled by the hormones gastrin-17 (G-17), pepsinogen I (PGI), and pepsinogen II (PGII), suggesting that these factors may be predictive of bleeding among peptic ulcer patients.

Research motivation

If left untreated, peptic ulcer can result in gastrointestinal bleeding and gastric tumors. Therefore, accessible biomarkers such as serum factors predictive of bleeding risk are important tools for early diagnosis and treatment guidance, and may reduce the incidence of severe complications.

Research objectives

To examine if serum G-17, PGI, PGII, and (or) PGI/PGII ratio (PGR) can predict bleeding risk among peptic ulcer patients.

Research methods

We compared serum G-17, PGI, PGII, and PGR between 199 peptic ulcer patients with bleeding (n = 92) or without bleeding (n = 107), and then assessed the efficacy of each factor for bleeding prediction by receiver operating characteristic curve analysis.

Research results

Serum G-17 was significantly higher among peptic ulcer patients with upper gastrointestinal bleeding, whereas serum PGI, PGII, and PGR did not differ significantly between bleeding and non-bleeding patients. A serum G-17 greater than 9.86 pmol/L distinguished bleeding from non-bleeding patients with 90.2% sensitivity and 68.2% specificity.

Research conclusions

Elevated serum G-17 is predictive of bleeding risk among peptic ulcer patients. Lowering serum G-17 should be a major goal of clinical intervention.

Research perspectives

Prospective studies are warranted to assess if elevated serum G-17 can predict bleeding complication prior to disease onset. The development of drugs able to regulate G-17 secretion is also desired to help reduce bleeding risk.

REFERENCES

Wang JX et al. Serum G-17 and bleeding ulcer risk


Observational Study

Predictive risk scales for development of pressure ulcers in pediatric patients admitted to general ward and intensive care unit

Wen-Jun Luo, Xue-Zhen Zhou, Jia-Ying Lei, Ying Xu, Rui-Hua Huang

Background

More than ten special scales are available to predict the risk of pressure ulcers in children. However, the performances of those scales have not yet been compared in China.

Aim

To compare the Waterlow, Braden Q, and Glamorgan scales, and identify more suitable pressure ulcer evaluation scale for the pediatric intensive care unit (PICU).

Methods

Trained nurses used the Waterlow, Braden Q, and Glamorgan scales to assess pediatric patients at Sun Yat-sen Memorial Hospital (China) within 24 h of admission from May 2017 to December 2020 in two stages. Skin examination was carried out to identify pressure ulcers every 3 d for 3 wk.

Results

The incidence of pressure ulcers was 3/28 (10.7\%) in the PICU and 5/314 (1.6\%) in the general pediatric ward. For children in the general ward, the Waterlow, Braden Q, and Glamorgan scales had comparable area under the operating characteristic curve (AUC) of 0.870, 0.924, and 0.923, respectively, and optimal cut-off values of 14, 14, and 29 points. For PICU, the Waterlow, Braden Q, and Glamorgan scales had slightly lower AUC of 0.833, 0.733, and 0.800, respectively, and optimal cut-off values of 13, 16, and 27 points. Braden Q demonstrated a satisfactory specificity, and during the second stage of the study for PICU patients, the AUC of the Braden Q scale was 0.810, with an optimal cut-off value of 18.35 points.

Conclusion

The Waterlow, Braden Q, and Glamorgan scales have comparable performance,
the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

Country/Territory of origin: China

Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

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while the Braden Q scale demonstrates a better specificity and can be successfully used by pediatric nurses to identify patients at high risk of pressure ulcers in PICU.

Key Words: Pressure ulcer; Risk assessment; Children; Intensive care unit

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Core Tip: The present study explored and analyzed commonly used Waterlow, Braden Q, and Glamorgan scales for the predictive diagnostic value of pressure ulcers in pediatric patients. In this study, the Braden Q scale had the highest specificity, which might serve as a valuable tool to predict pressure ulcers in pediatric intensive care unit (PICU) patients. The Waterlow, Braden Q, and Glamorgan scales have comparable performance, while the Braden Q scale demonstrated a better specificity and can be successfully used by pediatric nurses to identify patients at high risk of pressure ulcers in PICU.

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INTRODUCTION

Children admitted to the medical care centers are at an increased risk of pressure ulcers[1-3]. The prevalence of pressure ulcers in pediatric patients ranges from 1.72% to 18.6% in different countries and ages and is higher in pediatric intensive care units (PICUs) than in general pediatric wards[4-6]. Owing to the unstable hemodynamic status and the prolonged bed rest, hospitalized children have a high risk of pressure ulcers. Additionally, compared to adults, hospitalized children have more difficulty expressing pain, discomfort, or the need for repositioning[7]. Pressure ulcers in children could have detrimental effects, including pain, infection, negative psychosocial impact due to scarring or alopecia, prolonged hospitalization time, and increased treatment costs[8]. Thus, identifying pediatric patients at risk for pressure ulcer development would allow timely intervention to prevent the occurrence of pressure sores.

Outside of China, at least 12 pediatric risk assessment scales for pressure ulcers have been described and assessed in the clinical setting, including the Braden Q[9], Glamorgan[10], and Waterlow scales[11]. The Braden Q scale was frequently used to assess the risk in pediatric patients[12] and validated in patients aged 3 wk to 8 years using receiver operating characteristic (ROC) curve analysis. Subsequently, the development of pressure ulcers was predicted based on an area under the ROC curve (AUC) of 0.83 and a cut-off score of 16 points, a sensitivity of 0.88, and a specificity of 0.58[13,14]. A meta-analysis showed that the pooled sensitivity and specificity of the Braden Q scale for pediatric patients were 0.73 and 0.61, respectively[15], and another meta-analysis provided the same conclusion[16]. The Glamorgan scale has also been validated for use in children[10], with a sensitivity of 0.984 and specificity of 0.674 at a cut-off score of 15 points[10], although one study has questioned its validity in a low-risk setting[17]. The Waterlow scale has a high specificity and low sensitivity and is recommended for use in conjunction with clinical evaluation[18].

A small number of studies have compared the utilities of different risk assessment scales in the prediction of pressure ulcer development in children. Anthony et al[19] compared the Braden Q, Glamorgan, and Garvin scales and concluded that the Glamorgan risk assessment scale had the best predictive ability. Conversely, Willock et al[9] found that the Braden Q and Glamorgan scales performed similarly when used in neonatal and PICUs and that the Braden Q scale might have an advantage over the Glamorgan scale in general pediatric wards. Kottner et al[20] conducted a systematic review of 15 publications utilizing 12 different pediatric pressure ulcer risk scales and...
concluded that no single instrument could be considered superior to the others. Thus, despite the availability of numerous scales to assess the risk of pressure ulcers in children, the tool with the best predictive utility in clinical practice is yet to be identified. Interestingly, the optimum risk assessment scale might vary depending on the patient’s anatomy, physiology, and health condition, which could depend on age and whether the patient is in a general pediatric ward or PICU.

In China, only a few studies have evaluated pediatric pressure ulcer risk assessment scales[21,22], and the clinical nursing practice guidelines also lack evidence-based research. In addition, the majority of pediatric pressure ulcer prevention programs are derived from adult assessment scales, ignoring the anatomical and physiological differences between adults and children. Based on these, there is an urgent need for validating and comparing different approaches to the pressure ulcer risk assessment in China. The present study aimed to evaluate the Waterlow, Braden Q, and Glamorgan risk assessment scales in pediatric patients admitted to the Sun Yat-sen Memorial Hospital (China), in order to identify more suitable pressure ulcer evaluation scale for the PICU.

MATERIALS AND METHODS

Study participants
This prospective cohort study enrolled children admitted to the general pediatric ward and PICU of our hospital in two stages, from May 2017 to August 2017 (first stage) and from January 2018 to December 2021 (second stage), respectively.

The inclusion criteria were as follows: (1) Age 28 d-14 years; (2) Admitted to the general pediatric ward or PICU of our hospital; (3) Stayed in the ward/PICU for at least 24 h; and (4) No pressure ulcers were present at the time of admission. The exclusion criterion were as follows: (1) Lost to follow-up, i.e., a full dataset for skin assessment was not available for the 3-wk follow-up period due to termination of the assessments (for whatever reason); (2) Discharge from the hospital; or (3) Death.

This study was approved by the ethics committee of Sun Yat-sen Memorial Hospital [approval number: 2017(23)]. All patients or their legal guardians provided informed written consent before participation in the study.

Administration of Waterlow, Braden Q, and Glamorgan risk assessment instruments
The participating nurses administered the Waterlow, Braden Q, and Glamorgan risk assessment tools to each child within 24 h of admission, in accordance with the scoring rules of each scale. All participating nurses had undergone standardized training and assessment in the administration of these scales to maximize the consistency and reliability of the evaluation[14]. The Waterlow scale contains several items (build/weight for height, visual assessment of the skin, sex/age, continence, mobility, appetite, tissue malnutrition, neurological deficit, major surgery/trauma, and medication) and identifies three risk categories: At risk (score 10-14), high risk (score 15-19), and very high risk (score ≥ 20)[11]. The Braden Q scale consists of seven subscales (mobility, activity, sensory perception, moisture, friction and shear, nutrition, and tissue perfusion/oxygenation) each scored 1-4, with the total score ranging from 7 (highest risk) to 28 (lowest risk)[9]. The Glamorgan scale contains nine items (mobility, equipment/objects/hard surface pressing on the skin, significant anemia, persistent pyrexia, poor peripheral perfusion, inadequate nutrition, low serum albumin, weight, and incontinence) with the total score ranging from 0 to 42[10].

Six nurses were selected for data collection, among those who have more than 3 years of experience in the pediatric pressure ulcers care. Selected nurses have completed unified training and assessment to ensure reliability and consistency of the evaluation. Two nurses as a group collected the data for skin assessment simultaneously to ensure the accuracy of data collection.

Skin assessment
Each patient was followed for 3 wk with regular skin assessments to check for the development of any pressure ulcers. These skin assessments were performed by trained nurses blinded to the risk assessment scale scores. The first assessment was made 24 h after admission, and subsequent assessments were made every 3 d. Therefore, a total of eight skin assessments were carried out for each patient. Any pressure ulcers identified were classified as stage 1 (intact skin with localized non-branchable erythema), stage 2 (partial-thickness skin loss with exposure of dermis), stage 3 (full-thickness skin loss), or stage 4 (full-thickness skin and tissue loss) based
on the 2016 revised version of the National Pressure Ulcer Advisory Panel staging system[23].

**Statistical analysis**

Statistical analyses were performed using SPSS 22.0 (Inclusion Body Myositis Corp, Armonk, New York, United States). ROC curve analysis was used to analyze the ability of each scale to predict the development of pressure ulcers. The AUC, optimal cut-off value, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated.

### RESULTS

**Baseline demographic and clinical characteristics of study participants**

A total of 342 children admitted during the first stage of the study were included in the final analysis; 28 patients (mean age: 78.3 ± 15.3 mo; 13 males, 46.4%) were admitted to the PICU and 314 (mean age: 56.7 ± 19.4 mo; 197 males, 62.7%) were admitted to the general ward. The baseline characteristics of the study participants are summarized in Table 1. Among them, children with blood tumors accounted for 64.3% of the total patients in intensive care unit and 42.4% of the total patients in the general ward.

A total of 349 children were admitted to the PICU during the second stage of the study; among them, 7 were admitted for < 24 h. Finally, a total of 342 children (mean age: 70.3 ± 49.8 mo; 188 males, 55.0%) were included in the final analysis. The baseline characteristics of the study participants are summarized in Table 2.

**Incidence, categories, and locations of pressure ulcers**

The incidence of pressure ulcers during the 3-wk follow-up during the first stage was 3/28 (10.7%) for children in the ICU and 5/314 (1.6%) for children in the general ward. For children in the ICU, one ulcer (3.6%) was stage 1, and two ulcers (7.1%) were stage 2. For children in the general ward, three ulcers (1.0%) were stage 1, and two ulcers (0.6%) were stage 2. The locations of the pressure ulcers are listed in Table 3.

The incidence of pressure ulcers during the second stage was 13/342 (3.8%) for children in the ICU. Among these, nine ulcers (2.6%) were stage 1 and four (1.2%) were stage 2. The locations of the pressure ulcers are presented in Table 4.

For the second stage of the study, pressure ulcers were detected in 12/13 (92.3%) patients; seven cases had hematological tumor disease, including five cases (5/7, 71.4%) with hematopoietic stem cell transplantation, and four/six (66.7%) of the remaining cases after surgery required follow-up chemotherapy after tumor biopsy. Therefore, 11/13 (85%) cases of pressure ulcers had malignant tumors. Barthel rating scale was used to evaluate the patients’ performance in activities of daily living. The scores of 13 patients were 10-25 points, which belonged to severe dependence. Based on the children’s body mass index (BMI), assessed according to the criteria of the World Health Organization, there were four cases with BMI < 1 standard deviation (SD), one with BMI < 2 SD, and three with BMI < 3 SD (Table 5).

During the second stage, the laboratory examination of patients with pressure ulcer showed that the D-dimer results of 11 (84.6%) patients were > 0.55, and the C-reactive protein level in 10/13 (76.9%) patients was > 5. Furthermore, 9/13 (69.2%) patients had anemia with varying hemoglobin values (hemoglobin < 100 g/L; Table 6).

**ROC curve analysis of abilities of the three scales to predict pressure ulcer development**

For children in the ICU, the AUC values for the Waterlow, Braden Q, and Glamorgan scales were 0.833, 0.733, and 0.800, respectively (Figure 1). Although this indicated that the Waterlow scale might have the best overall accuracy in predicting the development of pressure ulcers in the PICU, the interpretation should be made with caution due to the wide 95% confidence intervals (CIs) (Table 3). The Waterlow, Braden Q, and Glamorgan scales had optimal cut-off values of 13, 16, and 27 points, respectively. With the optimal cut-off value, the sensitivity was 0.667 for all three scales, while the specificity was 0.720 for the Waterlow scale, 0.840 for the Braden Q scale, and 0.720 for the Glamorgan scale. Table 3 compares the sensitivity, specificity, PPV, and NPV between the three risk assessment scales for PICU patients.

For children admitted to the general ward, the Waterlow, Braden Q, and Glamorgan scales had an AUC of 0.870, 0.924, and 0.923, respectively (Figure 2). Although this
Table 1 Baseline demographic and clinical characteristics of the study participants (first stage of the study, May 2017-August 2017)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Intensive care unit (n = 28)</th>
<th>General pediatric ward (n = 314)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mo)</td>
<td>78.3 ± 15.3</td>
<td>56.7 ± 19.4</td>
</tr>
<tr>
<td>Male, n</td>
<td>13 (46.4%)</td>
<td>197 (62.7%)</td>
</tr>
<tr>
<td>Waterlow scale score</td>
<td>10.9 ± 6.0</td>
<td>4.6 ± 2.7</td>
</tr>
<tr>
<td>Braden Q scale score</td>
<td>17.8 ± 4.3</td>
<td>24.6 ± 3.5</td>
</tr>
<tr>
<td>Glamorgan scale score</td>
<td>26.9 ± 5.6</td>
<td>7.5 ± 9.2</td>
</tr>
<tr>
<td>Patients with squeezing or rubbing of the skin, n</td>
<td>28 (100%)</td>
<td>57 (18.2%)</td>
</tr>
<tr>
<td>Patients with pain at admission, n</td>
<td>8 (28.6%)</td>
<td>11 (3.5%)</td>
</tr>
<tr>
<td>Patients with mechanical ventilation, n</td>
<td>19 (67.9%)</td>
<td>7 (2.3%)</td>
</tr>
<tr>
<td>Patients with blood tumor, n</td>
<td>18 (64.3%)</td>
<td>133 (42.4%)</td>
</tr>
<tr>
<td>Death, n</td>
<td>4 (14.2%)</td>
<td>1 (0.3%)</td>
</tr>
</tbody>
</table>

Data are presented as the mean ± SD.

Table 2 Baseline demographic and clinical characteristics of the study participants (second stage, from January 2018-2020)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Intensive care unit (n = 342)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mo)</td>
<td>70.3 ± 49.8</td>
</tr>
<tr>
<td>Male, n</td>
<td>188 (55.0%)</td>
</tr>
<tr>
<td>Length of stay &gt; 1 d ≤ 10 d, n</td>
<td>291 (85.0%)</td>
</tr>
<tr>
<td>Length of stay &gt; 10 d, n</td>
<td>51 (14.9%)</td>
</tr>
<tr>
<td>Braden Q scale score</td>
<td>26.9 ± 5.6</td>
</tr>
<tr>
<td>Patients with blood tumor, n</td>
<td>210 (61.4%)</td>
</tr>
<tr>
<td>Patients with immune system diseases, n</td>
<td>30 (8.77%)</td>
</tr>
<tr>
<td>Patients with respiratory diseases, n</td>
<td>41 (12.0%)</td>
</tr>
<tr>
<td>Postoperative patients, n</td>
<td>48 (14.0%)</td>
</tr>
<tr>
<td>Other patients, n</td>
<td>13 (3.8%)</td>
</tr>
<tr>
<td>Pressure ulcer incidence, n</td>
<td>13 (3.8%)</td>
</tr>
<tr>
<td>Patients with mechanical ventilation, n</td>
<td>19 (67.9%)</td>
</tr>
<tr>
<td>Transfer out</td>
<td>281 (82.2%)</td>
</tr>
<tr>
<td>Leave hospital</td>
<td>39 (11.41%)</td>
</tr>
<tr>
<td>Death, n</td>
<td>22 (6.43%)</td>
</tr>
</tbody>
</table>

suggested a superior overall predictive accuracy for the Braden Q and Glamorgan tools when used in general wards, no definitive conclusion could be drawn due to the substantial overlap of the 95% CIs (Table 3). The optimal cut-off values for the Waterlow, Braden Q, and Glamorgan scales were 14, 14, and 29 points, respectively. At the appropriate optimal cut-off value, the Waterlow, Braden Q, and Glamorgan scales had a sensitivity of 0.600 and specificity of 0.990, 0.980, and 0.790, respectively. Table 3 lists the sensitivity, specificity, PPV, and NPV for the three risk assessment scales when used in the patients in the general ward.

DISCUSSION

The main finding of the present study was that all three risk assessment scales showed a reasonable performance in the prediction of pressure ulcer development in hospitalized pediatric patients. The Waterlow scale had the highest AUC value among the
### Table 3 Pressure ulcer incidence, stage, and location (first stage of the study, May 2017-August 2017)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Intensive care unit (n = 28)</th>
<th>General pediatric ward (n = 314)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pressure ulcer incidence</td>
<td>3 (10.7%)</td>
<td>5 (1.6%)</td>
</tr>
<tr>
<td>NPUAP stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 1</td>
<td>1 (3.6%)</td>
<td>3 (1.0%)</td>
</tr>
<tr>
<td>Stage 2</td>
<td>2 (7.1%)</td>
<td>2 (0.6%)</td>
</tr>
<tr>
<td>Location of pressure ulcer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scalp</td>
<td>1 (33.3%)</td>
<td>0</td>
</tr>
<tr>
<td>Nose</td>
<td>1 (33.3%)</td>
<td>0</td>
</tr>
<tr>
<td>Face</td>
<td>0</td>
<td>2 (40%)</td>
</tr>
<tr>
<td>Toe</td>
<td>0 (0%)</td>
<td>2 (40%)</td>
</tr>
<tr>
<td>Thumb</td>
<td>0</td>
<td>1 (20%)</td>
</tr>
<tr>
<td>Ankle</td>
<td>1 (33.3%)</td>
<td>0</td>
</tr>
<tr>
<td>Patients with mechanical ventilation, n</td>
<td>0 (0%)</td>
<td>5 (100%)</td>
</tr>
</tbody>
</table>

NPUAP: National Pressure Ulcer Advisory Panel.

### Table 4 Pressure ulcer incidence, stage, and location (second stage of the study, January 2018-2020)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Intensive care unit (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pressure ulcer incidence, n</td>
<td>13 (3.8%)</td>
</tr>
<tr>
<td>Patients with mechanical ventilation, n</td>
<td>12 (92.3%)</td>
</tr>
<tr>
<td>Patients with blood tumor, n</td>
<td>7 (61.4%)</td>
</tr>
<tr>
<td>Postoperative patients, n</td>
<td>6 (14.0%)</td>
</tr>
<tr>
<td>NPUAP stage</td>
<td></td>
</tr>
<tr>
<td>Stage 1</td>
<td>9 (69.2%)</td>
</tr>
<tr>
<td>Stage 2</td>
<td>4 (30.8%)</td>
</tr>
<tr>
<td>Location of pressure ulcer</td>
<td></td>
</tr>
<tr>
<td>Occiput</td>
<td>3</td>
</tr>
<tr>
<td>Nose</td>
<td>3</td>
</tr>
<tr>
<td>Buttocks</td>
<td>2</td>
</tr>
<tr>
<td>Ear</td>
<td>1</td>
</tr>
<tr>
<td>Head</td>
<td>1</td>
</tr>
<tr>
<td>Cervix</td>
<td>1</td>
</tr>
<tr>
<td>Heel</td>
<td>1</td>
</tr>
<tr>
<td>Toe</td>
<td>1</td>
</tr>
<tr>
<td>Transfer out</td>
<td>11 (84.6%)</td>
</tr>
<tr>
<td>Leave hospital</td>
<td>1 (7.7%)</td>
</tr>
<tr>
<td>Death, n</td>
<td>1 (7.7%)</td>
</tr>
</tbody>
</table>

In the present study, the AUC values of the Waterlow, Braden Q, and Glamorgan scales were 0.833, 0.733, and 0.800, respectively, in the PICU and 0.870, 0.924, and 0.923, respectively, in the general ward (Table 7). The AUC value range was 0.5-1.0; a
Table 5 Diagnosis, self-care ability score, nutrition score, and related information of patients with pressure ulcer (second stage of the study, from January 2018 to 2020)

<table>
<thead>
<tr>
<th>Inpatient number</th>
<th>Sex (M/F)</th>
<th>Age (mo)</th>
<th>Weight (kg)</th>
<th>Main diagnosis</th>
<th>Other diagnosis</th>
<th>Time of staying in PICU (d)</th>
<th>Branden Q score</th>
<th>Barthel score</th>
<th>BMI score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1047089</td>
<td>F</td>
<td>60</td>
<td>18.5</td>
<td>Primary lymphoma of bone (stage IV)</td>
<td>After resection of left occipital tumor</td>
<td>4</td>
<td>14</td>
<td>10</td>
<td>18.5</td>
</tr>
<tr>
<td>1093493</td>
<td>F</td>
<td>60</td>
<td>21</td>
<td>TI-7 mixed intraspinal and extraspinal ganglioneuroblastoma (low risk)</td>
<td></td>
<td>2</td>
<td>13</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>632852</td>
<td>F</td>
<td>108</td>
<td>33</td>
<td>Severe aplastic anemia after hematopoietic stem cell transplantation</td>
<td>Intracranial hemorrhage; graft versus host disease</td>
<td>26</td>
<td>18</td>
<td>20</td>
<td>21.1</td>
</tr>
<tr>
<td>1116677</td>
<td>F</td>
<td>133</td>
<td>32</td>
<td>Left thalamic and intraventricular variant astrocytoma (WHO stage III)</td>
<td></td>
<td>6</td>
<td>15</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>1126874</td>
<td>F</td>
<td>6</td>
<td>6.5</td>
<td>Postoperative complications of resection of right skull base myofibrolastoma</td>
<td>Bronchopneumonia</td>
<td>15</td>
<td>13</td>
<td>10</td>
<td>15.4</td>
</tr>
<tr>
<td>1066251</td>
<td>M</td>
<td>144</td>
<td>25</td>
<td>Acute lymphoblastic leukemia after hematopoietic stem cell transplantation</td>
<td>Severe pneumonia; hyperacute graft versus host disease</td>
<td>19</td>
<td>18</td>
<td>25</td>
<td>11.3</td>
</tr>
<tr>
<td>831463</td>
<td>M</td>
<td>156</td>
<td>45</td>
<td>Cervical spinal cord injury</td>
<td>Multiple cervical fractures</td>
<td>40</td>
<td>13</td>
<td>10</td>
<td>15.9</td>
</tr>
<tr>
<td>829101</td>
<td>M</td>
<td>48</td>
<td>17.7</td>
<td>Severe aplastic anemia after hematopoietic stem cell transplantation</td>
<td>Acute graft versus host disease (stage IV)</td>
<td>42</td>
<td>10</td>
<td>10</td>
<td>18.1</td>
</tr>
<tr>
<td>850224</td>
<td>F</td>
<td>110</td>
<td>24</td>
<td>Postoperative complications of resection of ameloblastoma of left mandible</td>
<td></td>
<td>3</td>
<td>14</td>
<td>10</td>
<td>13.2</td>
</tr>
<tr>
<td>825633</td>
<td>M</td>
<td>36</td>
<td>10</td>
<td>Acute lymphoblastic leukemia after hematopoietic stem cell transplantation</td>
<td>Severe pneumonia; hyperacute graft versus host disease (stage IV)</td>
<td>11</td>
<td>16</td>
<td>10</td>
<td>11.8</td>
</tr>
<tr>
<td>868274</td>
<td>F</td>
<td>8</td>
<td>5</td>
<td>Postoperative complications of right submandibular gland cyst resection</td>
<td>Protein energy malnutrition</td>
<td>5</td>
<td>16</td>
<td>10</td>
<td>11.1</td>
</tr>
<tr>
<td>858433</td>
<td>F</td>
<td>121</td>
<td>25</td>
<td>Right mandible osteosarcoma after surgery and chemotherapy</td>
<td>Abnormal liver function</td>
<td>7</td>
<td>16</td>
<td>10</td>
<td>14.8</td>
</tr>
<tr>
<td>852006</td>
<td>M</td>
<td>24</td>
<td>12.4</td>
<td>Acute lymphoblastic leukemia after hematopoietic stem cell transplantation</td>
<td>Severe pneumonia; acute graft versus host disease</td>
<td>37</td>
<td>12</td>
<td>10</td>
<td>17.2</td>
</tr>
</tbody>
</table>

PICU: Pediatric intensive care unit; BMI: Body mass index; WHO: World Health Organization.

high value reflected better overall diagnostic/predictive accuracy in the clinical setting [24]. Thus, based on the AUC values, our findings indicated that the Waterlow scale might exhibit the best overall accuracy in the PICU, whereas the Braden Q and Glamorgan instruments might have superior accuracy in the general pediatric ward. However, these interpretations should be made with caution due to the large overlap of 95% CIs and would need to be tested in a future study with large sample size.

In the present study, the optimal cut-off values for the Waterlow, Braden Q, and Glamorgan scales were 13, 16, and 27 points, respectively, when administered to patients in the PICU and 14, 14, and 29 points, respectively, when administered to patients in the general ward. In the PICU, the sensitivity of all three scales was 0.667, while the specificity was 0.720, 0.840, and 0.720 for the Waterlow, Braden Q, and Glamorgan scales, respectively. Although the AUC value was the highest for the Waterlow scale, the Braden Q scale had the highest specificity suggesting that it may be the most useful tool for PICU. In the general ward, the sensitivity was 0.600 for all three scales, and the specificity was 0.990, 0.980, and 0.790 for the Waterlow, Braden Q, and Glamorgan scales, respectively. Thus, the Braden Q and Waterlow scales had better specificities than the Glamorgan scale. Although our data are preliminary, we tentatively suggested that the Braden Q tool has the best overall performance in both...
According to the previously obtained results, the Braden Q scale demonstrated the most satisfactory performance and we used it to predict pressure ulcers in pediatric patients during the second stage of the study, from January 2018 to December 2020. The AUC value of the Braden Q scale was 0.810, the optimal cut-off value was 18.35 points, the sensitivity was 1.0, and the specificity was 0.553, which were slightly higher compared to results obtained during the first stage (Figure 3).

In previous studies, the Braden Q scale had a sensitivity of 0.88 and specificity of 0.58 [13,14], while the Glamorgan scale had a sensitivity of 0.984 and specificity of 0.674 [10]. Although the previous studies did not distinguish between patients in the PICU and general ward, the sensitivity values were higher and specificity values lower than those obtained in both settings (i.e., PICU and general ward) in our study. Other studies conducted in the PICU yielded a sensitivity of 0.88 (cut-off value 20 points) for the Waterlow scale, 0.83 (cut-off value 16 points) for the Braden Q scale, and 0.87 (cut-off value 29 points) for the Glamorgan scale, while the sensitivity values for children in the general pediatric ward and the PICU.

Table 6 Test results on the day of pressure ulcer diagnosis for pediatric intensive care unit patients (second stage of the study, from January 2018 to 2020)

<table>
<thead>
<tr>
<th>Inpatient number</th>
<th>White blood cell count</th>
<th>Red blood cell count</th>
<th>Hemoglobin value</th>
<th>Platelet calculation</th>
<th>Blood pH value</th>
<th>CRP</th>
<th>D-Dimer (0-0.55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1047089</td>
<td>2.92</td>
<td>3.09</td>
<td>88</td>
<td>594</td>
<td>7.314</td>
<td>9.3</td>
<td>4.1</td>
</tr>
<tr>
<td>1093493</td>
<td>12.11</td>
<td>3.65</td>
<td>114</td>
<td>227</td>
<td>7.401</td>
<td>&lt; 5</td>
<td>1.35</td>
</tr>
<tr>
<td>632852</td>
<td>1.57</td>
<td>2.57</td>
<td>71</td>
<td>43</td>
<td>7.438</td>
<td>102.3</td>
<td>2.37</td>
</tr>
<tr>
<td>1116677</td>
<td>13.71</td>
<td>3.23</td>
<td>97</td>
<td>194</td>
<td>7.435</td>
<td>75.1</td>
<td>2.77</td>
</tr>
<tr>
<td>1126874</td>
<td>6.24</td>
<td>3.37</td>
<td>91</td>
<td>247</td>
<td>7.301</td>
<td>62</td>
<td>0.23</td>
</tr>
<tr>
<td>1066251</td>
<td>9.56</td>
<td>2.86</td>
<td>108</td>
<td>66</td>
<td>7.374</td>
<td>&lt; 5</td>
<td>0.33</td>
</tr>
<tr>
<td>831463</td>
<td>9.56</td>
<td>2.86</td>
<td>108</td>
<td>66</td>
<td>7.385</td>
<td>&lt; 5</td>
<td>0.33</td>
</tr>
<tr>
<td>829101</td>
<td>13.8</td>
<td>2.97</td>
<td>87</td>
<td>375</td>
<td>7.392</td>
<td>&lt; 5</td>
<td>7.85</td>
</tr>
<tr>
<td>850224</td>
<td>9.66</td>
<td>2.48</td>
<td>75</td>
<td>28</td>
<td>7.331</td>
<td>57.9</td>
<td>2.59</td>
</tr>
<tr>
<td>825633</td>
<td>11.7</td>
<td>2.69</td>
<td>78</td>
<td>220</td>
<td>7.439</td>
<td>58.7</td>
<td>1.27</td>
</tr>
<tr>
<td>868274</td>
<td>5.68</td>
<td>3.63</td>
<td>101</td>
<td>67</td>
<td>7.441</td>
<td>18.3</td>
<td>7.8</td>
</tr>
<tr>
<td>858433</td>
<td>9.93</td>
<td>4.45</td>
<td>110</td>
<td>645</td>
<td>7.35</td>
<td>23.9</td>
<td>1.48</td>
</tr>
<tr>
<td>852006</td>
<td>5.61</td>
<td>2.88</td>
<td>89</td>
<td>239</td>
<td>7.402</td>
<td>72.2</td>
<td>2.65</td>
</tr>
</tbody>
</table>

CRP: C-reactive protein.

95%CI: 95% confidence interval; AUC: Area under the receiver operating characteristic curve; NPV: Negative predictive value; PPV: Positive predictive value.

Table 7 Receiver operating characteristic curve analysis of abilities of Waterlow, Braden Q, and Glamorgan risk assessment scales to predict development of pressure ulcers in pediatric patients (first stage of the study, between May 2017 and August 2017)

<table>
<thead>
<tr>
<th>Scale</th>
<th>AUC (95%CI)</th>
<th>Optimal cut-off</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensive care unit</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Waterlow</td>
<td>0.833 (0.653-1.000)</td>
<td>≤ 13</td>
<td>0.667</td>
<td>0.720</td>
<td>0.100</td>
<td>0.900</td>
</tr>
<tr>
<td>Braden Q</td>
<td>0.733 (0.508-0.959)</td>
<td>≤ 16</td>
<td>0.667</td>
<td>0.840</td>
<td>0.090</td>
<td>0.910</td>
</tr>
<tr>
<td>Glamorgan</td>
<td>0.800 (0.629-0.971)</td>
<td>≤ 27</td>
<td>0.667</td>
<td>0.720</td>
<td>0.100</td>
<td>0.900</td>
</tr>
<tr>
<td>General ward</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Waterlow</td>
<td>0.870 (0.718-1.000)</td>
<td>≤ 14</td>
<td>0.600</td>
<td>0.990</td>
<td>0.010</td>
<td>0.990</td>
</tr>
<tr>
<td>Braden Q</td>
<td>0.924 (0.838-1.000)</td>
<td>≤ 14</td>
<td>0.600</td>
<td>0.980</td>
<td>0.010</td>
<td>0.990</td>
</tr>
<tr>
<td>Glamorgan</td>
<td>0.923 (0.839-1.000)</td>
<td>≤ 29</td>
<td>0.600</td>
<td>0.790</td>
<td>0.013</td>
<td>0.987</td>
</tr>
</tbody>
</table>
Luo WJ et al. Braden Q risk assessment of pressure ulcers in PICU

Figure 1 Area under the operating characteristic curve values for the Waterlow, Braden Q, and Glamorgan scales in children in the pediatric intensive care unit.

the general ward were 0.83 (cut-off value 25 points) for the Waterlow scale, 0.87 (cut-off value 18 points) for the Braden Q scale, and 0.98 (cut-off value 33 points) for the Glamorgan scale[17]. Furthermore, the AUC values for the Waterlow, Braden Q, and Glamorgan scales in previous studies were 0.69, 0.83, and 0.73, respectively, in the PICU and 0.45, 0.83, and 0.47, respectively, in the general ward[25,26]. These data differed slightly from those reported in the present study, which could be attributed to the varied underlying medical conditions and general health status of the patients between different studies. These discrepancies might have influenced the risk of the development of pressure ulcers and their incidence.

Concurrently, in order to confirm the integrity of the results obtained in the first stage of the study, the second stage was undertaken in order to evaluate Braden Q scale performance in PICU from January 2018 to December 2020. The results showed that the Braden Q scale had an optimal AUC value in predicting pressure ulcers in PICU, which was slightly better than the previous data in 2017, supporting the hypothesis that the Braden Q scale could successfully predict the occurrence of pressure ulcers in PICU. In addition, 60% of the children with severe diseases included in the second stage of the study had blood cancer and the Braden Q scale was useful in predicting the pressure ulcer in this group of patients. Conversely, for children with pressure ulcers, during both stages of the study, mechanical ventilation was associated with an increased risk, which needs further follow-up.

The second stage of the study included 342 cases from 2018 to 2020, and children with blood cancer accounted for a large proportion of the patients. Among the 13 cases of pressure ulcer, 92.3% were on ventilator-assisted breathing, and in those who developed pressure ulcer, the hemoglobin level was low (55-114) g/L in 9 (69.2%) cases and < 100 g/L in 9 (21.1%) cases. In addition, nutritional status, tissue perfusion, and oxygenation are reflected in the Braden Q scale, thus we recommend closer observation in the above issues to prevent the occurrence of pressure ulcers (Table 8).

The scoring for some of the items in these risk assessment scales was subjective, resulting in disparities between results, obtained in different stages. The values should be adjusted in accordance with the patient’s test results, the score of physical indicators, and the objective values from the nursing records, such as blood pressure and excretion.
### Table 8 Score of each item of Branden Q score for pediatric intensive care unit patients (second stage of the study, from January 2018 to 2020)

<table>
<thead>
<tr>
<th>Inpatient number</th>
<th>Mobility</th>
<th>Activity</th>
<th>Sensory perception</th>
<th>Moisture</th>
<th>Friction-shear</th>
<th>Nutrition</th>
<th>Tissue perfusion and oxygenation</th>
<th>Total score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1047089</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>14</td>
</tr>
<tr>
<td>1093493</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>4</td>
<td>13</td>
</tr>
<tr>
<td>632852</td>
<td>3</td>
<td>1</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>18</td>
</tr>
<tr>
<td>1116677</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>15</td>
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<tr>
<td>1126874</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td>1066251</td>
<td>3</td>
<td>1</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>18</td>
</tr>
<tr>
<td>831463</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td>829101</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>850224</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>14</td>
</tr>
<tr>
<td>825633</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>16</td>
</tr>
<tr>
<td>868274</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>4</td>
<td>16</td>
</tr>
<tr>
<td>858433</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>16</td>
</tr>
<tr>
<td>852006</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>12</td>
</tr>
</tbody>
</table>

Figure 2 Area under the operating characteristic curve values for the Waterlow, Braden Q, and Glamorgan scales in children admitted to the general ward.

The data obtained from the first stage in 2017 or second stage in 2018-2020 differ from some of the reports published previously. Nonetheless, our results provide information on the putative clinical application of the three risk assessment scales in the prediction of pressure ulcer development in hospitalized children. In our study, the Braden Q scale was an optimal tool for predicting pressure ulcers in PICU patients.
and additional studies across multiple centers with a larger sample size would substantiate the current findings.

In addition, the constituent items of the Braden Q scale include hemoglobin content, blood oxygen saturation and friction items of independent patients. These items can better reflect the status of children with blood tumors. The Braden Q scale demonstrated the highest specificity and could be successfully used as a tool for the prediction of pressure ulcers in PICU patients.

CONCLUSION

The Waterlow, Braden Q, and Glamorgan scales have comparable performance, while the Braden Q scale demonstrates a better specificity and can be successfully used by pediatric nurses to identify patients at high risk of pressure ulcers in PICU.

ARTICLE HIGHLIGHTS

Research background
Many scales are available to predict the risk of pressure ulcers in children. However, the performances of those scales have not yet been compared in China.

Research motivation
To explore the value of pressure ulcer evaluation scales in Chinese pediatric patients.

Research objectives
To compare the Waterlow, Braden Q, and Glamorgan scales, and identify more suitable pressure ulcer evaluation scale for the pediatric intensive care unit (PICU).

Research methods
Trained nurses used the Waterlow, Braden Q, and Glamorgan scales to assess pediatric patients at Sun Yat-sen Memorial Hospital (China) within 24 h of admission, from May 2017 to December 2020 in two stages. Skin examination was carried out to identify pressure ulcers every 3 d for 3 wk.
Research results
For PICU, the Waterlow, Braden Q, and Glamorgan scales had slightly lower area under the operating characteristic curve (AUC) of 0.833, 0.733, and 0.800, respectively, and optimal cut-off values of 13, 16, and 27 points. Braden Q demonstrated a satisfactory specificity, and during the second stage of the study for PICU patients, the AUC of the Braden Q scale was 0.810, with an optimal cut-off value of 18.35 points.

Research conclusions
The Waterlow, Braden Q, and Glamorgan scales have comparable performance, while the Braden Q scale demonstrates a better specificity and can be successfully used by pediatric nurses to identify patients at high risk of pressure ulcers in PICU.

Research perspectives
In our study, the Braden Q scale is an optimal tool for predicting pressure ulcers in PICU patients, and additional studies across multiple centers with a larger sample size would substantiate the current findings.

REFERENCES
17. Kottner J, Kenzler M, Wilborn D. Interrater agreement, reliability and validity of the Glamorgan Scale...


25 Wang YB. Waterlow pressure sores Risk Factor Assessment Table to evaluate the effectiveness of preventing pressure sores. *Zhongguo shiyong huli zazhi* 2015; 31 (5): 359-360

Clinical significance of signet ring cells in surgical esophageal and esophagogastroduodenal adenocarcinoma: A systematic review and meta-analysis

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Author contributions: Ma HT made substantial contributions to the conception and design of the work; Wang YF and Xu SY searched and selected the materials and extracted the data; Wang YF and Xu SY wrote this manuscript; Yan Wang and Che GW revised the paper carefully and also contributed to the statistical analysis; Wang YF and Xu SY contributed equally to this work; and all authors have read and approved the final manuscript.

Conflict-of-interest statement: The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

PRISMA 2009 Checklist statement: This systematic review and meta-analysis were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

Country/Territory of origin: China

Specialty type: Medicine, research

Abstract

BACKGROUND
The clinical significance of signet ring cells (SRCs) in surgical esophageal and esophagogastroduodenal adenocarcinoma (EEGA) remains unclear now.

AIM
To explore the association between the presence of SRCs and the clinicopathological and prognostic characteristics in surgical EEGA patients by combining and analyzing relevant studies.

METHODS
The PubMed, Web of Science, and EMBASE electronic databases were searched for the relevant literature up to March 28, 2021. The relative risk (RR) with 95% confidence interval (CI) was calculated to assess the relationship between SRCs and clinicopathological parameters of surgical EEGA patients, and the hazard ratio (HR) with 95%CI was calculated to explore the impact of SRC on the prognosis. All statistical analyses were conducted with STATA 12.0 software.

RESULTS
A total of ten articles were included, involving 30322 EEGA patients. The pooled results indicated that the presence of SRCs was significantly associated with
tumor location (RR: 0.76, 95%CI: 0.61-0.96, \( P = 0.022 \); \( I^2 = 49.4\% \), \( P = 0.160 \)) and tumor-node-metastasis stage (RR: 1.30, 95%CI: 1.02-1.65, \( P = 0.031 \); \( I^2 = 73.1\% \), \( P = 0.002 \)). Meanwhile, the presence of SRCs in surgical EEGJA patients predicted a poor overall survival (HR: 1.36, 95%CI: 1.12-1.65, \( P = 0.002 \); \( I^2 = 85.7\% \), \( P < 0.001 \)) and disease-specific survival (HR: 1.86, 95%CI: 1.55-2.25, \( P < 0.001 \); \( I^2 = 63.1\% \), \( P = 0.043 \)).

**CONCLUSION**

The presence of SRCs is related with advanced tumor stage and poor prognosis and could serve as a reliable and effective parameter for the prediction of postoperative survival and formulation of therapy strategy in EEGJA patients. However, more high-quality studies are still needed to verify the above findings.

**Key Words:** Signet ring cells; Esophageal and esophagogastric junction adenocarcinoma; Clinicopathological characteristics; Prognosis; Systematic review; Meta-analysis

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**Core Tip:** Our manuscript indicated that the presence of signet ring cells (SRCs) was significantly associated with the tumor location (\( P = 0.022 \)) and tumor-node-metastasis stage (\( P = 0.031 \)). Meanwhile, the presence of SRCs in surgical esophageal and esophagogastric junction adenocarcinoma (EEGJA) patients predicted a poor overall survival (\( P = 0.002 \)) and disease-specific survival (\( P < 0.001 \)). The presence of SRC was related with advanced tumor stage and poor prognosis and could serve as a reliable and effective parameter for the prediction of postoperative survival and formulation of therapy strategy in EEGJA patients. However, more high-quality studies are still needed to verify the above findings.

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**INTRODUCTION**

Esophageal carcinoma is the eighth most common tumor worldwide with an estimated 456000 new cases in 2012 and an increasing incidence has been observed in recent decades (7.9/100000 in males and 1.4/100000 in females)[1-3]. Although great progress has been made in the surgical and adjuvant therapy of esophageal cancer in recent years, the survival of esophageal cancer patients remains poor due to the advanced stage at the time of diagnosis[4]. In Western countries, adenocarcinoma is the most common pathological subtype of esophageal cancer, although squamous cell carcinoma accounts for the highest proportion in Asian countries[5]. Signet ring cell (SRC) carcinoma is a rare mucinous subtype of adenocarcinoma that has been reported to be related with aggressive biology in gastrointestinal cancer[6,7].

Actually, the clinical significance of SRCs in gastric and colorectal carcinomas has been widely verified. Nie et al[8] included 19 studies involving 35947 cases and demonstrated that gastric carcinoma patients with SRCs tended to be younger (weighted mean difference = -3.88, \( P = 0.001 \)) and predominantly female [odds ratio (OR): 1.60, \( P < 0.001 \)]. Besides, the presence of SRCs was associated with a worse overall survival (OS) [hazard ratio (HR): 0.57, \( P = 0.002 \)] but advanced stage patients with SRCs were related with a worse prognosis (HR: 1.17, \( P < 0.001 \)); however, in the total population, no significant difference in OS between non-SRC and SRC patients was observed (HR: 1.02, \( P = 0.830 \)). Besides, analyzing 2454 colorectal cancer patients, Tan et al[9] demonstrated that the presence of SRCs was an independent prognostic risk factor in colorectal cancer patients (SRC ratio < 50%: 2.182, \( P = 0.005 \); SRC ratio > 50%: 1.699, \( P = 0.016 \)). Meanwhile, it has been reported that patients with an SRC ratio > 50% are more likely to experience an advanced stage.
Wang YF et al. SRCs in EEGJA patients

of disease and worse survival than patients with an SRC ratio < 50%[10]. However, these meta-analyses focused on the gastric and colorectal carcinomas which are more likely to be combined with SRCs and their results were inconsistent with the studies about esophageal and esophagogastric junction adenocarcinoma (EEGJA). Meanwhile, for EEGJA, the clinical significance of SRCs remains unclear because of the inconsistent reports[11-20].

Therefore, we conducted this systematic review and meta-analysis to explore the clinical significance of the presence of SRCs in EEGJA patients and the impact of SRCs on the clinicopathological and prognostic characteristics, which might contribute to the prediction of prognosis and formulation of treatment strategy for EEGJA patients.

MATERIALS AND METHODS

This systematic review and meta-analysis were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines[21].

Inclusion criteria

The inclusion criteria were as follows: (1) Patients were pathologically diagnosed with EEGJA; (2) All patients received surgical therapy; (3) Patients were divided into two groups according to the presence or absence of SRCs, and prospective randomized controlled trials (RCTs) or retrospective cohort studies were both available; (4) Clinicopathological parameters or prognosis between the two groups were compared and relevant data were provided; (5) Although the HRs with corresponding 95% confidence intervals (CIs) were not directly reported in articles, the Kaplan-Meier survival curves were provided to calculate them; and (6) The articles were published in English.

Literature retrieval

The PubMed, Web of Science, and EMBASE electronic databases were searched from the establishment date to March 28, 2021. The following terms were used: “esophageal”, “esophagus”, “esophagogastric”, “gastroesophageal”, “adenocarcinoma”, and “significance of signet ring cell”. A combination of subject terms and free words was applied. Besides, the references cited in included studies were also reviewed for availability (Figure 1).

Exclusion criteria

The exclusion criteria were as follows: (1) Duplicated studies or studies with severely overlapped data; (2) Case reports, reviews, meeting abstracts, and animal trials; and (3) Adenocarcinomas located in other sites like the stomach were also enrolled without subgroup analysis for EEGJA patients.

The titles and abstracts were screened first and irrelevant publications were excluded. Then full texts of potentially related studies were further reviewed for availability.

The literature retrieval and selection were conducted by two investigators (Wang YF and Xu SY).

Data extraction

The data extraction was conducted by two authors (Wang YF and Xu SY) through the Microsoft Excel sheet independently. The following information was extracted from each included studies: The author, publication year, country where the study was conducted, sample size, tumor location (esophageal vs esophagogastric), tumor-node-metastasis (TNM), SRC ratio, sex, smoking, family history, lymph node metastasis status, relative risk (RR), and HR with 95%CI or corresponding data for their calculation.

The association of SRCs with sex, smoking, family history, tumor location, lymph node metastasis, and TNM stage were measured in this study. For the prognostic role of SRCs in EEGJA, the primary outcome was the OS and the second outcomes included the disease-free survival (DFS) and disease-specific survival (DSS).

Quality assessment

The Newcastle-Ottawa Scale (NOS) was applied to evaluate the quality of included studies[22]. This scale includes object selection, comparability, and exposure assessment and objectively evaluates the risk of bias with the maximum score of 9, and
studies with a score ≥ 6 were considered to have high quality. The quality assessment was performed by two authors (Wang YF and Xu SY) independently. Any disagreement was solved by team discussion.

**Statistical analysis**
All statistical analyses were conducted with STATA 12.0 software. The RR and HR with corresponding 95% CI were calculated to assess the association between the presence of SRCs and clinicopathological characteristics and prognosis of EEGJA patients, respectively. If the HR with 95% CI was not reported in articles directly, they would be calculated from Kaplan-Meier curves. The heterogeneity among the included studies was evaluated by $I^2$ statistics and Q test. When significant heterogeneity was observed [$I^2 > 50\%$ and $(or) P < 0.1$], the random effects model was applied; otherwise, the fix effects model was used. The sensitivity analysis and meta-regression analysis were performed to detect the source of heterogeneity and evaluate the stability of pooled results. Besides, the Begg’s funnel plot and Egger’s test were conducted to detect publication bias. Significant publication bias was defined as $P < 0.05$.

**RESULTS**

**Literature retrieval**
Initially, 631 records were searched and then 90 duplicated records were excluded. After reviewing the titles and abstracts, 503 records without any relativity were excluded. Then, 17 full tests were assessed for eligibility after eliminating 21 publications according to our exclusion criteria. Finally, ten retrospective articles were included in this systematic review and meta-analysis.

**Basic characteristics**
Among the ten included articles, Chirieac et al.[11] and van Hootegem et al.[17] enrolled two different subgroups of patients, which were regarded as two studies separately. Thus, a total of 12 retrospective cohort studies from ten publications were included, involving 30322 EEGJA patients. Most cases were from America and the sample size ranged from 163 to 14224. Three studies only enrolled esophageal adenocarcinoma patients. All studies were high-quality studies with an NOS score of 6 or higher. Detailed information is presented in Table 1.

**Association between presence of SRCs and clinicopathological characteristics of EEGJA patients**
The pooled results indicated that SRCs were more likely to occur in esophageal adenocarcinoma rather than esophagogastroduodenal adenocarcinoma (RR: 0.76,
Table 1 Basic characteristics of included studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Sample size</th>
<th>Location</th>
<th>TNM</th>
<th>SRC ratio</th>
<th>Endpoint</th>
<th>NOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yoon et al[12]</td>
<td>2010</td>
<td>United States (MCTR)</td>
<td>796</td>
<td>Esophageal + EGJ</td>
<td>NR</td>
<td>&gt; 0%</td>
<td>OS, DSS, DFS</td>
<td>6</td>
</tr>
<tr>
<td>Yendamuri et al[13]</td>
<td>2013</td>
<td>United States (SEER)</td>
<td>11825</td>
<td>Esophageal</td>
<td>I-IV</td>
<td>&gt; 0%</td>
<td>OS</td>
<td>7</td>
</tr>
<tr>
<td>Nafteux et al[14]</td>
<td>2014</td>
<td>Belgium</td>
<td>779</td>
<td>Esophageal + EGJ</td>
<td>I-IV</td>
<td>1%-50%, &gt; 50%</td>
<td>DSS</td>
<td>7</td>
</tr>
<tr>
<td>Chen et al[16]</td>
<td>2017</td>
<td>China</td>
<td>671</td>
<td>Esophageal</td>
<td>I-III</td>
<td>1%-50%, &gt; 50%</td>
<td>OS</td>
<td>8</td>
</tr>
<tr>
<td>Van Hootegem et al[17]</td>
<td>2019</td>
<td>Australia</td>
<td>298</td>
<td>Esophageal + EGJ</td>
<td>NR</td>
<td>&gt; 0%</td>
<td>OS, DFS</td>
<td>7</td>
</tr>
<tr>
<td>Van Hootegem et al[17]</td>
<td>2019</td>
<td>Australia</td>
<td>391</td>
<td>Esophageal + EGJ</td>
<td>NR</td>
<td>&gt; 0%</td>
<td>OS, DFS</td>
<td>7</td>
</tr>
<tr>
<td>Corsini et al[18]</td>
<td>2020</td>
<td>United States (ACC: 2006-2018)</td>
<td>819</td>
<td>Esophageal</td>
<td>NR</td>
<td>1%-10%, 11%-49%, ≥ 50%</td>
<td>OS</td>
<td>8</td>
</tr>
<tr>
<td>Solomon et al[20]</td>
<td>2021</td>
<td>Israel</td>
<td>163</td>
<td>Esophageal + EGJ</td>
<td>I-III</td>
<td>&gt; 0%</td>
<td>OS</td>
<td>6</td>
</tr>
</tbody>
</table>

SRC: Signet ring cell; NOS: Newcastle-Ottawa Scale; EGJ: Esophagogastric junction; Surg: Surgery; nCT: Neoadjuvant chemotherapy; OS: Overall survival; DSS: Disease-specific survival; DFS: Disease-free survival; SEER: Surveillance, Epidemiology, and End Results; R: Recurrence; ACC: Anderson Cancer Center; MCTR: Mayo Clinic Tumor Registry; RTCT: Response to chemotherapy; NCD: National Cancer Database; DS: Downstaging; TNM: Tumor-node-metastasis; NR: Not reported.

95% CI: 0.61-0.96, P = 0.022; F = 49.4%, P = 0.160) and TNM stage III/IV EEGJA patients (RR: 1.30, 95% CI: 1.02-1.65, P = 0.031; F = 73.1%, P = 0.002). However, no significant relation was observed between SRCs and the sex (RR: 0.99, 95% CI: 0.87-1.13, P = 0.917; F = 39.4%, P = 0.105), smoking (RR: 0.86, 95% CI: 0.55-1.35, P = 0.507; F = 86.9%, P = 0.006), family history (RR: 1.157, 95% CI: 0.762-1.757), and lymph node metastasis (RR: 1.05, 95% CI: 0.92-1.20, P = 0.488; F = 7.2%, P = 0.340) (Table 2).

**Association between presence of SRCs and prognosis of EEGJA patients**

A total of 11 studies explored the relationship of SRCs with the OS of EEGJA patients (16-18, and 20-25), and the pooled results demonstrated that the presence of SRCs predicted a much poor OS (HR: 1.36, 95% CI: 1.12-1.65, P = 0.002; F = 85.7%, P < 0.001) (Figure 2). Meanwhile, four studies assessed the impact of SRCs on the DFS of EEGJA patients[12,15,17] and the pooled results did not predict a significant association between SRCs and DFS (HR: 1.21, 95% CI: 0.94-1.57, P = 0.145; F = 63.1%, P = 0.043) (Figure 3). Besides, after combining two studies[17,19], a significant relationship was observed between the presence of SRCs and poor DSS (HR: 1.86, 95% CI: 1.55-2.25, P < 0.001; F = 0.0%, P = 0.323) (Table 3).

**Sensitivity analysis and publication bias**

According to Figure 4, the sensitivity analysis revealed that the pooled results were stable and reliable.

Besides, the Begg’s funnel plot was symmetrical (Figure 5) and the P value of Egger’s test was 0.572, which indicated nonsignificant publication bias.

**Meta-regression analysis**

Due to the significant heterogeneity of the OS, meta-regression analysis was conducted based on some variables including the publication year, country, sample size, location, SRC ratio, TNM stage, and NOS score. Unfortunately, none of these parameters were
### Table 2 Association between signet-ring cells and clinicopathological characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>Sex (male)</th>
<th>Smoking</th>
<th>Family history</th>
<th>Tumor location (esophageal)</th>
<th>Lymph node metastasis</th>
<th>TNM stage (III/IV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chirieac et al[11] 2005</td>
<td>0.722 (0.254-2.053)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.895 (0.522-1.532)</td>
</tr>
<tr>
<td>Yoon et al[12] 2010</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Yendamuri et al[13] 2013</td>
<td>0.975 (0.783-1.214)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1.267 (1.060-1.513)</td>
</tr>
<tr>
<td>Nafteux et al[14] 2014</td>
<td>0.882 (0.558-1.395)</td>
<td>-</td>
<td>0.636 (0.451-0.896)</td>
<td>-</td>
<td>-</td>
<td>1.048 (0.702-1.563)</td>
</tr>
<tr>
<td>Patel et al[15] 2014</td>
<td>0.518 (0.309-0.867)</td>
<td>-</td>
<td>-</td>
<td>1.357 (0.907-2.028)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Chen et al[16] 2017</td>
<td>1.461 (0.945-2.258)</td>
<td>0.667 (0.495-0.899)</td>
<td>1.157 (0.762-1.757)</td>
<td>-</td>
<td>-</td>
<td>1.095 (0.811-1.480)</td>
</tr>
<tr>
<td>Van Hootegem et al[17] 2019</td>
<td>1.138 (0.662-1.956)</td>
<td>-</td>
<td>0.888 (0.649-1.216)</td>
<td>0.929 (0.677-1.275)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Corsini et al[18] 2020</td>
<td>0.771 (0.460-1.292)</td>
<td>1.061 (0.923-1.219)</td>
<td>-</td>
<td>-</td>
<td>1.038 (0.888-1.215)</td>
<td>-</td>
</tr>
<tr>
<td>Sathe et al[19] 2020</td>
<td>1.164 (0.912-1.485)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1.832 (1.542-2.177)</td>
</tr>
<tr>
<td>Solomon et al[20] 2021</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Overall</td>
<td>0.99, 0.87-1.13, $P = 0.917$</td>
<td>0.86, 0.55-1.35, $P = 0.507$</td>
<td>1.157 (0.762-1.757)</td>
<td>0.76, 0.61-0.96, $P = 0.022$</td>
<td>1.05, 0.92-1.20, $P = 0.488$</td>
<td>1.30, 1.02-1.65, $P = 0.031$</td>
</tr>
</tbody>
</table>

TNM: Tumor-node-metastasis.

### Table 3 Results of meta-analysis

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>HR</th>
<th>95%CI</th>
<th>$P$ value</th>
<th>$I^2$</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival</td>
<td>11[11-15,15-20]</td>
<td>1.36</td>
<td>1.12-1.65</td>
<td>0.002</td>
<td>85.7</td>
</tr>
<tr>
<td>Disease-free survival</td>
<td>4[12,15,17]</td>
<td>1.21</td>
<td>0.94-1.57</td>
<td>0.145</td>
<td>63.1</td>
</tr>
<tr>
<td>Disease-specific survival</td>
<td>2[12,14]</td>
<td>1.86</td>
<td>1.55-2.25</td>
<td>&lt; 0.001</td>
<td>0.0</td>
</tr>
</tbody>
</table>

HR: Hazard ratio; CI: Confidence interval.

DISCUSSION

The current systematic review and meta-analysis demonstrated that the presence of SRCs was significantly associated with tumor location (RR: 0.76, $P = 0.022$) and TNM stage (RR: 1.30, $P = 0.031$). Meanwhile, the presence of SRCs in surgical EEGJA patients predicted a poor OS (HR: 1.36, $P = 0.002$) and DSS (HR: 1.86, $P < 0.001$). The presence of SRCs might be an independent prognostic factor in EEGJA patients and contribute to the evaluation of prognosis and decision making.

Interestingly, Chirieac et al[11] demonstrated that the presence of SRCs predicted a much poor prognosis in patients who received surgery alone ($P = 0.05$), but for patients who received neoadjuvant chemotherapy and surgery, the presence of SRCs predicted a better prognosis ($P = 0.02$). This phenomenon indicated that SRCs might play an essential role in the response to chemotherapy. In the study by Corsini et al[18], EEGJA patients with usual type had a much higher pathologic complete response than patients with SRCs (25% vs 10%, $P = 0.006$). Meanwhile, Solomon et al[20] also revealed that patients with SRCs were less sensitive to neoadjuvant chemoradiotherapy (OR: 6.118, 95%CI: 1.299-28.821, $P = 0.022$) and less likely to experience downstaging after neoadjuvant chemotherapy (OR: 0.306, 95%CI: 0.099-0.946, $P = 0.040$). The presence of SRCs may predicted a poor response to chemotherapy, which is opposite to the results reported by Chirieac et al[11]. Thus, more relevant studies are needed to further investigate the causes of heterogeneity.
Figure 2 Forest plot of association between presence of signet ring cells and overall survival\([11-13,15-20]\). HR: Hazard ratio; CI: Confidence interval.

<table>
<thead>
<tr>
<th>Study ID</th>
<th>HR (95%CI)</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chiorean et al(^{(1)}) (2005)</td>
<td>0.45 (0.23, 0.90)</td>
<td>5.00</td>
</tr>
<tr>
<td>Chiorean et al(^{(1)}) (2005)</td>
<td>1.45 (1.00, 2.12)</td>
<td>8.67</td>
</tr>
<tr>
<td>Yoon et al(^{(1)}) (2010)</td>
<td>1.58 (1.21, 2.05)</td>
<td>10.35</td>
</tr>
<tr>
<td>Yendamuri et al(^{(1)}) (2013)</td>
<td>1.18 (1.07, 1.30)</td>
<td>12.35</td>
</tr>
<tr>
<td>Patel et al(^{(1)}) (2014)</td>
<td>1.49 (1.10, 2.02)</td>
<td>9.75</td>
</tr>
<tr>
<td>Chen et al(^{(1)}) (2017)</td>
<td>4.23 (3.02, 5.92)</td>
<td>9.25</td>
</tr>
<tr>
<td>van Hootegem et al(^{(1)}) (2019)</td>
<td>1.08 (0.76, 1.54)</td>
<td>9.00</td>
</tr>
<tr>
<td>van Hootegem et al(^{(1)}) (2019)</td>
<td>0.86 (0.59, 1.24)</td>
<td>8.73</td>
</tr>
<tr>
<td>Consini et al(^{(1)}) (2020)</td>
<td>1.39 (1.02, 1.89)</td>
<td>9.68</td>
</tr>
<tr>
<td>Sathe et al(^{(1)}) (2020)</td>
<td>1.24 (1.13, 1.37)</td>
<td>12.35</td>
</tr>
<tr>
<td>Solomon et al(^{(1)}) (2021)</td>
<td>1.51 (0.75, 3.03)</td>
<td>4.87</td>
</tr>
<tr>
<td>Overall (I-squared) = 85.7%, ( P = 0.000 )</td>
<td>1.36 (1.12, 1.65)</td>
<td>100.00</td>
</tr>
<tr>
<td>Note: Weights are from random effects analysis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 3 Forest plot of association between presence of signet ring cells and disease-free survival\([12,15,17]\). HR: Hazard ratio; CI: Confidence interval.

<table>
<thead>
<tr>
<th>Study ID</th>
<th>HR (95%CI)</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yoon et al(^{(1)}) (2010)</td>
<td>1.49 (1.15, 1.93)</td>
<td>28.58</td>
</tr>
<tr>
<td>Patel et al(^{(1)}) (2014)</td>
<td>1.34 (1.02, 1.80)</td>
<td>27.01</td>
</tr>
<tr>
<td>van Hootegem et al(^{(1)}) (2019)</td>
<td>1.27 (0.90, 1.78)</td>
<td>23.61</td>
</tr>
<tr>
<td>van Hootegem et al(^{(1)}) (2019)</td>
<td>0.76 (0.51, 1.12)</td>
<td>20.79</td>
</tr>
<tr>
<td>Overall (I-squared) = 63.1%, ( P = 0.043 )</td>
<td>1.21 (0.94, 1.57)</td>
<td>100.00</td>
</tr>
<tr>
<td>Note: Weights are from random effects analysis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

still needed to identify the clinical role of SRC in the chemotherapy and radiotherapy of EEGJA patients.

Although the pooled results indicated that there was no significant association between the presence of SRCs and DFS of EEGJA patients (HR: 1.21, 95%CI: 0.94-1.57, \( P = 0.145 \)), Yoon et al\(^{(12)}\) and Patel et al\(^{(15)}\) both reported that patients with SRCs were more likely to experience a worse DFS (HR: 1.49, 95%CI: 1.15-1.93, \( P = 0.001 \); HR: 1.34, 95%CI: 1.02-1.80, \( P = 0.048 \)). Therefore, we believed that SRCs might also predict a poor DFS in EEGJA patients, which needs more studies to further verify.

Besides, Naufeux et al\(^{(14)}\) demonstrated that the presence of SRCs was significantly associated with a higher recurrence rate (56% vs 42% for usual type adenocarcinoma, \( P = 0.003 \)). In their multivariate analysis, SRC ratio > 50% was an independent risk factor for recurrence (OR: 2.070, 95%CI: 1.159-3.696, \( P = 0.014 \)), which also indicated that the presence of SRCs was related with a poor prognosis in EEGJA patients.

Actually, there are still several valuable fields about the clinical significance of SRCs in EEGJA patients that are worth further investigation. First, as mentioned above, the role that SRCs play in the chemotherapy and radiotherapy is unclear, and more studies comparing the clinical outcomes between EEGJA patients with and without neoadjuvant chemoradiotherapy or postoperative chemoradiotherapy are needed. Second, it is necessary to identify whether SRCs could serve as a reliable predictor for the selection of therapeutic strategies. Third, to explore the role of the proportion change of SRC during chemotherapy in predicting the prognosis of EEGJA patients might be significative. Fourth, according to previous reports, the proportion of SRCs may also be related with the prognosis of EEGJA patients and patients with different ratios of SRCs might have different survival rates.
There were some limitations in this study. First, all included studies were retrospective, which may cause some bias. Second, the association of SRCs with other parameters such as alcohol drinking, differentiation status, *Helicobacter pylori* infection, and age was not explored due to the lack of relevant data. Third, we failed to conduct subgroup analysis based on the clinicopathological parameters such as age, sex, and TNM stage because the detailed data were not available even if we contacted the authors of included studies.

**CONCLUSION**

The presence of SRCs is related with advanced tumor stage and poor prognosis and could serve as a reliable and effective parameter for the prediction of postoperative survival and formulation of therapy strategy in EEGJA patients. However, more prospective high-quality studies are still needed to verify our findings.

**ARTICLE HIGHLIGHTS**

**Research background**

The clinical role of signet ring cells (SRCs) in surgical esophageal and esophagogastric junction adenocarcinoma (EEGJA) remains unclear now.
Research motivation
To explore the clinical role of the presence of SRCs in surgical EEGJA patients.

Research objectives
To explore the association between the presence of SRCs and the clinicopathological and prognostic characteristics in surgical EEGJA patients.

Research methods
Several electronic databases were searched to identify the relevant articles. The relative risks and hazard ratios with their corresponding 95% confidence intervals were estimated, respectively.

Research results
The presence of SRCs was significantly associated with the tumor location ($P = 0.022$) and tumor-node-metastasis stage ($P = 0.031$). Meanwhile, the presence of SRCs in surgical EEGJA patients predicted a poor overall survival ($P = 0.002$) and disease-specific survival ($P < 0.001$).

Research conclusions
SRC was significantly related with advanced tumor stage and poor prognosis in EEGJA patients.

Research perspectives
The presence of SRCs could serve as a reliable and effective parameter for the prediction of postoperative survival and formulation of therapy strategy in EEGJA patients.

REFERENCES
12 Yoon HH, Khan M, Shi Q, Cassivi SD, Wu TT, Quevedo JF, Burch PA, Sinicrope FA, Diasio RB.


Percutaneous biliary stent combined with brachytherapy using $^{125}$I seeds for treatment of unresectable malignant obstructive jaundice: A meta-analysis

Wei-Yue Chen, Chun-Li Kong, Miao-Miao Meng, Wei-Qian Chen, Li-Yun Zheng, Jian-Ting Mao, Shi-Ji Fang, Li Chen, Gao-Feng Shu, Yang Yang, Qiao-You Weng, Min-Jiang Chen, Min Xu, Jian-Song Ji

Abstract

BACKGROUND
Malignant obstructive jaundice (MOJ) is a common pathologic manifestation of malignant biliary obstruction. Recently, several clinical trials have explored the clinical effectiveness of intraluminal $^{125}$I seed-based brachytherapy for MOJ patients, and various outcomes have been reported.

AIM
To assess the efficacy and safety of percutaneous biliary stents with $^{125}$I seeds compared to conventional metal stents in patients with unresectable MOJ.

METHODS
A systematic search of English-language databases (PubMed, Embase, Cochrane Library, and Web of Science) was performed to identify studies published prior to June 2020 that compared stents with or without $^{125}$I seeds in the treatment of unresectable MOJ. The outcomes analyzed included primary outcomes (stent patency and overall survival) and secondary outcomes (complications and liver function parameters).

RESULTS
Six randomized controlled trials and four retrospective studies involving 875 patients were eligible for the analysis. Of the 875 included patients, 404 were treated with $^{125}$I seed stents, while 471 were treated with conventional stents. Unadjusted pooled analysis demonstrated that compared to conventional stents,
I seed stents are safe and well tolerated.

Therefore, there were no significant differences in the occurrence of total complications [odds ratio (OR) = 1.12, 95% CI = 0.75-1.67, P = 0.57], hemobilia [OR = 1.02, 95% CI = 0.45-2.3, P = 0.96], pancreatitis [OR = 1.79, 95% CI = 0.42-7.53, P = 0.43], cholangitis [OR = 1.13, 95% CI = 0.60-2.13, P = 0.71], or pain [OR = 0.67, 95% CI = 0.22-2, P = 0.47]. In addition, there were no reductions in the levels of serum indices, including total bilirubin [mean difference (MD) = 10.96, 95% CI = -3.56-25.49, P = 0.14], direct bilirubin (MD = 7.37, 95% CI = -9.76-24.5, P = 0.4), alanine aminotransferase (MD = 7.52, 95% CI = -0.71-15.74, P = 0.07), and aspartate aminotransferase (MD = -4.77, 95% CI = -19.98-10.44, P = 0.54), after treatment. Publication bias was detected regarding the outcome overall survival; however, the conclusions were not changed after the adjustment.

CONCLUSION
Placement of stents combined with brachytherapy using I seeds contributes to a longer stent patency and higher overall survival than placement of conventional stents without extra complications or severe liver damage. Thus, it can be considered an effective and safe treatment for unresectable MOJ.

Key Words: Malignant obstructive jaundice; Brachytherapy; 125I seed; Patency; Survival; Meta-analysis

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Core Tip: In recent years, the incidence of malignant obstructive jaundice (MOJ) in Asia has been 40 times higher than that in the Western world, which is a vital issue that requires significant attention. Irradiation stents using I seeds have been widely applied in the treatment of unresectable MOJ. However, more convincing evidence-based reviews of the efficacy and safety of I seed stents are needed. We used the latest data to further validate the superiority of I seed stents, providing strong evidence for clinicians to make correct decisions in clinical practice. Furthermore, we found that I seed stents resulted in equivalent complication and serum index outcomes as conventional stents, indicating that I seed stents are safe and well tolerated.


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DOI: https://dx.doi.org/10.12998/wjcc.v9.i35.10979

INTRODUCTION
Malignant obstructive jaundice (MOJ) is a common pathologic manifestation of malignant biliary obstruction caused by various adenocarcinomas[1]. Since the disease process is insidious but develops rapidly, only a minority of MOJ patients (< 20%) are suitable for radical operation, leading to a poor overall prognosis[2]. For patients with unresectable MOJ or those who are unwilling to undergo surgery, biliary stent implantation is a mainstay to relieve the biliary obstruction and clinical symptoms caused by progressive neoplasms[3]. Nevertheless, the stent itself has no effect on tumor suppression. The ingrowth or overgrowth of tumors, biliary epithelial cell proliferation, and biliary sludge formation often cause restenosis[4,5]. Thus, extra antitumor therapies are needed to improve the prognosis of patients with unresectable MOJ[6-8].
Intraluminal iodine-125 (125I) seed brachytherapy, due to its antitumor growth function and specificity for destroying target tumors, has been widely applied in local tumor treatment[9-12]. Several studies have demonstrated that intraluminal 125I seed-based brachytherapy has excellent therapeutic effects in the treatment of unresectable MOJ[13-15]. However, most studies are single-center or retrospective with relatively small sample sizes, and the number of randomized controlled trials (RCTs) is still limited.

To provide more convincing clinical evidence, we conducted a meta-analysis to accurately assess the efficacy and safety of percutaneous biliary stents with 125I seeds compared with conventional stents in patients with unresectable MOJ.

**MATERIALS AND METHODS**

This meta-analysis was conducted according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines[16]. Institutional review board approval was not required for this analysis.

**Search strategy and selection criteria**

The following electronic databases were searched: PubMed, Embase, Cochrane Library, and Web of Science (before June 2020). The ClinicalTrials.gov website was also searched for randomized trials that were registered as completed but not yet published. Search terms such as “125I seed,” “brachytherapy,” “biliary stent,” “malignant obstructive jaundice,” and “malignant biliary obstruction” were included. The detailed search strategy is listed in Supplementary Table 1. In addition, the reference lists of identified studies were screened manually to include other potentially eligible trials. The following inclusion criteria were applied: (1) Studies involving adult patients (aged 18-90 years) with a confirmed diagnosis of MOJ; (2) studies comparing percutaneous biliary stent placement with the placement of 125I seeds and conventional metal stents; and (3) studies published in English. The following exclusion criteria were applied: (1) Abstracts without full texts; (2) studies registered but not completed; (3) studies that included patients whose data was published in multiple papers; and (4) studies with a sample size smaller than 20.

Each study (title and abstract) identified through the search strategy was screened for potential relevance by two authors (Chen WY and Kong CL). The full articles of studies chosen as being relevant were reviewed by the same authors for final inclusion. Differences of opinions were resolved by consensus.

**Data extraction**

The following data were independently extracted by two authors: Trial information (first author, year of publication, country, design, period of enrollment, intervention, number of included patients, and stent manufacturer and type), baseline patient characteristics (age, sex, causes of MOJ, and obstruction level), and outcomes (clinical effectiveness and complications). The extracted data were documented into a standardized Excel (Microsoft Corp, Redmond, WA, United States) file and were checked by another author. Any disagreement was resolved through discussion and a reassessment and recheck of the data and/or involvement of a senior author.

**Quality assessment**

All randomized controlled trials were analyzed using Cochrane Collaboration’s tool. The risk of bias assessment in trials was based on random sequence generation, allocation concealment, blinding of participants, personnel and outcome assessment, incomplete outcome data, selective reporting, and other factors. Each category was assessed as “yes” (low risk of bias), “no” (high risk of bias), or “unclear”. Cohort studies were assessed using the Newcastle–Ottawa Scale (NOS) with three main domains: Study group selection, comparability of cohorts, and ascertainment of outcomes. A study with an NOS score of 7 or higher was considered high quality.

**Outcomes and definitions**

This meta-analysis analyzed primary outcomes (stent patency and overall survival) and secondary outcomes (complications and liver function parameters). Stent patency was calculated from the date of stent placement to the first episode of stent restenosis. Stent restenosis was defined as the presentation of clinical signs of recurrent jaundice with elevated bilirubin levels along with biliary dilation on imaging study. Overall survival was defined as the interval between initial stenting and patient death or the
last follow-up. Classification of complications was performed according to the Common Terminology Criteria for Adverse Events (CTCAE 4.02) or the guidelines of the Society of Interventional Radiology Standards of Practice Committee[17]. Postoperative procedure-related complications mainly included hemobilia, pancreatitis, cholangitis, and pain. Liver function parameters were evaluated by assessing the change in serum indices before and 1 wk after treatment, including total bilirubin (TBIL), direct bilirubin (DBIL), alanine aminotransferase (ALT), and aspartate aminotransferase (AST).

Three types of $^{125}$I seed stents were mentioned in the included studies. Type I stents refer to self-expanded stents with $^{125}$I seed strand fixation in a drainage catheter. Type II stents refer to $^{125}$I seed-loaded stents. Type III stents refer to self-expanded stents with $^{125}$I seed strand fixation between the stent and the bile duct wall. The $^{125}$I seed strand is a combination of a 4F catheter and multiple $^{125}$I seeds.

**Statistical analysis**

Statistical analyses were performed using Review Manager (version 5.0) and Stata 15.1. For time-to-event data, the aggregated hazard ratio (HR) and its 95% confidence interval (95%CI) were applied to report the final pooled estimate. HRs and the corresponding 95% CIs were directly obtained if mentioned in the manuscript; however, if not, the HR and lnHR were estimated by the method of Tierney et al[18] from Kaplan–Meier curves or the calculated value of the O-E and V. The outcomes of dichotomous and continuous variables are expressed as odds ratios (ORs) and weighted mean differences, respectively. Statistical heterogeneity across the included studies was quantified by the $I^2$ statistic. When heterogeneity was significant ($I^2 > 50\%$), a random-effects model was applied to calculate the pooled effect sizes; otherwise, a fixed-effects model was used. Sensitivity analysis was performed by excluding one trial in each turn to explore the potential causes of heterogeneity. Subgroup analysis was conducted according to the type of $^{125}$I seed stent and study design (RCT and retrospective study). Potential publication bias was appraised using Egger’s and Begg’s tests. Publication bias was adjusted using the trim and fill method [19]. Two-sided $P < 0.05$ was considered significant.

**RESULTS**

**Search results and characteristics of the studies**

The PRISMA flow diagram for the selection process is presented in Figure 1. The initial database search yielded 244 potentially relevant studies, ten of which were included in this meta-analysis[13-15,20-26]. Of these studies, four were retrospective cohort studies and six were RCTs published between 2012 and 2018[13,14,20,21,25,26]. Five of these RCTs were single-center studies, while one was a multicenter study performed at 20 centers in China[21]. All of them were conducted in China and written in English. These studies included a total of 875 patients, among whom 404 (46.17\%) underwent biliary stent placement combined with brachytherapy using $^{125}$I seeds, and 471 (53.83\%) received conventional metal stents only for treatment. Percutaneous transhepatic biliary drainage was performed before stent placement in all cases. Three studies used type I stents[14,24,25], three used type II[20,21,26], and four used type III[13,15,22,23]. The target population was patients with unresectable MOJ, and the majority of them had cholangiocarcinoma ($n = 331, 37.83\%$) and pancreatic carcinoma ($n = 177, 20.23\%$). The trial information and patients’ baseline characteristics are shown in Table 1, while the intervention details for the deployment of $^{125}$I seeds and the main outcomes are listed in Table 2, with detailed data shown in Supplementary Tables 2 and 3.

**Quality assessment**

According to the Cochrane Collaboration’s tool, the risk of bias varied among the six RCT studies included in this meta-analysis, ranging from low to high levels (Supplementary Figures 1 and 2). All studies had a high risk of performance bias because it was difficult to conceal the grouping and interventional procedures from the participants, researchers, and outcome measurers. Three RCTs (50\%) did not describe the method of allocation concealment in detail. According to the NOS, the retrospective cohort studies had high quality scores, which were measured to be between 7 and 9 (Supplementary Table 4).
<table>
<thead>
<tr>
<th>Ref.</th>
<th>Design</th>
<th>Country</th>
<th>Period of enrolment</th>
<th>Groups</th>
<th>Number of patients</th>
<th>Age (yr)</th>
<th>Sex (male/female)</th>
<th>Obstruction levels</th>
<th>Causes of MOJ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen et al [25], 2012</td>
<td>Single-centre, RCT</td>
<td>China</td>
<td>Mar. 2009-Jan. 2010</td>
<td>125I + stent</td>
<td>17</td>
<td>61.2 ± 14.5</td>
<td>12/5</td>
<td>Hilar and distal</td>
<td>Cholangiocarcinoma (n = 7), hepatocellular carcinoma (n = 2), pancreatic cancer (n = 3), hepatic metastases from the stomach or colorectum (n = 5)</td>
</tr>
<tr>
<td>Chen et al [26], 2018</td>
<td>Single-centre, RCT</td>
<td>China</td>
<td>Sep. 2014-Nov. 2016</td>
<td>125I + stent</td>
<td>13</td>
<td>66 (49, 88)</td>
<td>8/5</td>
<td>Lower</td>
<td>Pancreatic head carcinoma (n = 7), gallbladder carcinoma (n = 4), bile duct carcinoma (n = 2)</td>
</tr>
<tr>
<td>Jiao et al [14], 2017</td>
<td>Single-centre, RCT</td>
<td>China</td>
<td>Jan. 2013-Jan. 2015</td>
<td>125I + stent</td>
<td>31</td>
<td>60.4 ± 8.8</td>
<td>12/17</td>
<td>Hilar and distal</td>
<td>Primary adenocarcinoma (n = 19), metastatic adenocarcinoma (n = 12)</td>
</tr>
<tr>
<td>Zhu et al [20], 2012</td>
<td>Single-centre, RCT</td>
<td>China</td>
<td>Nov. 2008-Oct. 2010</td>
<td>125I + stent</td>
<td>12</td>
<td>62.5 ± 21.0</td>
<td>7/5</td>
<td>Hilar and distal</td>
<td>Primary adenocarcinoma (n = 8), metastatic adenocarcinoma (n = 4)</td>
</tr>
<tr>
<td>Zhu et al [21], 2018</td>
<td>Multicentre, RCT</td>
<td>China</td>
<td>Oct. 2013-Mar. 2016</td>
<td>125I + stent</td>
<td>164</td>
<td>65.0 (56.0, 75.0)</td>
<td>103/61</td>
<td>Hilar and distal</td>
<td>Biliary tract cancer (n = 80), pancreatic carcinoma (n = 46), lymph node metastases (n = 38)</td>
</tr>
<tr>
<td>Wang et al [24], 2017</td>
<td>Retrospective cohort study</td>
<td>China</td>
<td>Sep. 2010-Feb. 2013</td>
<td>125I + stent</td>
<td>24</td>
<td>57.3 (41, 80)</td>
<td>29/21</td>
<td>Hilar and distal</td>
<td>Cholangiocarcinoma (n = 18), pancreatic head carcinoma (n = 14), hilar lymph node metastasis (n = 12), ampullary carcinoma (n = 6)</td>
</tr>
</tbody>
</table>
Chen et al. 125I seed stents for MOJ patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Country</th>
<th>Start Date - End Date</th>
<th>Stent Type</th>
<th>Sample Size</th>
<th>Median Stent Patency</th>
<th>Location</th>
<th>Stent Group Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhou et al [22], 2019</td>
<td>Retrospective cohort study</td>
<td>China</td>
<td>Nov. 2015-Oct. 2017</td>
<td>125I + stent</td>
<td>45</td>
<td>61.7 (32, 87)</td>
<td>Hilar, middle and distal</td>
<td>Stent</td>
</tr>
<tr>
<td>Zhou et al [23], 2020</td>
<td>Retrospectively cohort study</td>
<td>China</td>
<td>Jan. 2017-June 2018</td>
<td>125I + stent</td>
<td>40</td>
<td>70.2 ± 13.8</td>
<td>Hilar</td>
<td>Stent</td>
</tr>
</tbody>
</table>

MOJ: Malignant obstructive jaundice; RCT: randomized controlled trial.

Egger’s and Begg’s tests were carried out to evaluate the potential publication bias for primary endpoints. There was no evidence that publication bias occurred in the outcome of stent patency (Egger’s test P = 0.705), whereas it was observed in the outcome of overall survival (Egger’s test P = 0.027). The conclusions were not changed after adjustment for publication bias by using the trim-and-fill method.

**Primary endpoints**

**Stent patency:** HR data for stent patency were extracted from seven studies[13,14,21,22,24-26]. The utilization of 125I seed stents resulted in a better stent patency than the use of conventional stents (HR = 0.36, 95%CI = 0.28-0.45, P < 0.0001; Figure 2A). There was no significant heterogeneity among these studies (I² = 0%, P = 0.48). The test for subgroup analyses revealed no significant difference in heterogeneity based on the type of 125I seed stent and type of study design. The results showed that compared with conventional stents, three 125I seed stent types were all associated with a significantly prolonged stent patency (Figure 3). Both RCTs and retrospective studies demonstrated that the 125I seed stent group was superior to the conventional stent group in patency (RCTs: HR = 0.42, 95%CI = 0.31-0.58, P < 0.00001; retrospective studies: HR = 0.28, 95%CI = 0.20-0.41, P < 0.00001; Figure 4A and B).

**Overall survival:** HR data for overall survival were extracted from eight studies[13-15,20-23,26]. In comparison with the use of conventional stents, the application of 125I seed stents resulted in a better overall survival (HR = 0.52, 95%CI = 0.42-0.64, P < 0.00001, Figure 2B). Heterogeneity among these studies was not significant (I² = 7%, P = 0.37). The test for subgroup analysis demonstrated no significant difference in heterogeneity according to the type of study design (P = 0.904). The results of a stratified analysis of RCTs and retrospective studies showed that the 125I seed stent group had a better overall survival than the conventional stent group (RCTs: HR = 0.42, 95%CI = 0.31-0.58, P < 0.00001; retrospective studies: HR = 0.60, 95%CI = 0.46-0.79, P = 0.0003; Figure 4C and D).
<table>
<thead>
<tr>
<th>Ref.</th>
<th>Intervention</th>
<th>Stent manufacturer and type</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen et al</td>
<td>125I seed strands performed after stent insertion</td>
<td>Nitinol self-expandable stent (Luminexx III; BARD); Type I</td>
<td>Laboratory values before and after stent placement, complications, stent patency</td>
</tr>
<tr>
<td>[25], 2012</td>
<td>Conventional stent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hasimu et al</td>
<td>Biliary stent with 125I seed strands</td>
<td>Nitinol self-expandable stent (S.M.A.R.T.; Cordis Corporation, Miami Lakes, FL, United States); Type III</td>
<td>Stent patency, survival, relief of symptoms, technical and clinical success, complications, laboratory values before and after stent placement, radiation safety</td>
</tr>
<tr>
<td>[13], 2017</td>
<td>Conventional stent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chen et al</td>
<td>125I seeds-loaded-biliary stent</td>
<td>Self-expandable stent (produced by Mirco-tech, Nanjing, China); Type II</td>
<td>Laboratory values before and after stent placement, complications, stent patency, survival, CR, PR, SD, PD</td>
</tr>
<tr>
<td>[26], 2018</td>
<td>Conventional stent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jiao et al</td>
<td>SEMS with 125I seed strands</td>
<td>A Nitinol self-expandable stent (Niti-S Biliary stent, Taewoong, Seoul, Korea); Type I</td>
<td>Technical success, laboratory values before and after stent placement, stent patency, overall survival, early or late complications</td>
</tr>
<tr>
<td>[14], 2017</td>
<td>Conventional stent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zhu et al</td>
<td>125I seeds-loaded-biliary stent</td>
<td>Outer self-expandable 125I radioactive seeds-loaded stent and inner conventional self-expanding biliary nitinol alloy stent (Nanjing MicroInvasive Medical Inc., Nanjing, China); Type II</td>
<td>Technical success, jaundice relief, radiation safety, complications (subjective and objective), survival, stent patency, laboratory values before and after stent placement</td>
</tr>
<tr>
<td>[20], 2012</td>
<td>Conventional stent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zhu et al</td>
<td>125I seeds-loaded-biliary stent</td>
<td>Inner conventional uncovered SEMS (Nanjing Micro-Tech Co. Ltd., Nanjing, China) and outer 125I seed-loaded stent; Type II</td>
<td>Stent restenosis, patency time, technical success, relief of jaundice, survival, complications</td>
</tr>
<tr>
<td>[21], 2018</td>
<td>Conventional stent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pan et al</td>
<td>Biliary stent with 125I seed strands</td>
<td>Biliary stent (E-Luminexx Biliary Stent; Wachhausstrasse 6D76227, BARD Corporation, Karlsruhe, Germany); Type III</td>
<td>Stent patency, overall survival, complications, laboratory values before and after stent placement, independent factors associated with survival</td>
</tr>
<tr>
<td>[15], 2020</td>
<td>Conventional stent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wang et al</td>
<td>Biliary stent with 125I seed strands</td>
<td>Biliary internal stent (Micro-Tech Co., Ltd. Nanjing, China); Type I</td>
<td>Success rate, laboratory values before and after stent placement, stent patency, survival</td>
</tr>
<tr>
<td>[24], 2017</td>
<td>Conventional stent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zhou et al</td>
<td>UCSEMS with 125I seed strands</td>
<td>Three types of SEMS [E-Luminexx (Bard Peripheral Vascular, Tempe, AZ, United States), S.M.A.R.T (Cordis, Milpitas, CA, United States), and Zilver (Cook Medical, Bloomington, IN, United States)]; Type III</td>
<td>Technical success, clinical success, complications, follow-up time, stent patency, survival, laboratory values before and after stent placement</td>
</tr>
<tr>
<td>[22], 2019</td>
<td>Conventional stent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zhou et al</td>
<td>SEMS with 125I seed strands</td>
<td>Self-expandable metallic stent (Cook Medical, Bloomington, IN, United States); Type III</td>
<td>Technical success, clinical success, laboratory values before and after stent placement, complications, overall survival, and stent patency</td>
</tr>
<tr>
<td>[23], 2020</td>
<td>Conventional stent</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*The 125I seed stents include three types. Type I: Self-expanded stent with 125I seed strand fixation in a drainage catheter; Type II: 125I seed-loaded stent; Type III: Self-expanded stent with 125I seed strand fixation between stent and the bile
Secondary endpoints

Complications: A total of nine studies provided incidence data for all complications or at least one kind of complication. Overall, both groups had low overall complication rates, with slightly worse results being observed in the $^{125}$I seed stent group than in the conventional stent group (19.2% vs 16.5%). However, this difference was not statistically significant (OR = 1.12, 95%CI = 0.75-1.67, $P$ = 0.57; Figure 5), and there was a low level of heterogeneity among these studies ($I^2$ = 0%, $P$ = 0.74). There were also no significant differences between the $^{125}$I seed stent group and the conventional stent group in the incidence of hemobilia (OR = 1.02, 95%CI = 0.45-2.3, $P$ = 0.96; $F$ = 0%, $P$ = 0.8), pancreatitis (OR = 1.79, 95%CI = 0.42-7.53, $P$ = 0.43; $F$ = 0%, $P$ = 0.65), cholangitis (OR = 1.13, 95%CI = 0.60-2.13, $P$ = 0.71; $F$ = 0%, $P$ = 0.83), or pain (OR = 0.67, 95%CI = 0.22-2, $P$ = 0.47; $F$ = 0%, $P$ = 0.97) (Figure 5).

Posttreatment reductions in the levels of serum indices: After the procedure, there was a significant decrease in liver function indices, including TBIL, DBIL, ALT, and AST. The numbers of studies that reported pretreatment and posttreatment TBIL, DBIL, ALT, and AST data were 8, 6, 7, and 4, respectively. We calculated the degree of reduction in each index, and found that there were no significant differences in the posttreatment reductions in the levels of TBIL (MD = 10.96, 95%CI = -3.56-25.49, $P$ = 0.14; $F$ = 0%, $P$ = 0.54), DBIL (MD = 7.37, 95%CI = -9.76-24.5, $P$ = 0.4; $F$ = 33%, $P$ = 0.19), ALT (MD = 7.52, 95%CI = -0.71-15.74, $P$ = 0.07; $F$ = 0%, $P$ = 0.51), and AST (MD = -4.77, 95%CI = -19.98-10.44, $P$ = 0.54; $F$ = 0%, $P$ = 0.77) between the $^{125}$I seed stent group and the conventional stent group (Figure 6).

DISCUSSION

This meta-analysis showed that biliary stents irradiated using $^{125}$I seeds resulted in a longer stent patency and higher overall survival than conventional stents in the treatment of unresectable MOJ. The same results were observed for the median or mean time of stent patency and overall survival in the included studies. However, due to the different presentations of the main results, this study transformed these original results into HR values rather than conducting a pooled analysis. The risk of restenosis was associated with patient death[21]. The longer stent patency was attributed to the short-distance irradiation effect of radioactive seeds embedded in the stents. Brachytherapy using $^{125}$I seed stents was developed to inhibit tumor ingrowth, relieve the obstruction, and finally prolong the survival time of patients with unresectable MOJ. This result further confirms the superior effect of irradiation stents using $^{125}$I seeds, which provides strong evidence for clinicians to make correct decisions in clinical
The implantation of stents irradiated using $^{125}$I is safe and well tolerated. All particle stents have some radiation hazards, and they also increase the complexity of the operation, which may cause certain damage to the intima and radiation damage to the gastrointestinal or bile duct during the treatment procedure[27]. However, our analysis showed that the treatment with $^{125}$I seed stents did not result in a higher incidence rate of complications than conventional stents. Additionally, none of the studies reported fatal complications, such as biliary or intestinal perforation or massive hemorrhage, and there was no device- or procedure-related mortality. Cholangitis is a more frequent complication associated with irradiated stents, with an incidence of 8.4% in the $^{125}$I seed stent group and 6.9% in the conventional stent group in this meta-analysis. However, this difference was not statistically significant. The incidence rates of other complications, such as hemobilia, pancreatitis, and pain, between the two groups were also comparable. Therefore, we concluded that no additional biliary complications occurred due to the use of $^{125}$I seed stents in patients with unresectable MOJ.
After implantation of the stents, the reductions in the serum indices of patients indicated improved therapeutic efficacy. Part of the biliary system is intrahepatic. Theoretically, irradiation biliary stent implantation may induce damage to the liver parenchyma. However, the reductions in the levels of serum indices (TBIL, DBIL, ALT, and AST) after treatment were not significantly different between the two groups, which demonstrated that the $^{125}$I seed stents were as effective as the conventional stents.

### Figure 3 Subgroup analysis of stent patency based on irradiation stent type.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Hazard Ratio)</th>
<th>SE</th>
<th>Weight</th>
<th>Hazard Ratio IV, Fixed, 95% CI</th>
<th>Hazard Ratio IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dechao Jiao 2017</td>
<td>-0.7765878</td>
<td>0.3568441</td>
<td>12.1%</td>
<td>0.48 (0.23, 0.92)</td>
<td></td>
</tr>
<tr>
<td>Hao Jiao 2017</td>
<td>-0.8675006</td>
<td>0.6339049</td>
<td>3.9%</td>
<td>0.42 (0.12, 1.45)</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Ch² = 0.84, df = 1 (P = 0.34); P = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect Z = 3.83 (P = 0.0001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Figure 4 Forest plot (subgroup, divided by randomized controlled trials and retrospective studies). A: Randomized controlled trial (RCT)-stent patency; B: Retrospective study-stent patency; C: RCT-overall survival; D: Retrospective study-overall survival.

After implantation of the stents, the reductions in the serum indices of patients indicated improved therapeutic efficacy. Part of the biliary system is intrahepatic. Theoretically, irradiation biliary stent implantation may induce damage to the liver parenchyma. However, the reductions in the levels of serum indices (TBIL, DBIL, ALT, and AST) after treatment were not significantly different between the two groups, which demonstrated that the $^{125}$I seed stents were as effective as the conventional stents.
Figure 5 Forest plot comparing rate of complications.

Table: Forest plot for comparing rate of complications.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>125I group Events</th>
<th>Control group Events</th>
<th>Odds Ratio M.H. Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ashaer Hasmim 2016</td>
<td>4</td>
<td>28</td>
<td>27</td>
</tr>
<tr>
<td>Cheung Zhou 2019</td>
<td>20</td>
<td>40</td>
<td>14</td>
</tr>
<tr>
<td>Dechao Jiao 2017</td>
<td>19</td>
<td>31</td>
<td>36</td>
</tr>
<tr>
<td>Haidong Zhu 2017</td>
<td>1</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>Haidong Zhu 2017</td>
<td>1</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>Tao Pan 2020</td>
<td>4</td>
<td>30</td>
<td>6</td>
</tr>
<tr>
<td>Vien Chen 2016</td>
<td>3</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td>Weizhong Zhou 2019</td>
<td>4</td>
<td>45</td>
<td>6</td>
</tr>
<tr>
<td>Yi Chen 2012</td>
<td>4</td>
<td>17</td>
<td>2</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>380</td>
<td>446</td>
<td>100.00%</td>
</tr>
</tbody>
</table>

**Total events**: 73

**Heterogeneity**: τ² = 5.12, df = 8 (P = 0.74), I² = 0%

Test for overall effect: Z = 0.43 (P = 0.67)

**1.1.1 Total rate**

**1.1.2 Hemobilia rate**

**1.1.3 Pancreatitis rate**

**1.1.4 Cholangitis rate**

**1.1.5 Pain rate**

**Test for subgroups**: Ch²(2) = 1.23, df = 4 (P = 0.77), I² = 0%

in improving liver function in patients with unresectable MOJ. Nevertheless, 125I seed stents have obvious advantages in inhibiting tumor growth. An investigation by Wang et al.[24] showed that the levels of tumor markers (CA-199 and CA-242) in the 125I seed stent group were significantly reduced after stent implantation, while no significant change was observed in the conventional stent group. This might be the reason why patients with unresectable MOJ treated with irradiated stents show amelioration of obstructive jaundice and a delayed disease process.

In terms of radiation safety, irradiation dose is the focus of brachytherapy[28]. The amount of 125I embedded in the stents is based on the tumor size and relevant recommendations of the Treatment Planning System (TPS, FIT Technology Ltd. Co., Beijing, China). The radiation doses used in all studies met the minimum threshold for effective brachytherapy treatment of adenocarcinoma (7.87 cGy and 30 Gy), while some of the studies used a higher dose (80–990 Gy) within the safety limits established through animal experiments and clinical trials[25]. A suitable dose has the optimal capacity to kill the primary tumor effectively. Although several previous reports indicated that a decrease in white blood cell count and immunoglobulin (IgA, IgG, and IgM) levels is associated with long-term and low-dose radiotherapy with 125I-based
Chen et al. 125I seed stents for MOJ patients

Figure 6 Forest plot comparing mean difference in post-treatment reductions in serum indices.

particles[29,30], the results of two included studies showed no significant differences between the pre- and post-procedure irradiated stent groups[20,26]. This again proved the safety of the radiation dose and 125I seed stents.

The curative effect of irradiated stents varies in patients with unresectable MOJ with different tumor etiologies and obstruction levels. However, due to the small sample size of enrolled patients, most studies did not explore the differences in the efficacy of irradiated stents for different pathological tumors, except for the study by Zhu et al[21]. In Zhu’s multicenter study, subgroup analysis of tumor etiology was performed, and the researchers first proposed that patients with biliary tract cancer could benefit more from irradiated stents using 125I seeds than those with pancreatic carcinoma and lymph node metastases. These results suggest that 125I seed stents provide better tumor control for localized malignant obstruction from the biliary tract. Nevertheless, obstruction can occur at any level within the biliary tract, most often in hilar and distal bile ducts. Zhou et al[23] and Chen et al[26] focused on the role of 125I seed stents in malignant hilar and lower biliary tract obstruction, respectively. The conclusions of these two studies are consistent with those of other studies, suggesting that 125I seed stents can serve as a safe, feasible, and effective method with minimal invasiveness for the treatment of obstruction at different levels within the biliary tract.

As mentioned in this analysis, there are three main types of 125I seed stents currently applied in the bile duct. Subgroup analysis based on the type of stent demonstrated that all three types of 125I seed stents were equally effective in prolonging stent patency.

125I seed strands have the advantages of replaceability and sustained radiation[31]. However, the use of a bile duct drainage tube as a carrier has certain limitations for invasive tumor growth along the bile duct wall. The radiation dose can be evenly distributed by using seed-loaded stents, but this type of stent is composed of two-layer stents and a large diameter sheath, which is not suitable for patients with hilar strictures. A self-expanded stent with 125I seed strand fixation between the stent and the bile duct wall is widely adopted in current studies due to its simple process and broader applicability. However, nonintegrated radiation stents still have many internal radiation stent-related issues that need to be solved.
This meta-analysis included RCTs and retrospective studies. In the subgroup analysis, a disparity between the results of RCTs and retrospective studies was not observed in stent patency and overall survival. Although RCTs provide a higher level of clinical evidence, retrospective studies have their own strengths as well, such as a potentially wider range of patients and therefore probably more real-world data. There was no significant heterogeneity in the test for subgroup differences, which indicated that the potential bias caused by the type of study design was small.

This meta-analysis still has several limitations: (1) There was a lack of stratified randomization and strict control of blinding in some research centers, which could influence the quality of this study to some extent; (2) the analysis had publication bias, which could be the result of the inclusion of studies concerning small sample sizes and only those that were written in English; (3) no studies involved in-depth comparative investigations of the applicable conditions and cost-effectiveness of three types of irradiated stents, which could limit the application of the results to some extent; and (4) all the studies were conducted in China, which could have had a potential impact on the generalizability of the results.

CONCLUSION
In conclusion, percutaneous biliary stents combined with brachytherapy using $^{125}$I seeds offers a longer stent patency and higher overall survival than conventional stents for patients with unresectable MOJ, resulting in equivalent complication and serum index outcomes. High-quality multicenter prospective randomized studies are needed to further assess the long-term therapeutic outcomes and safety of irradiated stents using $^{125}$I seeds and to define the selection criteria for stent type.

ARTICLE HIGHLIGHTS

Research background
Malignant obstructive jaundice (MOJ) is a common condition caused by various adenocarcinomas. Less than 20% of patients are suitable for radical surgery, leading to a poor overall prognosis. Recently, several clinical studies have raised concern regarding the clinical effectiveness of intraluminal $^{125}$I seed-based brachytherapy for patients with unresectable MOJ; hence, we analyzed evidence from randomized controlled trials (RCTs) and cohort studies comparing $^{25}$I seed stents and conventional stents.

Research motivation
Recently, there has been growing concern regarding the efficacy and safety of intraluminal $^{125}$I seed-based brachytherapy in the treatment of unresectable MOJ. However, most studies are single-center or retrospective with relatively small sample sizes and thus provide less convincing clinical evidence. The purpose of our study was to conduct a rigorous meta-analysis of RCTs and cohort studies on irradiated stents.

Research objectives
To investigate the clinical efficacy and safety of percutaneous biliary stents with $^{125}$I seeds compared with conventional metal stents in patients with unresectable MOJ.

Research methods
We performed a meta-analysis of RCTs and cohort studies. Four English-language databases (PubMed, Embase, Cochrane Library, and Web of Science) were searched up to June 2020 for studies comparing stents with and without $^{125}$I seeds in the treatment of unresectable MOJ.

Research results
A total of ten studies were included (6 RCTs and 4 cohort studies), involving a total of 875 patients. Our study revealed that compared with conventional stents, $^{125}$I seed stents extended the stent patency time and overall survival period. No extra complications or severe liver damage was caused by $^{125}$I seed stents. This topic remains to be studied, and more research is needed to further assess the long-term therapeutic outcomes and safety of stents irradiated using $^{125}$I seeds.
Chen et al. 125I seed stents for MOJ patients

Research conclusions
Percutaneous biliary stents combined with brachytherapy using 125I seeds offers a longer stent patency and higher overall survival than conventional stents for patients with unresectable MOJ, resulting in equivalent complications and serum index outcomes.

Research perspectives
To promote the clinical application of 125I seed stents for the treatment of MOJ, future studies are needed to conduct in-depth comparative studies on the applicable conditions and cost-effectiveness of the three types of irradiated stents. In addition, it is necessary to compare the efficacy of irradiation stents using 125I seeds for MOJ caused by different adenocarcinomas.

REFERENCES

WJCC | https://www.wjnet.com
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Prenatal ultrasonographic findings in Klippel-Trenaunay syndrome: A case report

Hou-Qing Pang, Qian-Qian Gao

Abstract

BACKGROUND
Klippel-Trenaunay syndrome (KTS) is a rare congenital disorder. A detailed prenatal ultrasound examination plays an important role in the diagnosis of KTS and the subsequent counseling and follow-up of the patient.

CASE SUMMARY
A 25-year-old woman attended our department for a regular examination. The whole of the right lower extremity and right buttock were observed to be markedly thicker compared to the left one at 18 wk of gestation. However, the lengths of the right femur, tibia and fibula were in the normal range. No marked edema and fluid/cystic spaces were detected in the lower limbs. There were no other organ abnormalities. The vasculature in the right limb was visibly dilated, with much higher intensive blood flow signals. No congenital embryonic veins were visible in both limbs. The right lower limb exhibited much more hypertrophy compared to the left limb two weeks later. Amniocentesis and genetic tests showed normal results with 46 XX. Despite the normal karyotype, the family opted to terminate the pregnancy. The post-mortem examination confirmed asymmetric hypertrophy of the right limb in the fetus and revealed a large area of marked dark-purple superficial capillary malformations occupying the skin of the right lower extremity. The enlargement of veins and soft tissue hypertrophy were also seen on postnatal X-ray and Magnetic Resonance Imaging. Autopsy revealed severe congestion in the right lower limb. A final diagnosis of KTS was made.

CONCLUSION
KTS may be diagnosed prenatally based on the typical features observed during ultrasound examination.
Key Words: Klippel-Trenaunay syndrome; Prenatal diagnosis; Ultrasonography; Case report

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Core Tip: Klippel–Trenaunay syndrome (KTS) is a rare congenital disorder. The prenatal ultrasound features include hypertrophy of one extremity, a difference between the length of the bones of the extremities, multiple cystic lesions of the extremities or internal organs, increasing blood flow signals and dilated veins or persistence of the embryonic veins. KTS may be diagnosed based on these typical characteristics in utero.

INTRODUCTION

Klippel–Trenaunay syndrome (KTS) is a rare congenital disorder characterized by a classical triad of port-wine stains, varicosities, bone and soft tissue hypertrophy, and other complications such as lymphedema and lymphangiomas, which may involve any region of the body[1]. The etiology of this disease remains unclear. Most cases can be diagnosed through a complete history and clinical examination after birth[2]. The detailed prenatal images and follow-up are crucial for the diagnosis of KTS and the subsequent counseling and management of the patient. Ultrasonographic detection is an essential method for the diagnosis of KTS in utero[3]. The present study documents the prenatal ultrasound findings of a case of KTS.

CASE PRESENTATION

Chief complaints
A 25-year-old woman attended our department for a regular examination.

History of present illness
The patient was 18 wk of gestation, with regular menstrual period and was gravida 1 parity 0. There was no history of other diseases during pregnancy.

History of past illness
The patient had no significant medical history.

Personal and family history
The personal and family history did not reveal any problems, including a history of vascular disorders.

Physical examination
On admission, her temperature was 36.7°C, respiratory rate was 23 breaths/min, and blood pressure was 120/80 mmHg. The obstetric examination revealed that the fundal height and abdominal circumference of the patient were consistent with her gestational age.

Laboratory examinations
Her mchual translucency measurement and triple test results were normal.

Imaging examinations
The whole of the right lower extremity and right buttock were observed to be...
markedly thicker compared to the left one at 18 wk of gestation. However, the lengths of the right femur, tibia, and fibula were in the normal range. No marked edema and fluid/cystic spaces were detected in the lower limbs (Figure 1A and B). There were no other organ abnormalities. On the basis of these characteristics on ultrasound images, a diagnosis of KTS was suspected. Therefore, a detailed examination of the lower-limb vascular system was performed. The external iliac veins, great saphenous veins, femoral/popliteal veins, and the lateral thigh area in both lower limbs were carefully examined. The vasculature in the right limb was visibly dilated, with much higher intensive blood flow signals. No congenital embryonic veins were visible in both limbs (Figure 1C and D). Examination of the vascular system also supported the diagnosis of KTS. In the examination conducted two weeks later, the right lower limb exhibited much more hypertrophy compared to the left limb. Amniocentesis and genetic tests showed normal results with 46 XX.

The post-mortem examination confirmed asymmetric hypertrophy of the right limb and revealed a large area of marked dark-purple superficial capillary malformations occupying the skin of the right lower extremity (Figure 1E). Enlargement of the veins and soft tissue hypertrophy were also observed in the postnatal X-ray and magnetic resonance imaging (MRI), although embryonic veins were absent (Figure 1F and G). Autopsy revealed severe congestion in the right lower limb (Figure 1H).

**FINAL DIAGNOSIS**

Following consultation with the geneticists and the professor of a vascular malformation clinic, a final diagnosis of KTS was made.

**TREATMENT**

Despite the normal karyotype, the family opted to terminate the pregnancy after a counseling session with the obstetric/pediatric team, considering a range of possible outcomes, including significant disability.

**OUTCOME AND FOLLOW-UP**

The patient underwent termination of the pregnancy. Two years later, the patient became pregnant and delivered a healthy female infant.

**DISCUSSION**

KTS is a rare and sporadic congenital disorder, which presents at birth, early infancy or childhood. The proposed pathogenesis of the disease mainly includes deep vein atresia, chronic venous hypertension, persistence of the embryological vascular system and mesodermal anomaly[1].

The etiology of KTS remains unknown. Most reported cases have not been associated with chromosome abnormalities. Whelan et al[4] reported a case of KTS associated with a single gene defect at 5q or 11p, thus, demonstrating that this genetic defect may result in increased angiogenesis leading to KTS[5]. In addition, a case with a terminal 2q37.3 deletion[6] and a case of loss of heterozygosity for 1q21.2 q44[7] were also reported.

Most of the reported cases had no genetic characteristics except a case with unproven autosomal dominant inheritance[8]. Most KTS cases were unilateral and affected the lower extremities. Both upper and lower limbs might be involved in 10% of patients. According to published reports, hemangioma lesions can also involve other organs and body parts, such as the liver, lung, spinal cord, cranial area, skull, intestinal tract, urinary tract, testis, adrenal glands, and peritoneal and retroperitoneal cavity[7,9-11].

Most patients have skin vascular nevi or wine stains to some extent and hypertrophy of the skeleton and soft tissue; thus, they were diagnosed according to these typical signs at birth[1]. A deep tissue cavernous hemangioma may gradually appear and aggravate in later childhood. The prenatal ultrasound features in utero
have been described in many studies[8,12-14]. They include marked asymmetrical hypertrophy of limbs, thickening of the subcutaneous soft tissue, multiple cystic lesions, increasing blood flow signals, dilated veins or persistence of embryonic veins. It is difficult to detect skin capillary malformations, we speculate that the fetoscope may be a useful tool to observe fetal skin vascular nevi or wine stains in utero.

One of the main features of KTS is anomaly of the limb vein system, which appears as the persistence of embryonic veins, and varicose enlargement hypoplasia of the limb venous system. Assimakopoulos et al[9] revealed a case associated with a hypertrophied great saphenous vein. We also found more blood flow signals and the dilation of deep veins, which was confirmed by MRI and autopsy after induced abortion in our case. These findings indicated that it is feasible to carry out a thorough prenatal ultrasound examination of the venous system in the lower extremities to obtain more information in order to diagnose KTS.

The clinical presentation varies from minimally symptomatic disease to life-threatening bleeding and embolism. The prognosis is correlated with the size of the masses and their growth. There were large and extensive anechoic areas or the involvement of internal organs in reviewed cases with poor prognosis[3]. Therefore, the ultrasound scan should be repeated and the area and progress of the cystic lesions monitored, which may increase the risk of intrauterine heart failure and bleeding in the postnatal stage.

It is worth noting that there are many more reported cases after birth than in utero. This indicates that many cases of fetal KTS are not diagnosed prenatally as the lesions are minimal or complex, and it is difficult to make an accurate diagnosis. KTS should be suspected when there is hypertrophy of one of the extremities, discrepancy in the bone length, surface masses on the limbs and/or trunk, and unexplained cystic lesions of the internal organs or limbs. Therefore, necessary examinations should be performed to determine the location and severity of the lesions and to provide a reliable basis for the selection of appropriate treatment methods. MRI is another useful method, which can offer more detail on the soft tissue and vasculature.

CONCLUSION

KTS may be diagnosed prenatally based on the typical features on ultrasound examination. Timely prenatal diagnosis and follow-up are important for subsequent prenatal counseling and adjustment of medical care and choices according to each
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REFERENCES


Immunoglobulin G4-related lymph node disease with an orbital mass mimicking Castleman disease: A case report

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Abstract

BACKGROUND
Immunoglobulin (Ig) G4-associated diseases are a group of systemic diseases involving multiple organs and are also known as IgG4-associated sclerosing diseases. IgG4-associated lymphadenopathy occurring in the lymph nodes is characterized by a lack of specificity due to its clinicopathological characteristics and must be differentiated from a variety of lesions, such as Castleman disease, lymphatic follicular reactive hyperplasia, and lymphoma.

CASE SUMMARY
A 65-year-old male patient, with Guillain-Barre syndrome for 5 years, presented to our hospital complaining of bilateral orbital mass for 2 years. After hospitalization, the results of the patient’s laboratory tests showed that immunoglobulin subgroup IgG4 was 33.90 g/L and IgG was 30.30 g/L, but serum interleukin-6 was normal. The pathological morphology of orbital mass and cervical lymph node were consistent, which showed that a large number of plasma cells and eosinophils were observed in the lymphatic follicles, and the interstitial fibrous tissue was proliferative. Immunohistochemistry showed that CD20 (B cells) (+), CD3 (T cells) (+), CD38 (+), IgG (+), IgG4 positive cells > 100/high powered field, and IgG4/IgG > 40%. Combined with clinical and immunohistochemical results, lymphadenopathy was consistent with Castleman disease-like IgG4-associated sclerosing disease. Prednisone acetate treatment was given at 40 mg/d. After 2 wk, the superficial lymph nodes and orbital masses shrank, and the IgG4 level decreased. As prednisone acetate was regularly used at a reduced dosage, no recurrence of the disease has been observed.
CONCLUSION
This case suggested that it is necessary to proceed cautiously in clinical practice with such patients, and immunoglobulin, complement, interleukin-6, C-reactive protein, and other examinations should be performed to confirm the diagnosis.

Key Words: IgG4-associated disease; Castleman disease; Lymphadenopathy; Orbital neoplasm; Pathological morphology; Case report

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INTRODUCTION
Immunoglobulin (Ig) G4-related disease (IgG4-RD) is a group of systemic immune diseases characterized by elevated serum IgG4, a large amount of IgG4+ plasma cell infiltration in tissues, occasional eosinophilic granulocytes, interstitial fibroplasia, and small phlebitis obliterans[1-3]. Castleman disease is a clinically rare lymphoproliferative disorder. Castleman disease and IgG4-RD may present some common clinical manifestations, such as enlarged lymph nodes and elevated serum IgG4 levels, which make the clinical diagnosis and differential diagnosis more difficult and challenging [4]. Here, we report a case of IgG4-related lymph node disease with an orbital mass mimicking Castleman disease and review the relevant literature.

CASE PRESENTATION
Chief complaints
A 65-year-old male patient was admitted to the hospital on January 21, 2020 due to a “bilateral orbital mass for 2 years.”

History of present illness
Two years prior, the patient developed binocular swelling, exophthalmos, and decreased vision accompanied by hand tremor without any other accompanying symptoms, and the above symptoms became progressively worse.

History of past illness
He suffered from Guillain-Barre syndrome 5 years ago and left hand tremor after recovery.

Personal and family history
The patient denied alcohol consumption and allergies to food or medicines.
**Physical examination**
Right orbital mass and bilateral cervical lymph node enlargement was observed. The large one was about 1.6 cm × 0.9 cm. No other obvious positive signs were found.

**Laboratory examinations**
After hospitalization, the results of the patient’s laboratory tests showed that the erythrocyte sedimentation rate was 47.0 mm/h, D-dimer was 1450.00 ng/mL, immunoglobulin subgroup IgG4 was 33.90 g/L, IgG was 30.30 g/L, total protein was 64.7 g/L, and albumin was 26.1 g/L. Antinuclear antibody was weakly positive (titer 1:100), complement C3 was 0.79 g/L, complement C4 was 0.10 g/L, and complement C1q was 102.20 mg/L. Urinary protein was 4+, but serum interleukin (IL)-6 was normal. Thyroid function, thyroid stimulating hormone receptor antibody, routine blood tests, C-reactive protein (CRP), brain natriuretic peptide (BNP)/pro-brain natriuretic peptide (PBNP), and rheumatoid factors were not significantly abnormal, and extractable nuclear antigen antibody spectrum, anti-cyclic citrate peptide antibody, anti-neutrophilic cytoplasmic antibody, and anti-phospholipid antibody were negative.

**Imaging examinations**
On January 9, 2021, orbital computed tomography (CT) performed in the outpatient department showed bilateral external eye muscle and periocular changes, exophthalmos, swelling of the right eyelid, and multiple bone resorption changes in the medial orbital wall on both sides.

On January 21, 2021, ultrasound examination showed nodular goiter (thyroid imaging reporting and data system 3 type) and right cervical lymph node enlargement.

On February 2, 2021, ultrasonography showed bilateral lymph node enlargement. The large one on the right was 1.6 cm × 0.9 cm, and the large one on the left was 1.9 cm × 1.1 cm.

On January 29, 2021, positron emission tomography/CT results showed that the bilateral ophthalmic muscles, lacrimal glands, intraorbital soft tissue, subcutaneous soft tissue nodules in the back, bilateral mediastinal pleura, and several superficial and deep lymph nodes all showed increased metabolism, accompanied by retroperitoneal fibrosis (Figure 1).

**Pathological morphology and immunohistochemistry**
On January 25, 2021, right orbital mass resection was performed, and postoperative pathological diagnosis showed that a large number of plasma cells and eosinophils were observed in the lymphatic follicles. The interstitial fibrous tissue was proliferative (Figure 2A and B). Immunohistochemistry showed CD20 (B cells) (+), CD3, CD4, and CD8 (T cells) (+), CD38 and CD138 (plasma cells) (+), S100 was scattered (+), CD1a was scattered (+), Langerin (-), Epstein-Barr encoding region (-), Ki-67 (+, approximately 40%), IgG (+), IgG4 positive cells > 100/high powered field, and IgG4/IgG > 40% (Figure 2C-F). Combined with clinical and immunohistochemical results, these results were consistent with IgG4-associated sclerosing disease.

On February 4, 2021, the pathological results of the left neck lymph node biopsy showed that the lymph node structure was still present, mainly exhibiting follicular hyperplasia, small blood vessels in the follicle were extended, and a large number of plasma cells were observed in the interfollicular area (Figure 3A and B). Immunohistochemical results showed that CD20 (B cells) (+), CD3 (T cells) (+), CD38 plasma cells (+), IgG (+), IgG4 (+), CD21 (follicular dendritic cell network) (+), Ki-67 (+); (approximately 90% in follicles and approximately 20% in the interfollicular area), and IgG4/IgG > 40% (Figure 3C-F). Combined with clinical and immunohistochemical results, lymphadenopathy was consistent with Castleman disease-like IgG4-associated sclerosing disease.

**FINAL DIAGNOSIS**
The final diagnosis of the presented case was Castleman disease-like IgG4-associated sclerosing disease.
Figure 1 Positron emission tomography computed tomography on January 29, 2020. Positron emission tomography computed tomography revealed that bilateral ophthalmic muscles, lacrimal glands, intraorbital soft tissue, subcutaneous soft tissue nodules in the back, bilateral mediastinal pleura, and several superficial and deep lymph nodes all showed increased metabolism, accompanied by retroperitoneal fibrosis.

TREATMENT

Prednisone acetate treatment was given at 40 mg/d. After 2 wk, the superficial lymph nodes and orbital masses shrunk, and the IgG4 level decreased upon re-examination.

OUTCOME AND FOLLOW-UP

At present, prednisone acetate was regularly used at a reduced dosage, and no recurrence of the disease has been observed.

DISCUSSION

IgG4-associated diseases are a group of systemic diseases involving multiple organs and are also known as IgG4-associated sclerosing diseases. Clinically involved organs include the pancreas, bile duct, retroperitoneum, lung interstitium, breast, kidney, salivary gland, liver, lymph node, and other tissues and organs, and the affected organs are different at different ages[5]. The typical histological features of IgG4-RD include dense lymphoplasmacytic infiltrates, storiform-type fibrosis, and obliterator phlebitis[6]. The diagnosis of at least two of the above three criteria is needed, usually diffuse lymphoplasmic cell infiltration and storiform-type fibrosis[7,8]. However, lymph nodes, the lung, and other organs and tissues often do not have the characteristic manifestations of storiform-type fibrosis and phlebitis obliterans. IgG4-correlated disease in the lymph nodes is easily misdiagnosed due to the lack of specificity of its clinical pathological features, which have been identified in a variety of pathological conditions, such as Castleman disease, inflammatory pseudotumor,
Figure 2 Pathological morphology and immunohistochemistry of orbital mass. A: At low magnification, the histological morphology showed lymphoproliferative tissue, scattered lymphoproliferative follicles, and interstitial fibrous tissue proliferation (× 50); B: Histological morphology at high magnification showed hyperplasia of small vessels in the follicles, and a large number of plasma cells infiltrated between the follicles (× 200); C: CD38 immunohistochemical staining showed a large number of positive plasma cells in the interfollicular space; D: Immunohistochemical staining of CD138 showed a large number of positive plasma cells in the interfollicle; E: Immunoglobulin (Ig) G positive plasma cells could be seen by immunohistochemical staining; F: IgG4-positive plasma cells could be seen by immunohistochemical staining; The IgG4/IgG ratio was greater than 40%. HE: Hematoxylin and eosin stain; Ig: Immunoglobulin.

and lymphoid follicle hyperplasia of reactivity (such as lymphoma), and final diagnosis should combine medical history, physical examination, serological examination, imaging, pathology, and immunohistochemistry[9-11].

Studies have shown that FDG positron emission tomography/CT has a sensitivity of 85.7% and a specificity of 66.1% in the diagnosis of IgG4-RD and may have a potential differential ability for patients with clinically suspected IgG4-RD[12]. We presented a case of IgG4-RD with Castleman disease-like alterations that included positron emission tomography/CT. IgG4 immunostaining was necessary for the diagnosis of IgG4-RD, and a proportion of IgG4+/IgG+ plasma cells greater than 40% and the IgG4+ cell count are important parameters[13,14]. This case met the criteria. Effective initial treatment with glucocorticoids is one of the characteristics of IgG4-RD, and rituximab therapy should be considered for patients for whom glucocorticoids are ineffective or who are dependent on glucocorticoids[15].

Castleman disease, first reported in 1956, is a clinically rare lymphoproliferative disorder. According to the different scope of involvement, it was divided into unicentric Castleman disease and multicentric Castleman disease (MCD). Histologically, the disease was divided into a clear vascular type, plasma cell type, and mixed type. MCD usually manifests as multiple lymph node enlargement, hepatosplenomegaly, kidney injury, pulmonary symptoms and signs, and ascites and can be accompanied by high fever, night sweats, and other systemic symptoms[16]. Because the disease is relatively rare in clinical practice, there is no unified first-line treatment plan at present, but simple glucocorticoids have poor efficacy. Combined chemotherapy, rituximab, or anti-IL-6 treatment are often necessary, and the prognosis
Figure 3 Pathological morphology and immunohistochemistry of cervical lymph nodes. A: At low power histological morphology, most of the lymphoid sinuses of the lymph nodes disappeared, and proliferative lymphatic follicles were evenly distributed throughout the lymph nodes. Lymphocytes in the mantle region were widened, and small blood vessels between the follicles were increased, with partial hyalinization, similar to Castleman disease morphological changes (× 50); B: At high magnification, small blood vessels in the follicles were observed to grow and proliferate, a large amount of lymphatic tissue proliferated between the follicles, and plasma cells were infiltrated (× 200); C: Immunohistochemical staining of CD21 showed a network of follicular dendritic cells scattered throughout the lymphatic follicles of the lymph node; D: CD38 immunohistochemical staining showed a large number of positive plasma cells in the interfollicular space; E: Immunoglobulin (Ig) G positive plasma cells could be seen by immunohistochemical staining; F: IgG4-positive plasma cells could be seen by immunohistochemical staining; the IgG4/IgG ratio was greater than 40%. HE: Hematoxylin and eosin stain; Ig: Immunoglobulin.

It has been reported that IgG4-associated lymphadenopathy may have Castleman disease-like characteristics, and some scholars believe that a subset of plasma cell Castleman disease is actually IgG4-associated lymphadenopathy [21,22]. IgG4-RD share similarities with Castleman disease, but there are also differences. MCD and IgG4-RD can be distinguished based on the following aspects: (1) Clinical manifestations: lymph node enlargement in MCD is more prominent and is often accompanied by fever, anemia, severe hypoproteinemia, and other systemic symptoms, while lymph node lesions of IgG4-RD are usually less than 2 cm in diameter and often involve the lacrimal glands, salivary glands, pancreas, and retroperitoneum; (2) Inflammation indicators: CRP, IL-6, and vascular endothelial growth factor are usually significantly increased in MCD patients; (3) In terms of immunoglobulin and complement, increased IgG in MCD patients may be accompanied by increased IgA and IgM, with normal complement levels, while the course of IgG4-RD may involve the activation process of complement, leading to decreased complement levels; (4) Pathological features: IgG4+ plasma cells may appear in MCD patients, but IgG4+/IgG+ plasma cells usually account for less than 40%; and (5) Therapeutic response of glucocorticoids: IgG4-RD patients respond well to initial treatment with glucocorticoids, while MCD patients generally respond poorly [4,23-25].
The patient in this case had lacrimal gland, lymph node, retroperitoneal, and other lesions, decreased complement C3, normal IL-6 levels, IgG4+/IgG+ plasma cells greater than 40%, and a good response to glucocorticoid treatment. All of these features were in line with IgG4-associated lymphadenopathy. However, the pathological morphology of this patient was very similar to that of Castleman disease, which may lead to misdiagnosis. Therefore, it is necessary to proceed cautiously in clinical practice with such patients, and Ig, complement, IL-6, CRP and other examinations should be performed to confirm the diagnosis.

CONCLUSION

There is no unified standard for the differentiation of IgG4-RD from plasma cell Castleman disease, and these diseases are sometimes difficult to distinguish from one another. It is necessary to proceed cautiously in clinical practice with such patients. Histopathological characteristics, laboratory testing, and clinical treatment should be considered comprehensively to provide a basis for clinical treatment and prognosis evaluation.

REFERENCES

1. Lanzillotta M, Bancuso G, Della-Torre E. Advances in the diagnosis and management of IgG4 related disease. BMJ 2020; 369: m1067 [PMID: 32546500 DOI: 10.1136/bmj.m1067]
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Treatment for subtrochanteric fracture and subsequent nonunion in an adult patient with osteopetrosis: A case report and review of the literature

Hao Yang, Guo-Xi Shao, Zhen-Wu Du, Zheng-Wei Li

Abstract

BACKGROUND
As a congenital metabolic bone disease caused by defective osteoclastic resorption of immature bone, osteopetrosis is characterized by diffused sclerosis of bones, brittle bones, easy fracturing, narrow medullary canals, and a weak fracture healing ability. At present, clear standards and principles for the treatment of fractures in patients with osteopetrosis are lacking. Non-operative treatment can prevent fracture hematoma and preserve the blood supply to the bone fragments, while being associated with frequent failures and higher mortality rates. Meanwhile, closed reduction and internal fixation with intramedullary nail (CRIF + IMN) approaches can also protect blood supply to the fracture site. However, IMN cannot be used for the vast majority of patients with osteopetrosis due to the narrowing of medullary canals. Thus, open reduction and internal fixation with plate remains the most appropriate surgical method for treating fractures in patients with osteopetrosis, but this approach is complicated by the lack of intramedullary hematopoiesis in such patients. Fracture healing primarily depends on the blood supply to the external periosteum. Open reduction can also easily destroy the periosteum and cause delayed fracture healing or even nonunion; however, CRIF may be the most practical approach. As a result, it would be prudent to solve the difficulty of drilling during the operation and the problem of postoperative nonunion.

CASE SUMMARY
In 2018, we treated an adult patient with osteopetrosis presenting with a subtrochanteric fracture. The fracture was fixed using a femoral locking
Osteopetrosis; Subtrochanteric fracture; Nonunion; Platelet-rich plasma

CONCLUSION

Osteosynthesis remains the first choice of treatment approach for fractures in patients with osteopetrosis, especially peritrochanteric fractures. Preoperative preparation is necessary to avoid risks such as drill bit breakage and iatrogenic fracture during the operation. Moreover, fractures in a patient with osteopetrosis present with a high risk of delayed union and nonunion, which can be potentially cured with PRP + rESWT.

Key Words: Osteopetrosis; Subtrochanteric fracture; Nonunion; Platelet-rich plasma; Radial extracorporeal shock wave therapy; Case report

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Core Tip: Osteopetrosis is a rare clinical disease which heightens the risk of fractures, but it is significantly difficult to perform surgical treatments in patients with osteopetrosis. Numerous risks such as drill bit breakage and iatrogenic fracture exist during the operation, which can lead to the failure of treatment. We present herein, a case of a subtrochanteric fracture in an adult patient with osteopetrosis that was fixed using a femoral locking compression plate. The postoperative consolidation was delayed, and the patient was subsequently treated with platelet-rich plasma (PRP) combined with radial extracorporeal shock wave therapy (rESWT). This case highlights the ultimate importance of preoperative preparation to avoid the potential risks of surgical failure. Furthermore, fractures in a patient with osteopetrosis have a high risk of delayed union and nonunion, which might be cured by PRP combined with rESWT.

INTRODUCTION

Osteopetrosis is a group of rare genetic diseases characterized by overly dense bones throughout the body[1,2]. Among the three types of osteopetrosis, autosomal recessive osteopetrosis (ARO) exhibits the most serious clinical symptoms, which generally manifest in infancy in the form of developmental malformations and abnormalities of multiple organs and systems, truly being a life-threatening disease[3].

Meanwhile, another form of osteopetrosis, autosomal dominant osteopetrosis (ADO), presents with mild symptoms[3,4], emerging in adulthood in most patients. The characteristic clinical manifestations of ADO include systemic bone sclerosis and narrowing, or even occlusion, of the medullary canal[5]. Moreover, the increased bone density actually weakens the bone, leading to a heightened risk of fractures[6].

Currently, there is no clear consensus on whether conservative or surgical treatments should be adopted for fractures in patients with osteopetrosis[7]. It is generally believed that non-operative treatment regimens should be selected for children, adolescents, and most of the patients presenting with upper limb fractures[8]. However, conservative treatment of femoral intertrochanteric, subtrochanteric, and femoral neck fractures can easily cause coxa vara deformities, delayed bone union, or nonunion[9]. In regard to these fractures, surgical treatment has been previously associated with more favorable prognoses[8]; however, surgical methods come with
their own set of technical challenges. First, fixation with plate or intramedullary nail is particularly difficult due to increased bone density\textsuperscript{[10]}. Second, there is an increased risk of iatrogenic fractures because of the brittle nature of the bones\textsuperscript{[11,12]}. Finally, there is also a postoperative risk of delayed consolidation and nonunion because of impaired bone remodeling\textsuperscript{[13]}. The current paper reports a case of a subtrochanteric fracture in an adult patient with osteopetrosis that was fixed using a femoral locking compression plate. The postoperative consolidation was delayed, and the patient was subsequently treated with platelet-rich plasma (PRP) combined with radial extracorporeal shock wave therapy (rESWT). Herein, we report the diagnosis and treatment process and the results of a 10 mo follow-up.

**CASE PRESENTATION**

**Chief complaints**

A 38-year-old male patient was admitted to our emergency department at the Second Hospital of Jilin University with complaints of hip pain, swelling, and limitation of motion due to a fall.

**History of present illness**

The patient suffered from swelling, pain, and limited movements of his left hip due to an accidental fall. He was subsequently rushed to a local hospital and diagnosed with “osteopetrosis and pathological fracture of the proximal femur” by X-ray examination. He came to our hospital for further diagnosis and treatment 9 h after injury.

**History of past illness**

The patient had no relevant medical history prior to the injury, and no history of surgery or blood transfusion.

**Personal and family history**

The patient denied any history of genetic disorders or inbreeding in his family, and stated that his childhood development was normal.

**Physical examination**

The patient’s vital signs were as follows: Temperature of 36.4 °C, heart rate of 86 bpm, respiratory rate of 20 breaths per minute, blood pressure of 134/84 mmHg, and 99% oxygen saturation in room air. Subsequent physical examination on admission revealed slight swelling of the left hip and left thigh, local tenderness and percussion pain, and limited movement of the left hip, with good flexion and extension of the left knee, left ankle, and left toe. The skin sensation of the left lower limb was slightly decreased. Meanwhile, the pulse of the left dorsal pedis artery and peripheral perfusion were good.

**Laboratory examinations**

Main abnormal indicators were as follows: Parathyroid hormone 111.90 pg/mL, urine specific gravity 1.010, uric acid 520 µmol/L, D-dimer 1.39 µg/mL, fibrinogen degradation product 6.8 µg/mL, blood phosphorus 1.61 mmol/L, white blood cell count 10.6 × 10\textsuperscript{9}/L, neutrophil percentage 84.1%, and lymphocyte count 11.3%.

Meanwhile, the main normal indicators were as follows: Hb 152g/L, PLT 144.5 × 10\textsuperscript{9}/L, PT 11.0 s, APTT 25.6 s, TT 13.6 s, U-BIL(-), UBG(-), KET(-), BLD(+), Calcitonin 3.86 pg/mL, TPOAb 36 U/mL, TG-Ab < 15.0 U/mL, FT3 4.45 pmol/L, and FT4 13.34 pmol/L.

**Imaging examinations**

Plain X-ray imaging illustrated discontinuous cortical bone of the left proximal femur, separation and displacement of the bone fragments, increased bone density of pelvic bones and bilateral femurs, thickened cortical bone, and narrowed bone marrow canal (Figure 1).
Figure 1 X-ray and three-dimensional reconstructive computed tomography of the patient after injury. A: Antero-posterior radiograph of the pelvis showing increased bone density of pelvic bones and bilateral femurs, thickened cortical bone, and narrowed bone marrow canal; B and C: Antero-posterior and lateral preoperative radiographs of the left subtrochanteric fracture; D: 3D reconstructive computed tomography of the left subtrochanteric fracture showed discontinuous cortical bone of the left proximal femur, and separation and displacement of the bone fragments.

**FINAL DIAGNOSIS**

Subtrochanteric fracture and osteopetrosis.

**TREATMENT**

Since the results of physical, imaging, and laboratory examinations indicated no contraindications, an operation was performed on the second day after admission. We chose the open reduction method and internal fixation with femoral locking compression plate to treat the fracture. First, general anesthesia was administered during the operation. We employed a bone holding device and Kirschner wire for temporary fixation. Facing the difficulty of drilling during the operation, we opted to use a low-speed and high torque electric drill, changing the drill bit several times and assisting with physiological saline cooling. Although the operation time was prolonged, the surgery was completed successfully (Figure 2).

**OUTCOME AND FOLLOW-UP**

After the operation, the patient received supportive treatment for prevention of infection and anticoagulants, and there were no perioperative or postoperative complications. The patient was transferred to a local hospital for follow-up treatment on the 7th day after operation. At 2, 3, and 10 mo postoperatively, plain radiography was performed, which showed that the fracture line was still clearly visible, with no obvious signs of fracture healing (Figure 3). Unfortunately, the follow-up demonstrated nonunion of the bone. After consultations with the treating physicians, the patient accepted treatment with three PRP + rESWT sessions. Antero-posterior and lateral radiographs obtained at the latest follow-up (10 mo after the last treatment) illustrated that the callus had grown at the original fracture site, and the medial fracture line almost disappeared (Figure 4).
The imaging results showed that internal fixation was accurate, with good apposition and alignment.

Figure 2 Postoperative X-ray images. The imaging results showed that internal fixation was accurate, with good apposition and alignment.

Figure 3 Plain radiography at 2, 3, and 10 mo postoperatively showed that the fracture line was still clearly visible, with no obvious signs of fracture healing. A: X-ray at 2 mo after operation; B: X-ray at 3 mo after operation; C: X-ray at 10 mo after operation.

The patient also walked and participated in many daily activities without any unusual complaints. However, there was a risk of plate fracture and refracture, since the lateral cortex had not achieved bone healing, even though the medial side healed. In this regard, the patient and his family were informed of the risk, and an iliac bone graft was recommended (pelvic CT examination revealed the presence of a certain amount of cancellous bone in the iliac bone). The patient and his family members expressed their understanding, but refused to accept the surgical treatment. It remains to be seen how this situation will be resolved in the long term.

DISCUSSION

Osteopetrosis, first reported by Albers-Schönberg in 1904, is precipitated by genetic mutations that result in the failure of osteoclast differentiation or functions and lead to reduced bone resorption. Consequently, all body’s bones become hard and brittle like marble due to inefficient resorption, so the condition is also known as “marble bone disease”, as well as “Albers-Schönberg disease” [14]. In addition, since the number and activity of osteoclasts are decreased, the patients with osteopetrosis present with an increased risk of developing hypocalcemia, which can further cause epilepsy and
hyperparathyroidism. Meanwhile, in infants, the disease not only impairs the bone remodeling system, but also causes myelopoiesis disorder due to narrowing of the medullary cavity, and secondary hepatosplenomegaly due to excessive extramedullary hemopoiesis\[15\]. Skeletal deformities of the head and face can also lead to hydrocephalus and stenosis of nerve foramen, which may damage optic and facial nerves\[16\]. A large proportion of children afflicted with osteopetrosis do not survive till adulthood, which represents a serious problem to parents all over the world\[14\]. In the case of a mild adult type of osteopetrosis, only the whole-body bone mass is increased and the medullary canals are narrowed, which do not result in developmental malformation and other abnormalities.

Further adding to the plight, the standards and principles for the treatment of fractures in patients with osteopetrosis are not yet clearly formulated\[7\]. Armstrong et al\[8\] conducted a survey of the membership of the Pediatric Orthopedic Society of North America, which incorporated the experience of 57 surgeons who treated 79 fractures in patients with osteopetrosis, with their findings illustrating that the majority of patients with osteopetrosis were successfully treated using the conservative approach. On the other hand, they also observed that non-operative treatment of femoral intertrochanteric, subtrochanteric, and femoral neck fractures could precipitate coxa vara deformities and delayed bone union or nonunion. In another study, Birmingham and McHale\[9\] treated a patient presenting with autosomal-dominant osteopetrosis, a subtrochanteric fracture, and an ipsilateral femoral neck fracture with a hip spica cast after 6 wk in traction. During the follow-up, they found that 2.5 years after the injury, the subtrochanteric fracture was united and in slight varus and external rotation. Furthermore, Kim et al\[13\] employed the intramedullary nailing (IMN) approach to treat two cases of adult osteopetrosis with subtrochanteric fractures. In the first case, IMN left a gap at the fracture site because the distal fragment was not effectively reamed, and the patient showed delayed union and subsequently underwent a dynamization procedure 6 mo postoperatively, which resulted in bone healing 10 mo after the dynamization. The second patient presented with a bilateral subtrochanteric fracture. The left femur fracture healed 8 mo after IMN, while on the right side, the patient underwent open reduction and internal fixation with a locking plate, as the medullary canal was too short and narrow. Intramedullary fixation was excluded, but the fracture line still did not disappear 20 mo after the operation. Moreover, Amit et al\[17\] treated subtrochanteric fractures in two patients with osteopetrosis by means of open reduction and internal fixation with a locking plate, and both the patients achieved bone healing 21 and 23 wk after operation, respectively.

Additionally, surgical treatment of patients with osteopetrosis presents with heightened difficulty compared to ordinary fracture patients. There is a certain risk of drill bit breakage and iatrogenic fracture during the operation, which can lead to failure of treatment\[9-12\]. However, as long as preoperative preparations and corresponding surgical strategies are well formulated in a timely manner, surgical treatment is still heralded as the first-choice treatment for fractures in patients with osteopetrosis \[7,18,19\]. Unfortunately, regardless of whether the operation is successful or not, the...
risk of delayed union or even nonunion still persists\[18\].

The hard-done work of our peers has highlighted that the risk of the aforementioned delayed postoperative union and the nonunion associated with impaired bone remodeling\[13,20\]. To elaborate, Matsuo et al\[21\] reported the case of an osteopetrosis patient presenting with a femoral shaft fracture below a plate who underwent open reduction and internal fixation with locking plate and wire cerclage. During follow-up, they observed that fracture healing was delayed postoperatively, and the plate fractured 14 mo after operation. The occurred fracture healed after treatment with a double locking plate. In the case of our patient, we did not rely on steel wire fixation, as we believe that plate fixation is accurate and provides enough stability. Steel plate fixation was performed following the AO principles, which indicate the use of a plate length greater than three times the fracture in comminuted fractures, and plate length greater than eight to ten times the fracture length in simple fractures. The principles further suggest a screw/plate ratio of less than 0.5 to create a long lever arm and decrease the bending loads on the distal screws. Lastly, a span of at least two or three screw holes should be left open over the fracture to decrease stress concentration\[22,23\]. We speculate that the reasons for poor healing may be linked to insufficient blood supply and osteogenetic factors. There is a wide variety of methods to promote bone healing for clinicians. Although autologous bone grafting is deemed as the “gold-standard” approach, it is associated with complications and additional treatment costs \[24\]. Nevertheless, there is no doubt that autogenous bone graft can augment fracture healing, but for patients with no obvious defects after fracture reduction\[25\], the usage of autogenous bone graft or even reamed nail + bone graft at the first operation remains to be further discussed. In our patient, the limb function was respectable, and accordingly he did not want to proceed with treatment associated with potential trauma. As a result, we tried to employ some minimally invasive methods to improve the probability of fracture healing, such as haemopoietic stem cell transplant (HSCT), PRP, and extracorporeal shock wave therapy (ESWT).

Various authors have highlighted the ability of HSCT to effectively restore normal bone resorption and hematopoiesis in severe autosomal recessive osteopetrosis\[26\], while also being associated with many potential adverse effects, including acute rejection, graft vs host disease, and veno-occlusive events\[27\]. Meanwhile, PRP is a well-known plasma product obtained by centrifugation and fractionation of autologous venous blood. The concentrated platelets can be used to produce various growth factors, such as PDGF, factor-β, VEGF, FGF, and others\[28\]. In addition, several in vitro studies have indicated that PRP can promote neovascularization\[29\] and enhance osteoprogenitor cell proliferation and differentiation\[30,31\]. However, many scholars still doubt the clinical effectiveness of PRP\[32,33\]. Lastly, ESWT is a physical stimulation therapy, which includes focused (fESWT) and radial (rESWT) therapy types\[34,35\]. In our case, we employed the rESWT type, which uses compressed air or a magnetic field to emit projectiles. The projectiles strike a metal applicator placed on the patient’s skin to generate stress waves\[35\], and these waves get transmitted into tissues and stimulate the process of bone fracture healing\[36-39\]. Furthermore, Kertzman et al\[38\] employed the rESWT approach to treat 22 patients with bone nonunion, 16 of whom achieved bone union after 6 mo. ESWT is widely used in the treatment of delayed union and nonunion of fracture and appears to be an effective treatment with no obvious complications\[39\].

**CONCLUSION**

Osteosynthesis is regarded as the first-choice treatment approach for fractures in patients with osteopetrosis, especially peritrochanteric fractures. Meanwhile, if the condition of medullary canal permits, the preferred choice is closed reduction and intramedullary nailing. However, for most patients with osteopetrosis, only open reduction and plate fixation are allowed, and there is a significantly higher risk of delayed union and nonunion in patients with osteopetrosis compared to normal patients. In order to solve this problem, low trauma intervention such as PRP and rESWT can be tried.

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REFERENCES


Yang H et al. Subtrochanteric fracture in osteopetrosis
Yang H et al. Subtrochanteric fracture in osteopetrosis


26 Walker DG. Bone resorption restored in osteopetrotic mice by transplants of normal bone marrow and spleen cells. *Science* 1975; 190: 784-785 [PMID: 1105786 DOI: 10.1126/science.1105786]


Early surgical intervention in culture-negative endocarditis of the aortic valve complicated by abscess in an infant: A case report

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Abstract

BACKGROUND
Surgical therapy of infective endocarditis (IE) involving aortic valves and mitral valves is widespread. However, there are few reports concerning patients with culture-negative endocarditis complicated by the appearance of comorbid valvular perforation and abscess. Therefore, real-time surveillance of changes in cardiac structure and function is critical for timely surgical management, especially in patients who do not respond to medical therapy.

CASE SUMMARY
Here, we report an atypical case in a 9-mo-old infant without congenital heart disease but with symptoms of intermittent fever and macular rashes. Physical examination, laboratory tests, and electrocardiograms suggested a diagnosis of IE, although the result of blood cultures was exactly negative. After treatment with antibiotic drugs, the patient got a transient recovery. On the 9th day, we proceeded with continuous echocardiogram due to fever again and the results revealed aortic valve abscess with perforation, regurgitation, vegetation, and pericardial effusion. Intraoperative monitoring revealed aortic valve perforation, presence of apothegmatic cystic spaces below the left coronary cusp of the aortic valve, and severe aortic valve regurgitation. Aortic valve repair was performed by autologous pericardial patch plasty. The patient was discharged after 4 wk of treatment and no complications occurred after surgery.

CONCLUSION
Our case demonstrated the necessity of serial echocardiography monitoring for possible adverse symptoms of IE in pediatric patients.

Key Words: Infective endocarditis; Aortic regurgitation; Abscess; Blood culture-negative;
INTRODUCTION

Infective endocarditis (IE), although uncommon, is a vital disease with an annual incidence ranging between 0.05 and 0.12 cases per 1000 pediatric admissions[1]. The incidence of pediatric IE has significantly increased over the past two decades with changes in risk factors, causative agents, and clinical manifestations deeply impacting its epidemiology[2]. This could be attributed to the increasing use of invasive diagnostic and therapeutic procedures in the management of IE[3]. Further, advances in echocardiography and surgical techniques over the past few years have considerably enhanced the accuracy of diagnosis and treatment for IE, even in patients with a structurally normal heart[4].

IE in children with a normal heart has become a discernible clinical entity[1], which could plausibly be associated with a potential immunosuppressed condition[5]. In an estimated 8%-10% of pediatric cases, IE has been reported to be the consensus of one easily recognizable risk factor with a normally structured heart.

Culture-negative endocarditis is a clinically challenging entity both diagnostically and therapeutically. The spectrum of epidemiology of culture-negative endocarditis has changed over the last five decades. In a recently published series, approximately 8%-36% of patients with clinically diagnosed endocarditis had persistently negative blood cultures[6-8]. The most common causes of culture-negative endocarditis include previous receipt of antimicrobial therapy and infections caused by fastidious organisms also known as the “HACEK” group which includes nutritionally deficient Streptococci, Pasturella spp., Helicobacter spp., Mycobacteria, fungal infections, infections involving intracellular organisms Bartonella spp., Tropheryma whippelii, Coxiella burnetii (Q fever), and Brucella spp. that are either detectable by serology or polymerase chain reaction of valvular tissue[9]. Moreover, it has been shown that a lower sensitivity of blood cultures for yeast and complete lack of sensitivity for filamentous fungi make the diagnosis of fungal IE limited[10].

Although echocardiogram aids in clinically confirming the diagnosis of endocarditis, culture-negative endocarditis often delays diagnosis. And the higher morbidity associated with culture-negative endocarditis could be primarily attributed to the increasing burden of diagnostic testing, delays in administration of antibiotics, and the extensive use of broad-spectrum anti-microbial agents[10]. Culture-negative endocarditis complicated by the presence of valvular perforation and/or abscess calls for immediate surgical operation. Valvular perforation may lead to severe valve destruction, intractable heart failure, and even death if timely surgical therapy is not administered[11]. The presence of an abscess further increases surgical complexity due to excavation of the annular tissue during an ongoing infectious process, making it difficult to perform valve replacement or repair[12]. Recently, guidelines recommend
prolonging the duration of antibiotic treatment for the management of IE\cite{1}. However, the indications for surgical intervention are not clearly explicit and are only limited to certain cases and indications\cite{13}. In addition, most of the current indications are based on consensus\cite{1}.

Here, we describe a 9-mo-old infant who was diagnosed with culture-negative endocarditis and complicated with the appearance of valvular perforation and abscess, but did not suffer from congenital heart disease. Further, in view of the above and the scarcity of literature on early surgical therapy in culture-negative endocarditis, we assessed the factors leading to severe valve destruction, the recognition of which is critical and timely for surgical intervention, especially for patients who do not respond to medical therapy.

**CASE PRESENTATION**

**Chief complaints**
A male infant aged 9 mo and 8 d, weighing 8 kg, born via spontaneous vaginal delivery, was presented to the emergency department for evaluation of intermittent fevers and red macula.

**History of present illness**
The patient had intermittent fever (less than 39 °C), red macula, dry and chapped lips, and a red rash around the mouth for 9 d. No other symptoms such as nausea, vomiting, diarrhea, and urinary symptoms were present. He was admitted to the hospital with a presumptive clinical diagnosis of Kawasaki disease on May 12, 2019.

**History of past illness**
The patient’s past medical history, family medical history, and vaccination status were insignificant.

**Physical examination**
On physical examination, the patient was conscious and comfortable and responded well. He was febrile with a temperature of 38.7 °C, had tachycardia with a heart rate of 142 beats per minute, but was hemodynamically stable with a normal respiratory rate of 34 breaths/min and normal blood pressure of 80/64 mmHg.

The sound of his breath in both lungs was rough and his neck was supple without lymphadenopathy. Skin examination showed red, needle-point-sized and maculo-papular rashes that were non-itchy, faded under pressure, and were distributed on his trunk. Heart examination revealed slightly rough systolic murmur over the third and fourth intercostal space at the left sternal border. Abdominal examination was unremarkable.

**Laboratory examinations**
Laboratory tests revealed an increased white blood cell count at 32.4 × 10\(^9\)/L (reference range: 10-13 × 10\(^9\)/L) and mild anemia with a hemoglobin level of 78 g/dL (reference range: 100-120 g/dL). The level of brain natriuretic peptide was mildly elevated. The levels of anti-streptolysin O, rheumatoid factors, C-reaction protein (CRP), and myocardial injury markers were normal; urine and stool tests for tetracycline hydrochloride, biochemical tests for antinuclear antibodies, and functional test for the thyroid were negative.

**Imaging examinations**
Chest computed tomography suggested the possibility of pneumonia following the admission. B-mode ultrasonography of the neck showed two to three enlarged cervical lymph nodes measuring 1.5 cm × 1.5 cm with good mobility. No abnormalities were observed in the liver and spleen.

Five consecutive sets of electrocardiograms (ECGs) revealed ST segment depression and a flat T wave. On the 9\(^{th}\) day, he developed a high-grade fever (38.4 °C), and color Doppler echocardiography revealed abscess with perforation in addition to the vegetation, aortic regurgitation, and pericardial effusion (Figure 1A). Color Doppler echocardiography was performed thrice on the 2\(^{nd}\) (May 13), 6\(^{th}\) (May 17), and 9\(^{th}\) day (May 20) post-admission (Figure 1).
Microbiological identification of potential causative agent

Four consecutive sets of blood cultures were performed and all of them were negative (May 12/13/17/20, 2019). Although positive blood cultures with Gram-positive cocci were reported from another hospital but paper reports were unavailable.

Further diagnostic work-up

After admission, the patient did not meet the diagnostic criteria for typical Kawasaki disease and incomplete Kawasaki disease after re-evaluation according to the American Heart Association guidelines in 2017, so infectious disease was considered. He started intravenous piperacillin sulbactam and cefazolin for 8 d. Following the initiation of antibiotics, his clinical symptoms improved significantly. His sensorium and body temperature were normal, respiratory status improved, and heart sound was louder and audible with an even heart rhythm besides rashes on his trunk and limbs disappeared. However, on the 9th day, he developed a high-grade fever (38.4 °C). A definite diagnosis was attained considering the clinical features as well as the results of laboratory tests and UCGs.

FINAL DIAGNOSIS

The final diagnosis of the presented case was culture-negative endocarditis.

TREATMENT

On the 10th day, aortic valve repair was planned for assistance in management. During surgery, no significant enlargements of the heart and aorta/pulmonary artery (1:1) were seen; aortic valve perforation, severe aortic regurgitation, vegetation, and apothegmatic cystic spaces on the left coronary cusp of the aortic valve were identified. Multiple vegetations were surgically excised from the left coronary cusp of...
the aortic valve. The abscess of the inferior aortic valve was drained. The left coronary valve was repaired by using autologous pericardial patch plasty, and the perforation of the left ventricle was closed with direct sutures.

OUTCOME AND FOLLOW-UP

The follow-up evaluations included complete medical history, clinical examination, and color Doppler echocardiography. Following surgery, the culture of vegetation obtained during surgery was negative. Two sets of blood cultures were documented to be negative. Postoperative reexamination of echocardiogram at weeks 2, 3, and 4 showed mild aortic regurgitation, normal cystic echo of the left coronary valve, and normal left ventricular systolic function (Figure 2). After 4 wk of treatment with intravenous piperacillin sulbactam (245 mg/kg/d, q8h), the patient was healthily discharged.

DISCUSSION

We describe the case of a 9-mo-old male infant who presented with intermittent fever and macular rashes that were persistent for 9 d after the admission. On our evaluation, the patient was febrile with a temperature of 38.7 °C, had tachycardia with a heart rate of 142 beats per minute, and had a slightly rough systolic murmur over the third and fourth intercostal space at the border of the left sternum. Persistent and “apparently” negative blood cultures together with ECGs and color Doppler echocardiogram confirmed the clinical diagnosis of culture-negative IE. According to the revised Duke criteria, the diagnosis and classification of IE mainly depend on blood culture.

However, the sensitivity of these criteria for diagnosing culture-negative endocarditis is ambiguous[14]. Of note, a previous study has observed a significantly higher prevalence of “possible endocarditis” in patients with negative cultures and further demonstrated that patients with culture-negative endocarditis were less likely to be classified as “definite endocarditis” by the revised Duke criteria[15]. Taken together, these studies suggest that the criteria for the diagnosis of pediatric culture-negative IE are variable and need to be carefully evaluated individually on a case-by-case basis.

It is thought that culture-negative endocarditis in patients with prior antibiotic therapy is caused by Gram-positive cocci, such as Staphylococci, Streptococci, and Enterococci—the bacteria usually associated with culture-positive endocarditis[16].

The possibility of “culture-negative” endocarditis after antibiotic use arises in our case as blood culture was carried out prior to the initiation of empirical antimicrobial therapy. Thereby, echocardiography is a crucial tool in the diagnosis and management of culture-negative endocarditis in the absence of positive blood cultures. In this case, we had performed serial color Doppler echocardiography for monitoring the minor changes of cardiac structure and coronary condition to ensure timely interventions before any possible clinical deterioration. We detected the vegetation and abscess in time, and then arranged surgery immediately under the condition that antibiotic treatments were not well responded to. Similarly, earlier studies have shown that in adult patients with culture-negative endocarditis and large vegetation, monitoring vegetation size by means of serial transesophageal echocardiography might prove to be useful to determine the efficacy of treatment[17].

Given that the patient had a structurally normal heart and did not show any risk factors for congenital heart disease, the clinical situation resembles atypical culture-negative IE. It is thought that many factors predispose pediatric patients with IE to potentially life-threatening complications that call for an early surgery[1]. Although a latent heart disease is the main predisposing factor for pediatric IE, many cases of IE without a preexisting heart disease have been reported[18]. A study by Zamorano et al [19] showed that patients with culture-negative IE have a higher rate of complications, such as valve rupture and perforation requiring immediate surgical attention, compared to those with positive blood culture. There is a paucity of data about pediatric IE with a normally structured heart and without predisposing factors. Of note, a review by Russell et al[20] related to the surgical outcome of IE identified that, of 35 cases of endocarditis requiring surgical intervention, 14 (40%) presented with no potential congenital heart defect. Other possible latent factors such as immunodeficiency, chronic parenteral nutrition, and those with central venous catheters near the heart or tunneled central venous catheters could be considered as predisposing conditions for IE[1]. A study by Carceller et al[21] showed that approximately 26% of
pediatric patients with IE had a serious systemic underlying disease without congenital heart defect, and about 7% were completely healthy. However, these potential predisposing factors were not identified in this case.

Interestingly, the lesion was located on the left side in this case, similar to that reported by Pachirat et al.[22] who showed that about 92% of patients had lesions located on the left side in contrast to only 8% on the right side.

Furthermore, Shamszad et al.[23] demonstrated that the left-sided lesions were the most that needed surgical intervention. The complex nature of this disease necessitates surgical treatment in about one half of patients with IE[13]. According to the guidelines (2016) published by the American Association for Thoracic Surgery, surgical indications for IE include severely-compromised valve function resulting in symptoms of heart failure, left-sided IE caused by Staphylococcus aureus, fungi, or other highly resistant microorganisms, IE complicated by a heart block, annular or aortic abscess or penetrating lesions, and persistent infection for 5-7 d despite an appropriate antibiotic course[24]. Irrespective of whether the nature of IE is culture-positive or culture-negative, the major indications for surgical treatment to prevent embolization are the presence of left-sided lesion(s) with severe stenosis or regurgitation or intractable heart failure or very large vegetation (> 30 mm)[5]. In this case, antibiotic therapy was performed at first and clinical symptoms were relieved. However, the situation deteriorated rapidly on the 9th day as the fever came back and the vegetation and abscess were detected. It reminds clinicians that even if there are no indications for surgery for the time being, it is necessary to keep an eye out for changes of cardiac construction and function.

An already complex etiology of IE is further complicated by the appearance of comorbid abscesses and valvular perforations. In the present case, intraoperative monitoring revealed aortic valve perforation, presence of apothegmatic cystic spaces below the left coronary cusp of the aortic valve, and severe aortic valve regurgitation.

Surgical treatment involving valve repair and valve replacement, could get excellent outcomes for native valve endocarditis including lesions of either the aortic or the mitral valves[25-28]. However, there is little information concerning aortic valve repair in patients with culture-negative endocarditis. For this case, aortic valve repair was performed by using autologous pericardial patch plasty. A previous study demonstrated that the augmentation or partial replacement of defective aortic cusps with autologous pericardium is a safe and feasible surgical alternative, and further advocated that aortic regurgitation can be treated effectively by aortic valve repair using pericardial patch plasty[29]. Nevertheless, the reason for the enlarged echo range of the aortic valve lateral flap in the postoperative children is not clear, and whether the infection still exists or the cystic cavity is normal after the operation remains to be followed.

**CONCLUSION**

Collectively, our case report suggests tailored management of pediatric IE in children without predisposing factors. Further, for cases with persistent fever and abnormal
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elevation of inflammatory factors (white blood cells and/or CRP), repeated blood cultures and color Doppler ultrasonography monitoring need to be performed to determine the most appropriate treatment option. Last but not least, we advocate that timely surgical intervention guided by serial echocardiography monitoring is crucial to prevent any further complications and enhance quick recovery.

REFERENCES


14 Lamas CC, Eykyn SJ. Blood culture negative endocarditis: analysis of 63 cases presenting over 25 years. Heart 2003; 89: 258-262 [PMID: 12591823 DOI: 10.1136/heart.89.3.258]


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Severe absence of intra-orbital fat in a patient with orbital venous malformation: A case report

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CASE REPORT

Severe absence of intra-orbital fat in a patient with orbital venous malformation: A case report

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Abstract

BACKGROUND
The orbital venous malformation is quite common in orbital diseases. Clinically, it is usually characterized by proptosis. However, among patients with distensible venous malformations, if the lesions continuously progress, they may induce enlargement of the orbital bone or orbital lipoatrophy, which in turn leads to enophthalmos.

CASE SUMMARY
Here, we report a patient who presented with enophthalmos and had a severe absence of intra-orbital fat secondary to orbital venous malformation. The patient was a 66-year-old female with a 20-year history of enophthalmos. Hertel exophthalmometry readings in a relaxed upright position were 4 mm OD and 13 mm OS with a 97 mm base. It was determined that she had positional proptosis. Physical examination also revealed a bulging mass on her hard palate. Computed tomographic scan and magnetic resonance imaging showed an expansion of the right orbit with local bony defects and multiple soft-tissue masses.

CONCLUSION
Long-term lack of awareness about the presence of orbital venous malformations, persistent venous congestion could lead to compression of the orbital fat, which in turn induces atrophy or the absence of intra-orbital fat.

Key Words: Absence of intra-orbital fat; Venous malformation; Enophthalmos; Entropion; Long medical history; Case report

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Core Tip: Timely diagnosis and treatment are critical to prevent secondary irreversible lesions. In patients with severe orbital venous malformations, delayed diagnosis and treatment may induce atrophy or the absence of intra-orbital fat. This case report provides a cautionary tale for patients with a long history of orbital venous malformations.

INTRODUCTION

The orbital venous malformation is very common in orbital diseases, which is characterized by a high incidence, high recurrence rate and limited treatment methods[1]. Superficial lesions of orbital venous malformation can be found at birth and grow in proportion to the body[2]. More than 90% of orbital venous malformations are solitary and sporadic lesions, and the remaining 10% are multiple, wide-ranging or with comorbidities[1]. The physical examination findings of orbital venous malformations were mainly presented as proptosis, compressible lesions and positive body position test[3]. In this case report, we report a case of a 66-year-old female who suffered a severe enophthalmos caused by a long history of orbital venous malformations. She was admitted to the hospital for treatment. Radiological features presented local bone defects in the right orbit, atrophy of orbital fat in the right orbit and venous calculi in addition to the space-occupying lesions of the malformed vein. As lipoatrophy was irreversible and untreatable in this patient, we finally performed a modified Hotz procedure for correction of her entropion.

CASE PRESENTATION

Chief complaints
A 66-year-old female presented with enophthalmos and entropion in her right eye for 20 years and aggravated for 1 year.

History of present illness
The patient had a history of orbital venous malformation for more than 20 years. In the last year, she had noticed decreased vision in her right eye under no obvious predisposing causes. She also complained of ocular discomfort caused by entropion. Now she was admitted to the hospital due to the worsening symptoms.

History of past illness
She had a 7-year history of hypertension. The blood pressure was controlled at 130/80 mmHg under the treatment of nifedipine controlled-release tablets.

Personal and family history
She was first found to have a venous malformation of the right buccal 30 years ago. Her anamnesis was significant for surgical treatment for buccal vascular anomalies.

Physical examination
She was found to have a severe absence of intra-orbital fat with her right eye sunken backward in the bony orbit. There was a separation of the eyelid and eyeball, where the upper orbit-temporal region could be observed (Figure 1A and B). Hertel exophthalmometry readings in a relaxed upright position were 4 mm OD and 13 mm OS with a 97 mm base. It was determined that she had positional “proptosis” (compared to a relaxed upright position). The degree of enophthalmos could be changed during the Valsalva maneuver. The visual acuity in the affected right eye was light perception (LP). Physical examination revealed a bulging mass on the hard palate (Figure 1C).
Laboratory examinations

There were no significant changes.

Imaging examinations

A plain computed tomographic scan detected enophthalmos with local bony defects on the right orbit. Phlebolith was visualized (Figure 2A). 3D modeling presented an obvious expansion of the right orbital cavity (Figure 2B). The absence of orbital soft tissue around her right eye was observed through magnetic resonance imaging (MRI), which also showed an irregular soft tissue mass with indistinct borders inside and outside the muscle pyramid in the right orbit that could become enlarged after pressurizing (Figure 2C and D).

FINAL DIAGNOSIS

Orbital venous malformation and entropion on the right eye. Persistent venous congestion leads to compression of the orbital fat, which in turn induces atrophy or the absence of intra-orbital fat.

TREATMENT

A modified Hotz procedure for correction of entropion was adopted to improve her symptoms of ocular discomfort caused by entropion.
Figure 2 Imaging examinations. A: The computed tomographic scan showing enophthalmos with local bony defects on the right orbit. A phlebolith is visualized; B: 3D modelling presents an obvious expansion of the right orbital cavity; C and D: Magnetic resonance imaging revealing an absence of orbital soft tissue around her right eye. It also showed an irregular soft tissue mass with indistinct borders inside and outside the muscle pyramid in the right orbit, which could become enlarged after pressurizing.

OUTCOME AND FOLLOW-UP

After the operation, the fluid infusion was given for the symptomatic treatment. The patient experienced no complications during hospitalization and was discharged four days after surgery. Strenuous exercise was not recommended.

DISCUSSION

Enophthalmos is the posterior movement of the eyeball within the bony orbit due to a change in the volume of the eyeball or orbital soft tissues relative to the orbital bones. Orbital soft tissues, including muscles and intra-orbital fat, are important components of orbital contents, accounting for approximately 50% of orbital cavity volume.[4,5]. The causes of enophthalmos can be divided into two categories: expansion of the orbital cavity and reduction of the orbital content volume. There are several conditions that can lead to the expansion of the orbital cavity, including orbital trauma, orbital bone defects, maxillary atelectasis and some orbital surgeries. Other conditions that can cause a reduction in the orbital content volume include orbital fat atrophy, orbital inflammation, resolved pseudotumors with fibrosis, Parry-Romberg syndrome, contraction of ocular muscle and sequelae of surgery[6].

The orbital vascular malformation is quite common in orbital diseases. According to angiogenesis, malformations can be classified as venous, arterial, lymphatic, or mixed [4]. As the most common type of vascular malformation in the orbit, orbital venous malformation can be divided into distensible and non-distensible lesions. Because of the communication of the distensible malformation and the venous circulation, patients with distensible lesions are often characterized by a positive response to the Valsalva maneuver, postural globe displacement or proptosis. However, if the lesions
continuously progress, they may induce enlargement of the orbital bone or orbital lipoatrophy, which in turn leads to enophthalmos[7].

Here, we report a patient who had a severe absence of intra-orbital fat with her right eye sunken backward in the bony orbit in a relaxed upright position. As a rare symptom of orbital venous malformation, entropion occurred in this patient because of extreme enophthalmos.

Considering that she had a long medical history of orbital venous malformation, it is likely that persistent venous congestion led to compression of the orbital fat, which induced orbital lipoatrophy. Venous malformation lesions are not solitary but widespread in this patient. In addition to orbital venous malformation, MRI detected multiple expansive soft tissue masses involving the upper lip and cheek. Physical examination also revealed a bulging mass on her hard palate.

Clinically, sclerotherapy, laser therapy, embolization, surgical resection, and radiotherapy are commonly used in the treatment of orbital venous malformation[4]. For this patient, considering that the lesions were multiple, involved deep structures and had a long duration, an effective treatment for orbital venous malformation was lacking. There are several existing therapeutic options for the treatment of orbital lipoatrophy, such as artificial material filling, lipoinjection or lipofilling. However, these treatments do not completely resolve orbital venous malformations and even have a risk of thrombohemorrhagic events. The persistence of venous malformations will compress periorbital tissue and affect the curative effect. As lipoatrophy was irreversible and untreatable in this patient, we finally performed a modified Hotz procedure for correction of her entropion. For bulging mass located on the hard palate of this patient, maxillofacial surgery recommended sclerotherapy. However, the patient rejected treatment, fearing the risks and the uncertain consequences of the sclerotherapy.

CONCLUSION

In conclusion, we reported on our case of a rare presentation of an absence of intra-orbital fat secondary to orbital venous malformation. We revealed that with a long-term lack of awareness about the presence of orbital venous malformations, persistent venous congestion leads to compression of the orbital fat, which in turn induces atrophy or the absence of intra-orbital fat. Both patients and physicians should be made aware that timely diagnosis and treatment are critical to prevent secondary irreversible lesions. This kind of case report could provide practical clinical experience for clinicians to improve the management of this disease.

REFERENCES

Pulmonary Langerhans cell histiocytosis and multiple system involvement: A case report

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Author contributions: Luo L contributed to data analysis and wrote the paper; Li YX contributed to the conception and design of the study; all authors revised the paper and approved the submitted version.

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Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C

Abstract

BACKGROUND
Pulmonary Langerhans cell histiocytosis (PLCH) is a relatively rare type of lung disease, common in middle-aged smoking men. It is characterized by proliferation and infiltration of Langerhans cells, and the formation of multiple parabronchial mesenchymal nodules in lung tissue, and may lead to organ dysfunction. There are no typical symptoms and signs, and it is easily misdiagnosed or missed, and therefore deserves clinical attention and further discussion.

CASE SUMMARY
We describe the case of a nonsmoking 46-year-old man with PLCH diagnosed based on clinical manifestations of fever and dry cough, with a history of hypothyroidism and diabetes insipidus for 9 years. Computed tomography (CT)-and CT-guided puncture examinations revealed no abnormalities, and he ultimately underwent thoracoscopic biopsy to confirm the diagnosis. The pathological diagnosis was PLCH. Thyroid function was maintained by medication. Pituitary magnetic resonance imaging showed that the pituitary stalk had become thinner.

CONCLUSION
LCH often involves multiple systems. Moreover, the pathogenesis is not clear, clinical manifestations lack specificity, and diagnosis requires special attention. Diagnosis of PLCH can significantly benefit from comprehensive multidisciplinary analysis.

Key Words: Pulmonary Langerhans cell histiocytosis; Multiple systems; Hypothyroidism;
Diabetes insipidus; Case report

We describe the case of a 46-year-old man with pulmonary Langerhans cell histiocytosis, diagnosed due to clinical manifestations of fever and dry cough, with a history of hypothyroidism and diabetes insipidus for 9 years. The pathological diagnosis was lung Langerhans cell histiocytosis. Thyroid function was maintained by medication. Pituitary magnetic resonance imaging showed that the pituitary stalk had become thinner. A comprehensive multidisciplinary analysis can significantly improve disease diagnosis.

INTRODUCTION

Langerhans cell histiocytosis (LCH) is a group of diseases characterized by abnormal clonal accumulation of CD207+ CD1a+ cells that resemble epidermal mononuclear phagocytes, i.e., Langerhans cells. These factors cause local or systemic infiltration and granuloma formation, constituting a potentially fatal condition[1]. Furthermore, LCH can involve multiple systems in adults, including osteolytic lesions and the lungs, pituitary, thyroid, liver, lymph nodes and skin[2]. As one of the most commonly affected organs, the lung may be involved as an isolated organ or as part of multisystemic LCH. Chest imaging typically reveals nodules, cavities and cysts in both lungs, mainly in the upper and middle fields. In cases with hypothalamus involvement, polydipsia and diabetes insipidus (DI) may occur. Although LCH rarely invades the thyroid gland, it is often accompanied by lymphocytic thyroiditis (mainly diffuse or nodular swelling), and in approximately 70% of cases, thyroid hypofunction ensues[3].

We report the case of a nonsmoking 46-year-old man with a history of hypothyroidism and DI who visited his doctor due to respiratory symptoms. This case illustrates the refractoriness of multisystem LCH in adults and highlights the important characteristics of LCH biology. We discuss this case in detail to raise awareness and to highlight its characteristics and potential complications in the clinic.

CASE PRESENTATION

Chief complaints
A 46-year-old man was referred to the First Affiliated Hospital of Dalian Medical University in April 2021 due to fever with dry cough for 9 mo.

History of present illness
Before attending the hospital, a chest CT examination was performed, and multiple nodules with blurred borders were found in both lungs, and a needle biopsy of the upper lobe of the left lung was performed under CT guidance. The cytology report showed a few ciliated columnar epithelial cells and lymphocytes, but no tumor cells. Pathological reports indicated fibrous tissue proliferation accompanied by scattered or focal infiltration of lymphocytes and neutrophils, and carbon foam deposition. He received symptomatic treatment, but his symptoms did not improve. One month later, CT-guided puncture was performed again, but there was still no positive result.

History of past illness
He had a history of hypothyroidism and DI for 9 years, but no history of smoking.
Personal and family history
He had a history of hypothyroidism and DI for 9 years, but no history of smoking. He had no family history.

Physical examination
Physical examination revealed no significant abnormalities.

Laboratory examinations
The patient’s laboratory test results are shown in Table 1.

Imaging examinations
Lung CT showed multiple lung lesions, multiple small nodules with blurred boundaries in both lungs, and cystic changes (Figure 1). Positron emission tomography–computed tomography (PET-CT) revealed multiple high metabolic nodules and masses in both lungs, suggesting an inflammation-related disease and the necessity for further pathological investigations. The mediastinum and both hilar regions exhibited slightly more lymph node metabolism, which was considered to be caused by inflammation. The thyroid gland was slightly smaller, with diffusely reduced density. To confirm the diagnosis, we conducted thoracoscopic lung biopsy, and the pathological diagnosis was (lower right lung dorsal segment) lung Langerhans cell tissue hyperplasia with organization. Immunohistochemical staining showed CD1a (+), S-100 (+), CD68 (weak+), and CD163 (-) (Figure 2). Pathological diagnosis indicated pulmonary Langerhans cell histiocytosis (PLCH). As LCH often involves multiple organs, pituitary magnetic resonance imaging (MRI) was performed considering the patient’s history of DI and hypothyroidism and the possibility of central nervous system involvement. Pituitary MRI showed a vacuolar sella, thinned pituitary stalk, and bilateral maxillary sinus cysts (Figure 3). A diagnosis of PLCH with multiple system involvement, central DI and hypothyroidism was clear. The disease involved a low-grade malignant tumor. Symptomatic treatment was initiated, and follow-up by the Hematology Department was required for further treatment of the PLCH. At follow-up, the patient did not receive further treatment, and his condition had not progressed.

FINAL DIAGNOSIS
PLCH with multiple system involvement, central DI and hypothyroidism.

TREATMENT
The disease is a low-grade malignant tumor. We gave symptomatic treatment to this patient, which required follow-up by hematology department for further treatment of PLCH.

OUTCOME AND FOLLOW-UP
At follow-up, the patient did not have further treatment, and his condition has not progressed.

DISCUSSION
LCH is an atypical clonal proliferation of mononuclear dendritic cells that can affect single or multiple systems, leading to organ dysfunction. Arico et al.[4] reported that among adult LCH patients, the lungs are affected in 58.4%, with 29.6% having central DI, and 68.6% having multiple system LCH. The BRAF V600E mutation, involving the mitogen-activated protein kinase signaling pathway, has been identified in LCH, but therapeutic options remain limited[5,6].

PLCH manifests in the lung during systemic LCH. It is a rare diffuse interstitial lung disease and usually occurs in young smokers. The most common symptoms of PLCH are dry cough, difficulty breathing, and chest pain. Approximately 70% of patients
Table 1 Laboratory examinations

<table>
<thead>
<tr>
<th>Laboratory examinations</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood gas</strong></td>
<td>pH 7.355, PO$_2$ 75 mmHg, PCO$_2$ 43.9 mmHg</td>
</tr>
<tr>
<td><strong>ACTH</strong></td>
<td>12.85 pg/mL (2.2-17.6 pmol/mL)</td>
</tr>
<tr>
<td><strong>TES</strong></td>
<td>4.47 nmol/L (14-25.4 nmol/L)</td>
</tr>
<tr>
<td><strong>COR(3:52 pm)</strong></td>
<td>527.49 nmol/L (7-9 am: 145.4-619.4 nmol/L, 3-5 pm 94.9-462.4 nmol/L)</td>
</tr>
<tr>
<td><strong>ESR</strong></td>
<td>36 mm/h (0-20 mm/h)</td>
</tr>
<tr>
<td><strong>IGF-1</strong></td>
<td>87 ng/mL (94-252 ng/mL)</td>
</tr>
<tr>
<td><strong>HGH</strong></td>
<td>0.32 ng/mL (0-3 ng/mL)</td>
</tr>
<tr>
<td><strong>PCT</strong></td>
<td>&lt; 0.02 ng/mL</td>
</tr>
<tr>
<td><strong>Routine blood</strong></td>
<td>WBC 5.13 × 10$^9$, N% 68.8%, HGB 118 g/L, PLT 179 × 10$^9$</td>
</tr>
<tr>
<td><strong>Coagulation</strong></td>
<td>PT 11.8 s, APTT 31.4 s, Fib 4.73 g/L</td>
</tr>
<tr>
<td><strong>Liver biochemistry</strong></td>
<td>ALT 75 U/L, AST 55 U/L, Prealbumin 148 mg/L, ALB 37.8 g/L</td>
</tr>
<tr>
<td><strong>CRP</strong></td>
<td>35.5 mg/L (&lt; 3.13 mg/L)</td>
</tr>
<tr>
<td><strong>Tuberculosis-SPOT</strong></td>
<td>Negative</td>
</tr>
<tr>
<td><strong>CEA, Cyfra21-1, NSE</strong></td>
<td>Negative</td>
</tr>
<tr>
<td><strong>Urine osmolality</strong></td>
<td>47 mOsm/kgH2O (600-1000 mOsm/kgH2O)</td>
</tr>
<tr>
<td><strong>Urine specific gravity (SG)</strong></td>
<td>1.001 (1.015-1.025)</td>
</tr>
<tr>
<td><strong>Thyroid function</strong></td>
<td>TSH 13.618 mIU/L, FT3 2.54 pmol/L, FT4 9.52 pmol/L, TG 1.58 mg/L</td>
</tr>
<tr>
<td><strong>Pulmonary function</strong></td>
<td>FEV1/FVC 66.28%, FEV1 96.6%, MVV 64.6%, M MEF 52.8%; Mild obstructive pulmonary ventilation dysfunction; Ventolin aerosol bronchodilation test negative; Normal lung diffusion capacity for carbon monoxide</td>
</tr>
</tbody>
</table>

PO$_2$: Partial pressure of oxygen in the blood; PCO$_2$: Partial pressure of carbon dioxide. ACTH: Adrenocorticotropic hormone; TES: Testosterone; COR: Cortisol; ESR: Erythrocyte sedimentation rate; IGF-1: Insulin-like growth factor-1; HGH: Human growth hormone; PCT: Procalcitonin; CRP: C-reactive protein; FEV1: Forced expiratory volume in one second; FVC: Forced vital capacity; MVV: Maximum ventilatory volume; MMEF: Maximum mid-expiratory flow.

have a disorder in lung diffusion capacity for carbon monoxide, with restrictive ventilatory dysfunction in the early stage of the disease and obstructive ventilatory dysfunction on progression[7]. Lung high-resolution CT shows multiple small nodules with blurred boundaries in both lungs, with cystic changes. During the development of the disease, the nodular lesions gradually decrease, and the fibrotic changes in lung tissue and multiple cystic vacuoles can be observed more clearly. The diagnosis of PLCH relies on lung biopsy. However, the detection rate using needle biopsy, including CT puncture guidance and bronchoscopy puncture guidance, is very low. Some adult LCH patients (10%-20% of cases) present with extrapulmonary involvement, such as DI and endocrine, skin and bone diseases.

The current patient was a middle-aged male with no history of smoking. His first symptoms were a dry cough and fever, and lung CT showed multiple proliferative lesions in both lungs, similar to inflammation, with blurred boundaries. His lung presentation was atypical, the results of two CT-guided biopsies were negative, and antibiotic treatment was not effective; the lungs showed slow progression. Pulmonary function findings indicated normal lung diffusion capacity for carbon monoxide. Considering that the consolidation of both lungs was located near the hilar region, the area of alveolar involvement was small, and there was no interstitial change in either lung, with little effect on diffusion function. A past medical history of DI and hypothyroidism should not be ignored. Although the thyroid function of the current patient was almost within the normal range due to medication, symptoms of polyuria were still present, and urine osmolality and specific gravity were significantly lower than normal. Thus, PLCH was suspected, but the cause still needed to be determined. PET-CT examination revealed involvement of no other organs or tissues. Surgical thoracoscopic lung biopsy was performed to remove part of the lesion tissue from the right lobe. The immunohistochemistry results showed CD1a (+), S-100 (+), CD68 (weak+), and CD163 (-), and the pathological diagnosis was lung Langerhans cell
tissue hyperplasia with organization. Therefore, histopathological examination is an important basis for the diagnosis of LCH. Langerhans histiocytosis is divided into three stages: (1) a cell-rich stage; (2) a proliferation stage; and (3) a fibrosis stage. The lung disease in our patient was in the proliferative stage. Most authors\[8-10\] believe that thickening of the pituitary stalk (> 3 mm) and the disappearance of a high signal in the posterior pituitary by MRI are characteristic of central DI, which can be combined with vasopressin test results and nephrogenic DI. The location of the pituitary stalk injury is related to the degree of neuron loss, which is more serious when horizontal damage occurs\[11\]. The pituitary MRI of this patient showed that the pituitary stalk had become thinner, which was atypical. Considering that the pituitary gland was involved in the early stage and the pituitary stalk was thicker, the pituitary entered the fibrosis phase as the disease progressed, manifesting as pituitary atrophy and thinning of the pituitary stalk. In this case, the thyroid was involved, which manifested as thyroid hypofunction. PET-CT showed that the thyroid gland was slightly smaller, with diffusely reduced density. Similar to the appearance of the pituitary gland, the thyroid gland also progressed to a fibrotic stage, with thyroid atrophy. A recent study reported\[12\] that LCH rarely invades the thyroid gland and that approximately 70% of cases are accompanied by thyroid hypofunction, mainly diffuse or nodular enlargement, possibly with calcification. Therefore, when a patient shows abnormal thyroid function, the hypothalamic pituitary hormone axis should be screened in detail to improve diagnosis.

In summary, the current patient presented at the hospital with respiratory symptoms and was diagnosed with LCH by lung biopsy; pathology and imaging revealed the proliferative phase. Combined with the patient’s central DI and hypothyroidism, it is believed that LCH began in the pituitary gland and thyroid and then entered the fibrosis stage as the disease progressed. There is another possibility that 9 years previously, the patient developed central DI due to hypothalamic-pituitary disease, with secondary hypothyroidism. He mainly presented with PLCH of single-organ involvement, but this possibility is extremely small: one person developed multiple diseases at the same time.
Figure 2 Pathological and immunohistochemistry findings. A: Lung tissue showing Langerhans infiltrated tissue (magnification: 100 ×); B: Image showing eosinophils with the nucleus stained blue and Langerhans cells (magnification: 200 ×); C: Langerhans cells (magnification: 400 ×); D: Specific immunohistochemical staining for CD1a (+); E: Specific immunohistochemical staining for CD68 (±); F: Specific immunohistochemical staining for S-100 (+); G: Specific immunohistochemical staining for CD163 (-).

Figure 3 Pituitary magnetic resonance imaging showing vacuolar sella, thinned pituitary stalk, and bilateral maxillary sinus cyst.

CONCLUSION

In summary, LCH remains an exceedingly rare entity in adults, frequently presenting as multiple system disease with important organ involvement. Pulmonary nodules and cystic lesions progress slowly, and antibiotics are ineffective; however, biopsy can improve the diagnostic rate. The possibility of LCH invasion should be strongly...
considered in patients with hypothalamic and pituitary diseases.

REFERENCES


Complete androgen insensitivity syndrome caused by the c.2678C>T mutation in the androgen receptor gene: A case report

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Informed consent statement: Written and informed consent was obtained from the parents of the proband for publication of this report.

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Abstract

BACKGROUND
Androgen insensitivity syndrome is an X-linked recessive genetic disease caused by mutations in the androgen receptor gene (AR). However, the underlying molecular mechanisms for the majority of AR variants remain unclear. In this study, we identified a point variant in three patients with complete androgen insensitivity syndrome (CAIS), summarized the correlation analysis, and performed a literature review.

CASE SUMMARY
The proband was raised as a girl. In infancy, she was first referred to hospital with a right inguinal hernia. Ultrasonography revealed the absence of a uterus and ovaries, and a testis-like structure located at the inguinal canal. Further diagnostic workup detected a 46, XY karyotype, and fluorescence in situ hybridization analysis showed the presence of the SRY gene. Histological analysis revealed the excised tissue to be testicular. Twelve years later, she was admitted to our hospital with a lack of breast development. Her pubic hair and breasts were Tanner stage I. She had normal female external genitalia. Blood hormone tests showed normal testosterone levels, low estradiol levels, and high gonadotropin levels. Her two siblings underwent similar examinations, and all three had a rare hemizygous missense mutation in AR: c.2678C>T. In vitro functional analyses revealed decreased nuclear translocation in AR-c.2678C>T mutation cells.

CONCLUSION
This case of CAIS was caused by an AR variant (c.2678C>T). Functional studies showed impaired nuclear translocation ability of the mutant protein.

Key Words: Androgen insensitivity syndrome; 46 XY disorders of sex development; Variants; Androgen receptor gene; Ligand-binding domain; Case report
INTRODUCTION

As a hereditary condition, androgen insensitivity syndrome (AIS, OMIM: 300068) is characterized by complete or partial resistance to the biological actions of androgen in male karyotype individuals[1], which is the most common cause of 46, XY disorders of sex development (46, XY DSD). Clinical manifestations range from phenotypic females (complete type) to mild hypovirilization (partial type), or men with mild manifestations of gynecomastia and/or infertility[2]. Characteristic features of complete androgen insensitivity syndrome (CAIS) include a female phenotype, breast development, absent or sparse pubic and axillary hair, a short blind-ending vagina, and an absence of the uterus and ovaries. In 46 XY males, the prevalence of CAIS is estimated to range from 1:20400 to 1:99100[3].

As an X-linked recessive genetic condition, AIS is caused by mutations in the androgen receptor gene (AR; OMIM: 313700). AR encodes a 110 kDa AR protein[4], known as the DHT receptor or NR3C4, which belongs to a family of nuclear receptors typically located in the cytoplasm. The AR normally forms a multimeric complex with heat shock proteins (HSPs). When androgen hormone reaches the cytoplasm, it causes a dissociation between the AR and HSPs, then binds to the AR itself and causes the migration of this new complex inside the nucleus. The AR then dimerizes and enhances the transcription of androgen-responsive genes by binding hormone response elements[5]. AR protein is composed of three major functional domains: an N-terminal domain (NTD), a DNA-binding domain (DBD), and a Ligand-binding domain (LBD).

The LBD first promotes the interaction between the receptor and HSPs in the cytoplasm, then with the androgen hormone it causes AR migration to the nucleus. The LBD is encoded by exons 4–8, and contains 11 α-helices associated with two anti-parallel β-sheets in a sandwich-like conformation with a central ligand binding pocket in which the ligand can bind[6].

To date, more than 1000 variants of AR have been recorded in the human gene mutation database (http://www.hgmd.cf.ac.uk/). Most mutations are in the AR-LBD, while mutations in the AR-DBD are less frequent, and AR-NTD mutations are very rare. Polymorphic mutations associated with AIS have been observed in the LBD domain. However, it is not clear how these mutations affect androgen sensitivities for AR through impaired physiology.

In this present study, one Chinese family of a proband and her siblings with CAIS was investigated. AR sequencing identified the same hemizygous missense mutation, p.P893L, in the LBD of AR in all three siblings. Moreover, computational analysis and functional study were performed to research the pathogenesis of this variant.
CASE PRESENTATION

Chief complaints
The proband (II-1) was admitted to our hospital because of a lack of breast development in 2018.

History of present illness
The proband (II-1)’s main symptom is the lack of breast development as a 12-year-old girl.

History of past illness
In the past, the proband (II-1) was once referred to hospital with a right inguinal hernia in 2006, as a 3-mo-old girl. Based on the clinical evaluations, the patient was diagnosed with 46, XY DSD. The male gonads were surgically removed because of the risk of malignant tumors.

Personal and family history
The proband (II-1) was the first child of Han Chinese nonconsanguineous parents. She was born full term with a birth weight of 2600 g and a length of 50 cm.

The proband (II-1) has two sisters (II-2, II-3). As the twin of the proband, the girl (II-2) underwent a similar physical examination, laboratory examination, karyotype analysis, imaging, surgery, and pathological examination. The third girl (II-3, a 4-year-old girl) was the younger sibling of the twins. Following a genetic diagnosis, laparoscopic surgery was performed to remove the gonads located in the pelvis because of the risk of malignant tumors. As expected, histological analysis of the excised gonads showed them to be testicular tissue. Both parents were healthy.

Physical examination
The proband (II-1)’s pubic hair and breasts were at Tanner stage I. She had normal female external genitalia without clitoromegaly. Her labia were normal, and the vagina and urethra had separate openings.

Laboratory examinations
In 2006, proband (II-1)’s chromosome karyotype was 46, XY karyotype, and fluorescent in situ hybridization analysis showed that the SRY gene was positive. Histological analysis revealed the excised tissue to be testicular. In 2018, blood hormone tests showed normal testosterone levels, low estradiol levels, and high gonadotropin levels (Table 1).

Imaging examinations
In 2006, the proband (II-1)’s ultrasound examination showed no uterus and ovaries, but revealed the presence of a testis-like structure located near the right hernia sac, and a testis-like structure at the lower part of the left inguinal canal.

Genetic analysis
AR sequencing was performed to provide a definitive diagnosis. Peripheral blood samples were obtained from the patients and their parents. DNA was extracted using the TaKaRa blood genome DNA extraction kit (TaKaRa Bio, Mountain View, CA, United States) following the manufacturer’s instructions. Sanger sequencing was performed and results were analyzed using Chromas Lite v2.01 software (Technelysium Pty Ltd., Tewantin, Australia). Pathogenicity was predicted using the bioinformatics tools Mutation Taster (www.mutationtaster.org), polymorphism phenotyping-2 (PolyPhen-2, http://genetics.bwh.harvard.edu/pph2), and Sorting Intolerant from Tolerant (SIFT, https://sift.bii.a-star.edu.sg/) programs.

Three-dimensional reconstruction of AR mutant protein
A structural representation of the AR mutant was generated using the molecular visualization system in the open-source foundation PyMOL 2.4 (https://pymol.org/2/). The PDB ID (4OEA) of wild-type (WT) human AR-LBD was retrieved from the RCSB database (http://www.rcsb.org).

Plasmid construction
The following plasmids were constructed using wild-type AR expression plasmids as templates, which were obtained from Hanbio Biotechnology Co. Ltd. (Shanghai,
Table 1  Blood hormonal characteristics of patients

<table>
<thead>
<tr>
<th>Items</th>
<th>Patient</th>
<th>Normal value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>II-1</td>
<td>II-2</td>
</tr>
<tr>
<td>Age</td>
<td>12-yr-old</td>
<td>12-yr-old</td>
</tr>
<tr>
<td>LH (mIU/mL)</td>
<td>8.03</td>
<td>12.35</td>
</tr>
<tr>
<td></td>
<td>&lt; 1.4 IU/L</td>
<td></td>
</tr>
<tr>
<td>FSH (mIU/mL)</td>
<td>61.7</td>
<td>72.3</td>
</tr>
<tr>
<td></td>
<td>&lt; 1.3 IU/L</td>
<td></td>
</tr>
<tr>
<td>Testosterone (ng/dL)</td>
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<td>13.4</td>
</tr>
<tr>
<td></td>
<td>0.5-20 ng/dL</td>
<td></td>
</tr>
<tr>
<td>Estradiol (pg/mL)</td>
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<td>&lt; 11.8</td>
</tr>
<tr>
<td></td>
<td>50-110 pg/mL</td>
<td></td>
</tr>
</tbody>
</table>

LH: Luteinizing hormone; FSH: Follicle-stimulating hormone.

Subcellular localization

Human embryo kidney 293T cells (HEK-293T) and monkey kidney COS-7 cells were cultured in 24-well plates until 70%-80% confluence and transfected with 0.5 ug pEGFP-AR WT, or pEGFP-AR P893L, as well as 0.5ug pEGFP-N1 control plasmid using Lipofectamine™ 2000 reagent (Thermo Fisher Scientific, Waltham, MA, USA) following the manufacturer’s protocol.

Genetic diagnosis and protein structure modeling

Genetic analysis revealed that all three siblings and their mother had a rare hemizygous mutation c.2678C>T (p. P893L) in exon 8 of AR. The father of the siblings had a WT sequence at this site, indicating that the variant showed maternal inheritance (Figure 1). Bioinformatics analysis using MutationTaster, SIFT, and Polyphen-2 predicted that the variant would be disease-causing, deleterious, and probably damaging, respectively, confirming it to have a very high pathogenic potential. Three-dimensional structural modeling indicated that the missense variant altered the LBD domain of the mutant AR protein relative to WT AR (Figure 2).

Impaired nuclear translocation

Subcellular localization results showed that EGFP-AR WT fusion proteins were translocated into the nucleus in vehicle-treated cells (Figure 3 D–F, M–O). EGFP-AR P893L fusion proteins were unable to enter the nucleus and showed a uniform distribution in the cytoplasm (Figure 3 G–I, P–R). These findings suggest that the p.P893L mutation affects the AR intracellular transport of AR by impairing nuclear translocation of the protein.
Wang KN et al. CAIS caused by c.2678C>T mutation

Figure 1 Pedigree of the family and genetic diagnosis of the subjects. A: Pedigree of the family: The proband (II-1) is indicated by an arrow. Squares represent males and circles represent females. Affected individuals are shown as filled black symbols, and half-filled symbols indicate clinically unaffected subjects carrying a heterozygous variant. Unfilled symbols indicate clinically unaffected subjects harboring the WT AR sequence. B: Genetic diagnosis: Sanger sequencing identified a heterozygous variant (c.2678C>T) in AR. Chromatograms show that the proband (II-1), siblings (II-2 and II-3), and their mother (I-2) harbor a heterozygous c.2678C>T variant of AR. The proband’s father (I-1) was unaffected at this site. Arrows indicate the location of the mutation.

Figure 2 Three-dimensional structure of androgen receptor gene-ligand-binding domain. The ligand-binding domain is composed of 11 α-helices associated with two anti-parallel β-sheets. The α-helices, β-sheets, and loops are colored blue, yellow, and purple, respectively. Wild type and variant residues are colored in red and represented as sticks.

Figure 3 Subcellular localization of androgen receptor gene in human embryo kidney 293T and COS7 cells. HEK-293T and COS7 cells were transfected with the fusion protein expression plasmid pEGFP-androgen receptor gene (AR) wild-type (WT), pEGFP-AR P893L, and the pEGFP-NC control plasmid. Twenty-four hours after transfection, cells were treated with 100 nM T. Laser confocal microscope images show that EGFP-AR WT is distributed in the nucleus (D-F, M-O), but that EGFP-AR P893L could not enter the nucleus so has a uniform distribution in the cytoplasm (G-I, P-R).

**FINAL DIAGNOSIS**

The final diagnosis of the proband and siblings is CAIS.
TREATMENT

Both older patients started to receive estrogen replacement therapy with oral estradiol valerate since the age of 12.5 years.

OUTCOME AND FOLLOW-UP

During long-term follow-up, blood hormone tests showed normal testosterone levels, low estradiol levels, and high gonadotropin levels. Both older patients (aged 15 years at the time of this study) showed pubic hair at Tanner stage IV, and breasts at Tanner stage III. The younger sibling (aged 7 years at the time of this study) had pubic hair and breasts that were still at Tanner stage I.

DISCUSSION

In this study, the hemizygous variant c.2678C>T (p.P893L) in the LBD of AR was found to be causative of CAIS phenotypes for the three patients. Moreover, our in vitro functional study showed that nuclear translocation was decreased in AR-c.2678C>T mutation cells.

This variant (p.P893L) has been reported twice as a causative factor of CAIS[8,9]. However, few structural and functional studies[10,11] have been undertaken until now. Our in vitro work showed that the c.2678C>T missense variant affected the intracellular transport of AR by weakening its translocation from the cytoplasm to the nucleus. Subsequently, this may lead to the loss of AR biological function which could explain the pathogenicity of this variant.

The LBD (amino acids 646-920) contains specific binding sites for androgens, various transcription factors of coactivation and the activation function-2 (AF-2) region[12]. The LBD region is fundamental for specific hormone receptor binding, nuclear translocation, and androgen-induced transcription. LBD variants with low to intermediate transcriptional activation displayed aberrant Kd values for hormone binding and decreased nuclear translocation[13]. In the previously reported study[8] about this mutation (p.P893L), cotransfection studies with an androgen-responsive reporter gene revealed a diminished transactivation property of the mutant androgen receptor. In the current variant, the amino acid substitution of proline to leucine occurs in the direct vicinity of the proposed C-terminal α-helix of the LBD containing the AF-2 transcriptional activating function core. Proline is a very rigid residue, so induces a particular backbone conformation that might be required at this position. The substitution to leucine may disturb this.

Clinically, malignant transformation of the gonads is the most feared complication in women with CAIS; timing of gonadectomy to prevent cancer is an issue of debate. Historically, individuals with CAIS were managed by the removal of gonadal tissue to avert the risk of gonadal malignancy[14]. However, clinical practice has recently changed. The oncological risk of CAIS children is relatively low and remains low until adulthood (0.02%-3%). Deans et al[15] found that the neoplastic risk for women under the age of 30 is approximately 0.02%, while the tumor risk for women over that age is up to 22%. Chaurdy et al[16] reported a neoplastic risk ranging from 0.8% to 22%, and an overall risk for 133 patients over 20 years of age was around 1.5%. Thus, gonadectomy could be postponed until after pubertal age to guarantee initial spontaneous pubertal development and avoid the need for hormonal replacement therapy[17,18]. In any case, gonadectomy after puberty is still controversial.

CONCLUSION

In summary, the c.2678C>T (p.P893L) AR variant was identified as a causative factor of CAIS in three siblings. This variant was shown by functional studies to impair nuclear translocation of the protein.
ACKNOWLEDGEMENTS

The authors would like to thank the proband and her family for providing blood samples and agreeing to participate in this research.

REFERENCES


Ultrasound guiding the rapid diagnosis and treatment of perioperative pneumothorax: A case report

Gang Zhang, Xiao-Yan Huang, Lan Zhang

Abstract

BACKGROUND
Pneumothorax is one of the most common causes of acute dyspnea. In patients under general anesthesia, the symptoms may not be obvious, which may delay diagnosis and treatment. Computed tomography is the gold standard for the diagnosis of pneumothorax, but is not suitable for rapid diagnosis of this complication. In contrast, lung ultrasonography can provide rapid diagnosis and treatment of pneumothorax.

CASE SUMMARY
The patient was a 53-year-old man admitted for rupture of the spleen caused by an accidental fall and emergency splenectomy was planned. Anesthesia was induced, and tracheal intubation was performed successfully with a video laryngoscope. About 2 min after tracheal intubation, the airway peak pressure increased to 50 cm H₂O and the oxygen saturation dropped to 70%. According to the BLUE protocol, a recommended area of the chest was scanned by ultrasound. The pleural slide sign disappeared and obvious parallel line sign could be seen in the left lung. The boundary of pneumothorax (lung points) were rapidly confirmed by ultrasound. To avoid lung injury, a closed thoracic drainage tube was placed in the involved area. On day 9 after surgery, the patient was discharged from the hospital without any complications.

CONCLUSION
Perioperative pneumothorax is rare but dangerous. It can be rapidly diagnosed and treated with ultrasound guidance.
Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report’s scientific quality classification
Grade A (Excellent): A
Grade B (Very good): B
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

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Core Tip: Perioperative pneumothorax is a rare but dangerous complication that requires rapid diagnosis and urgent treatment. Computed tomography is the gold standard for diagnosis pneumothorax but it is not applicable to confirm this complication during surgery. Lung ultrasonography, with the advantages of being radiation-free and convenient, can provide rapid diagnosis and treatment of pneumothorax.

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INTRODUCTION

Pneumothorax is one of the most common causes of acute dyspnea. Sudden chest pain, shortness of breath, or even respiratory failure are the main clinical features. Because of the sudden change in pressure in the pleural cavity, the venous return blood flow is blocked and the stability of the circulatory system is affected. Therefore, early diagnosis and treatment are urgently needed. In patients under general anesthesia, the symptoms may not be obvious, which can delay diagnosis and treatment. Pneumothorax is a rare but serious perioperative complication leading to perilous hypoxemia during general anesthesia. Especially for patients with poor cardiopulmonary reserve, early diagnosis has a great impact on the prognosis[1].

Although chest computed tomography (CT) is the gold standard for the diagnosis of pneumothorax[2], it is not suitable for rapid diagnosis because of its high radiation exposure and long transport time. In contrast, lung ultrasound (LUS) has the advantages of being radiation-free and convenient, which can provide dynamic assessment and rapid diagnosis[3].

It was first reported that pneumothorax can be diagnosed by ultrasound in 1987. Wernecke et al[4] reported that it can be indicated by the disappearance of lung sliding. When pneumothorax is suspected during surgery, ultrasound scanning can be performed rapidly in the suspected area following the BLUE protocol[5]. Abnormal sonographic signs such as the pleural slide sign, parallel line sign in M-mode, and lung points indicate pneumothorax. Moreover, lung points can not only be a gold standard for the diagnosis of pneumothorax, but also determine the boundary of the pneumothorax and guide the placement of a closed thoracic drainage tube. It takes 2-3 min to complete the examination, and pneumothorax can be excluded or diagnosed within 1 min[6]. In this case, the prompt ultrasound diagnosis and treatment of pneumothorax resulted in an excellent patient prognosis.

CASE PRESENTATION

Chief complaints
A 53-year-old man (85 kg and 170 cm) was admitted for rupture of spleen caused by an accidental fall.

History of present illness
Emergency splenectomy was planned under general anesthesia. Preoperative emergency ultrasound examination including the heart, chest, and abdomen were performed, and it was found that spleen had been ruptured and was accompanied by active bleeding, complicated with progressive hemochrome reduction, which was the main reason for the patient to undergo emergency surgery. Preoperative ultrasound showed no heart or chest abnormalities. The patient did not complain of dyspnea preoperatively, and preoperative CT showed no hemothorax or pneumothorax.
Initial vital signs before anesthesia were a blood pressure of 126/82 mm Hg, heart rate of 75 bpm, and an oxygen partial pressure (SpO₂) of 95% while inhaling air. Anesthesia was induced with sufentanil 0.3 µg/kg, rocuronium 0.1 mg/kg, and propofol 3 mg/kg. Tracheal intubation was successfully performed with video laryngoscopy, and positive pressure ventilation was performed with an airway peak pressure of 14 cm H₂O. Because the patient’s thick chest wall, breath sounds were difficult to auscultate. About 2 min after tracheal intubation, it was difficult to ventilate. The airway peak pressure increased progressively, reaching a maximum of 50 cm H₂O and SpO₂ dropped, reaching a minimum of 70%. Because of obesity and the thick chest wall, the cause of respiratory failure could not be determined by traditional auscultation. Following the BLUE protocol, a recommended area of the chest was scanned by bedside ultrasound. The pleural slide sign disappeared in the upper and lower blue points of the left lung, and in M-mode, an obvious parallel line sign could be seen below the pleura. The boundary of pneumothorax (lung points) was rapidly confirmed by ultrasound. To avoid lung injury and secondary pneumothorax, a closed thoracic drainage tube was placed in the area guided by ultrasound. The interval from suspicion of pneumothorax to placement of the drainage tube was less than 3 min. After many bubbles had emerged from the water seal bottle, the airway pressure dropped to 20 cm H₂O and the SpO₂ returned to 96%-100%. After the patient’s vital signs stabilized, the splenectomy continued and was successfully completed. The patient was sent to the intensive care unit (ICU) with an endotracheal tube for further treatment after surgery. On day 1 after surgery, the endotracheal tube was removed. On day 6, the closed thoracic drainage tube was removed. On day 9, the patient was discharged from the hospital without any complications.

**Laboratory examinations**

Anemia (hemoglobin 85 g/L).

**Imaging examinations**

Focused assessment with sonography in trauma (FAST) has been extensively utilized and studied in blunt and penetrating trauma[7]. Following the FAST protocol, organ damage can be rapidly evaluated by the amount of free fluid in the chest, abdominal, and pelvic cavities. In this case, preoperative emergency ultrasound examination of the heart, chest and abdomen found that spleen had been ruptured and active bleeding was complicated by progressive hemochrome reduction, which was also the main reason for the patient to undergo emergency surgery. Preoperative ultrasound showed no abnormalities in the heart or chest. Following the BLUE protocol, LUS confirmed that the pleural slide sign had disappeared in the recommended area of the left lung, and in M-mode, an obvious parallel line sign was seen below the pleura (Figure 2B). The boundary of the pneumothorax (lung points) was rapidly confirmed by ultrasound (Figure 2C).

**FINAL DIAGNOSIS**

A clear diagnosis perioperative pneumothorax was based on imaging examination and intraoperative findings.

**TREATMENT**

To avoid lung injury and secondary pneumothorax, a closed thoracic drainage tube was placed in the area guided by ultrasound. From suspicion of pneumothorax to the placement of closed thoracic drainage tube, the total time was less than 3 min.

**OUTCOME AND FOLLOW-UP**

After a large number of bubbles emerged from the water seal bottle, the airway pressure dropped to 20 cm H₂O and the oxygen saturation returned to 96%-100%. After the patient’s vital signs stabilized, the splenectomy continued and was successfully completed. The patient was sent to ICU with an endotracheal tube for further treatment after surgery. On day 1 after surgery, the endotracheal tube was removed. On day 6, the drainage tube was removed. On day 9, the patient was
Figure 1 Preoperative computed tomography showing the absence of hemothorax or pneumothorax.

Figure 2 Chest computed tomography and ultrasound. A: Computed tomography of pneumothorax. Position 1: Pneumothorax; Position 2: Boundary of pneumothorax (lung point); Position 3: No pneumothorax; B: Parallel lines sign with the sonography probe at position 1; C: Lung point sign with the sonography probe at position 2; D: Beach sign with the sonography probe at position 3. White arrows indicate the pleura.

discharged from the hospital without any complications.
DISCUSSION

If pneumothorax occurs under general anesthesia, positive pressure ventilation causes accumulation of a large amount of air in the pleural space, leading intractable hypoxemia. Because of absence of specific symptoms like chest pain, cough, and dyspnea under general anesthesia, pneumothorax may be not diagnosed promptly. Pathological changes leading by pneumothorax can provide a large amount of diagnostic information. Because of the high sensitivity of CT, it is the gold standard for the diagnosis of pneumothorax. However, patients often require long-distance transport for CT examination, which is time-consuming and risky for critical patients. If not suitable for the rapid diagnosis required for perioperative pneumothorax. Ultrasound is a reliable modality to provide rapid and accurate information, it has been shown that pulmonary ultrasound is superior to X-ray for the diagnosis of lung disease[8]. The diagnostic accuracy of ultrasound for a variety of lung diseases is comparable to CT, and it is becoming the preferred tool for rapid assessment of pulmonary disease[9].

How ultrasound is performed: BLUE protocol

The examiner’s hands place on the patient’s anterior chest wall (excluding the thumbs), with the little finger of the upper hand close to the clavicle and the fingertips close to the median sternal line. The upper BLUE point is at the third and fourth metacarpophalangeal joints of the upper hand, and the lower BLUE point is at the center of the lower palm. The two points are thought to be the highest points at which gas is the most concentrated. The two BLUE points are recommended for rapid diagnosis or exclusion of pneumothorax during the perioperative period (Figure 3). It was reported that small-volume pneumothorax caused by blunt trauma mainly occurred in the parasternal regions[10], which was consistent with the BLUE protocol recommendation for rapid localization of the upper and lower BLUE dots adjacent to the sternum to diagnose the complication[11].

How to diagnose pneumothorax by ultrasound features

Ultrasound diagnosis of pneumothorax is based on both exclusion and confirmed diagnosis. If pneumothorax is suspected in perioperative period, bedside ultrasound should be performed immediately. Pneumothorax can be excluded by the pleural slide sign[12], which is a normal pulmonary sign of relative movement between the visceral and parietal pleura which is visible by ultrasound during respiratory movement. The negative predictive value for the diagnosis of pneumothorax by pleural slide sign has been reported as 100%. Pneumothorax can thus be excluded quickly and accurately by the existence of the surface pleural slide sign[13]. When pneumothorax is present, the visceral and parietal pleurae will be separated by gas. Therefore, the disappearance of the pleural slide sign on ultrasound is the initial step in the diagnosis of pneumothorax[14]. However, the positive predictive value of the disappearance of pleural slide sign for the diagnosis of pneumothorax is estimated as 87% in the normal population, 56% in ICU patients, and only 27% in cases of respiratory failure[15]. Tracheal intubation, single lung ventilation, atelectasis, pulmonary fibrosis, ARDS, pleural adhesion, phrenic nerve palsy, cardiac and respiratory arrest, and other factors may also lead to disappearance of the pleural slide sign. In M-mode echocardiography, normal lung tissue resembles a beach with respiratory movement (Figure 2). Without respiratory movement, lung tissue in cases of pneumothorax resembles parallel lines (Figure 2). Ultrasound diagnosis of pneumothorax depends on lung point and is regarded as a gold standard with a specificity of 100%. For the patients with pneumothorax, as the probe moves laterally along the chest wall, a specific area (lung point) can be detected. A pleural slide sign, meaning that the parietal pleura is in contact with the visceral pleura, is observed on one side, and no slide is observed on the other, which means that the pleurae are separated by air[16]. The lung points can slide along the pleural line with respiratory movements, and determine the boundary of pneumothorax[15].

Lung points indicates the area of transition between collapsed lung tissue, with loss of sliding between the pleurae, and normal lung tissue. In M-mode echocardiography, A “beach sign,” which indicates normal tissue, suddenly changes to a “parallel lines sign,” which indicates pneumothorax[14] (Figure 2).

In addition to the rapid diagnosis of perioperative pneumothorax, pulmonary ultrasound can also be used to guide the management of pneumothorax. In this case, once the pneumothorax was diagnosed, ultrasound was used to guide the placement of a closed thoracic drainage tube by indicating the pneumothorax boundary (lung points). After drainage, the patient’s airway pressure significantly decreased and
Patel et al. [18] reported that ultrasound-guided thoracic catheterization reduced the cost of treatment, length of hospital stay, and incidence of complications such as pneumothorax and hemorrhage. Lung ultrasound is easy to learn. In a randomized controlled trial, anesthesiologists were found to be proficient in diagnosing pneumothorax by ultrasound after 4 weeks of online or classroom training [19].

Although ultrasound can help anesthesiologists diagnose pneumothorax quickly and conveniently, there are limitations. It is difficult to obtain satisfactory images in patients with open trauma, obesity, or pulmonary disease, which may lead to a missed diagnosis of pneumothorax [20]. Many studies have confirmed lung points as the gold standard to diagnose pneumothorax by ultrasound, but a lung point detected by ultrasound in an 83-year-old patient, was found to be a pulmonary bulla on CT and X-ray examination. That was the first reported case of lung points in a patient who was not diagnosed with pneumothorax [14]. Mild and moderate pneumothorax can be diagnosed by lung points, but lung points may not be seen in severe pneumothorax because of complete disappearance of lung sliding and the parallel lines sign.

CONCLUSION
Perioperative pneumothorax is a rare but dangerous complication requiring urgent diagnosis and treatment. Once it occurs, the positive pressure generated by mechanical ventilation may cause the lung on the affected side to collapse rapidly, leading intractable hypoxemia. Lung ultrasound is a bedside modality that is becoming widely used for the rapid diagnosis and treatment of pneumothorax.

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REFERENCES


Chronic colchicine poisoning with neuromyopathy, gastric ulcers and myelosuppression in a gout patient: A case report

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Abstract

BACKGROUND
Colchicine has been widely used as an anti-gout medication over the past decades. However, it is less commonly used due to its narrow therapeutic range, meaning that its lethal dose is close to its therapeutic dose. The lethal dose of colchicine is considered to be 0.8 mg/kg. As chronic colchicine poisoning has multiple manifestations, it poses a challenge in the clinician’s differential diagnosis. Historically, the drug was important in treating gout; however, clinical studies are currently underway regarding the use of colchicine in patients with coronavirus disease 2019 as well as its use in coronary artery disease, making this drug more important in clinical practice.

CASE SUMMARY
A 61-year-old male with a history of gout and chronic colchicine intake was admitted to our Emergency Department due to numbness and weakness of the lower limbs. The patient reported a history of colchicine intake for 23 years. After thorough examination, he was diagnosed with colchicine poisoning, manifesting as neuromyopathy, multiple gastric ulcers and myelosuppression. We advised him to stop taking colchicine and drinking alcohol. We also provided a prescription of lansoprazole and mecobalamin, and then asked him to return to the clinic for re-examination. The patient was followed up for 3-mo during which time his gout symptoms were controlled to the point where he was asymptomatic.

CONCLUSION
Colchicine overdose can mimic the clinical manifestations of several conditions. Physicians easily pay attention to the disease while ignoring the cause of the disease. Thus, the patient’s medication history should never be ignored.

Key Words: Colchicine poisoning; Neuromyopathy; Myelosuppression; Gastric ulcer; Gout; Case report
INTRODUCTION

Colchicine is known for its anti-inflammatory effects, and was historically used for gout. However, due to its narrow therapeutic range, there have been numerous reports regarding acute and chronic colchicine poisoning. Therefore, it has seldom been used in the clinical setting in recent years. Due to more generalized studies on colchicine, chronic colchicine poisoning has raised concerns among physicians. The ongoing GRECCO-19[1] study aims to identify whether colchicine may positively intervene in the clinical course of coronavirus disease 2019. At the same time, the LoDoCo2[2] and COLCOT[3] trials have demonstrated the effects of colchicine on the secondary prevention of coronary artery disease. These studies have made the use of colchicine more generalized, while long-term use of colchicine increases the risk of chronic colchicine poisoning. Thus, it is essential for clinicians to realize chronic colchicine poisoning.

CASE PRESENTATION

Chief complaints

A 61-year-old male was admitted to the emergency department (ED) due to numbness and weakness of the lower limbs, which was his second hospital admission.

History of present illness

The patient reported a history of colchicine consumption for gout. He initially only took colchicine temporarily for joint pain control or preventive purposes before drinking alcohol. He then started taking high doses of colchicine over the recent five years as his gout progressed. He reported discontinuously taking 30 mg monthly on average over the past five years. He also complained of diarrhea after taking colchicine. He was diagnosed with multiple gastric ulcers by gastroscopy (Figure 1) and pathology, for which he received a subtotal gastrectomy approximately 6 mo ago.

History of past illness

The patient had hypertension for over 10 years.

Personal and family history

He had a history of alcohol abuse.

Physical examination

Physical examination showed that the patient was afebrile, with no abnormal findings on heart and lung and abdominal examinations. However, multiple joint tenderness was present, consistent with gout. The patient’s muscle strength scores were 4 and 3 bilaterally in the upper and lower limbs, respectively.

Laboratory examinations

After admission, we ordered a complete blood count (CBC), liver and kidney function...
tests, C-reactive protein, erythrocyte sedimentation rate (ESR), tumor markers and other blood tests. Additionally, we performed an electromyogram, a positron emission tomography-computed tomography (PET-CT) scan, and brain nuclear magnetic resonance imaging (MRI). The CBC revealed the following: Leukocytes $2.72 \times 10^9/L$, neutrophils $1.75 \times 10^9/L$, hemoglobin $76$ g/L, reticulocyte ratio $1.43\%$, indicating microcytic hypochromic anemia and leukopenia; carbohydrate antigen 724 (CA724) > 500 U/mL, which was highly increased; the ESR was 107 mm/h, which was also increased, for which we considered gout and infection as the most probable etiologic factors. Serum uric acid level was 449 µmol/L, which was also elevated. The patient’s serum ferritin, vitamin B12 and folic acid levels were all within the normal ranges. The patient’s potassium level was 3.2 mmol/L, calcium level was 2.1 mmol/L, and phosphate level was 0.71 mmol/L, suggesting hypokalemia, hypocalcemia and hypophosphatemia. After consulting a neurologist, we considered Guillain-Barre syndrome (GBS) as a preliminary diagnosis. In order to reach a precise diagnosis, we performed a lumbar puncture, bone marrow puncture and biopsy. The biopsy results demonstrated myelodysplasia. No abnormalities were detected in the cerebrospinal fluid, which excluded GBS.

**Imaging examinations**
The PET-CT scan did not reveal any structural lesions such as malignant tumors, but showed an infection of the right inferior molar teeth. Brain MRI was also normal. The electromyogram delineated neurogenic damage of the upper and lower limbs.

**FINAL DIAGNOSIS**
The examination results led to a dilemma: What is the correct diagnosis in this patient? Considering the history of chronic colchicine intake, we suspected that all of the patient’s clinical manifestations might be side effects of colchicine therapy. Colchicine poisoning can manifest as myelosuppression, neuromyopathy, and gastrointestinal symptoms, which were all present in this patient. Based on these facts, we eventually diagnosed the patient with chronic colchicine poisoning manifested as myelosuppression, neuromyopathy and multiple gastric ulcers combined with right inferior molar teeth infection.

**TREATMENT**
Following admission, the patient suddenly developed a fever, his numbness and weakness progressed to both upper limbs, and he was unable to ambulate normally. Given the lack of a precise protocol for colchicine overdose, we counseled the patient to stop taking colchicine, and then administered recombinant human granulocyte...
factor to increase his leukocyte count. Ceftizoxime was also given to treat any concurrent infection. Lansoprazole was prescribed to treat his gastric ulcers. However, the patient still developed chalkstones, which is a manifestation of gout. Based on the PET-CT scans, we suspected that bacterial infection secondary to myelosuppression was the cause of his fever. After consulting a rheumatologist, we administered benzbromarone to reduce the patient’s serum uric acid levels. Considering his history of gastric ulcer, we did not administer nonsteroidal anti-inflammatory drugs (NSAIDS). After 7 d of hospitalization, the patient’s infection was controlled, he was afebrile and his leukocyte count was back to normal. However, his hemoglobin level did not change and his symptoms of neuromyopathy persisted. The patient was now in a stable condition, the recovery from colchicine poisoning was a slow process and many complications such as gastric ulcers were irreversible. He was then discharged and transferred to the rehabilitation ward for further recovery. We counseled him to stop taking colchicine and drinking alcohol, and prescribed lansoprazole, mecobalamin, cefdinir (for 7 more days) and advised him to return to the clinic for follow-up after a month.

OUTCOME AND FOLLOW-UP

We followed the patient for 3 mo during which time his gout symptoms were controlled. His hemoglobin level rose to 110 g/L, he was afebrile, and his weakness and numbness were almost completely alleviated. The patient was still unable to walk. His leukocyte count was within the normal range. The patient was admitted to the rehabilitation ward for further recovery.

DISCUSSION

Colchicine has been reported to be rapidly absorbed from the gastrointestinal tract[4]. The serum concentration of colchicine has been shown to peak 0.5-3 h after ingestion [4]. Colchicine poisoning consists of three phases. First, the gastrointestinal phase: 0–24 h post-ingestion. Second, the multi-organ failure phase: 1-7 d post-ingestion. Third, the recovery phase: 7-21 d post-ingestion[4]. This patient experienced diarrhea after taking colchicine, which was consistent with the gastrointestinal phase. The patient presented to the ED with neuromyopathy, bone marrow suppression, hypokalemia, hypocalcemia and hypophosphatemia, which were consistent with the multi-organ failure phase. Many patients die during this phase. Nevertheless, this patient survived the multi-organ failure phase and entered the recovery phase after being discharged from the ED. Moreover, chronic colchicine toxicity has also been reported to induce neuromyopathy and myocardial failure[4]. Considering this patient’s chronic colchicine use, he met the diagnostic criteria for chronic colchicine poisoning. Related reports confirm that colchicine-induced neuromyopathy usually resolves after discontinuation[4].

Multiple gastric ulcers are a rare and seldom reported manifestation of colchicine poisoning. According to the instructions on the drug’s manual, gastric changes can occur in patients with long-term intake. Therefore, the patient’s multiple gastric ulcers were a manifestation of chronic colchicine poisoning. Colchicine poisoning manifesting as neuromyopathy has been reported several times in patients with long-term intake[5,6]. This patient with chronic colchicine intake developed neurogenic damage of the upper and lower limbs, consistent with previous reports. Nowadays, more knowledge on colchicine is available; thus, there have been fewer reports of neuromyopathy in recent years. However, this clinical manifestation of colchicine poisoning cannot be ignored.

Bone marrow suppression has also been reported as a clinical manifestation of colchicine poisoning in some patients. It has been reported that granulocyte colony-stimulating factor is effective in treating leukopenia[7]. This patient had leukopenia and anemia, and the bone marrow biopsy confirmed the diagnosis of myelodysplasia. We treated his bone marrow suppression with recombinant human granulocyte factor, a type of granulocyte colony-stimulating factor (G-CSF). Following treatment with G-CSF, the patient’s leukocyte count returned to normal. The patient also developed a fever after admission, and the PET-CT scan confirmed the diagnosis of infection. We thought that this infection was secondary to bone marrow suppression. As tooth infections are usually responsive to third-generation cephalosporins, we managed his infection with ceftriaxone. The patient was afebrile after 7 days of antibiotic therapy.
With ongoing clinical trials on colchicine use in more generalized diseases, the probability of chronic colchicine poisoning is on the rise. Colchicine poisoning has multiple clinical manifestations, and is usually misdiagnosed as physicians usually do not inquire about colchicine intake while taking the patient’s history.

**REFERENCES**


6 Choi SS, Chan KF, Ng HK, Mak WP. Colchicine-induced myopathy and neuropathy. Hong Kong Med J 1999; 5: 204-207 [PMID: 11821595 DOI: 10.12809/hkmj208390]


Treatment of a giant low-grade appendiceal mucinous neoplasm: A case report

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Abstract

BACKGROUND
Low-grade appendiceal mucinous neoplasm (LAMN) is extremely rare and easily misdiagnosed before surgery.

CASE SUMMARY
We report the treatment of an asymptomatic case of LAMN diagnosed by magnetic resonance imaging (MRI) and surgical findings. A 70-year-old woman presented with an adnexal mass found by physical examination in July 2020. Gynecologic ultrasonography revealed a cystic mass in the right adnexa, and computed tomography showed a cystic mass in the pelvic cavity. All tumor markers were normal. A further MRI examination suggested mucinous neoplasm in the right pelvic cavity, excluding the possibility of adnexal cyst. Laparoscopic exploration found a huge cystic mass of about 10 cm × 7 cm that originated from the apex of the appendix, with spontaneous rupture. LAMN was confirmed by pathological examination. As of May 2021, no disease recurrence occurred after an open appendectomy.

CONCLUSION
This case indicates that we should pay more attention to female patients who are clinically diagnosed with an adnexal mass at admission.. The physical examination should be done carefully, and the laboratory and imaging examination results should be comprehensively analyzed to avoid misdiagnosis and to ensure prompt diagnosis and treatment, and to improve prognosis. MRI may be a better option for the diagnosis of appendiceal mucinous neoplasm.

Key Words: Appendiceal mucinous neoplasm; Diagnosis; Cystic mass; Pelvic cavity; Appendectomy; Case report
INTRODUCTION

Low-grade appendiceal mucinous neoplasm (LAMN) is a rare heterogeneous disease, characterized by well-differentiated tumors. It is often complicated by spontaneous or iatrogenic rupture that results in pseudomyxoma or distant metastasis of the abdominal wall, which can be life threatening[1]. LAMN is easily misdiagnosed because most patients are asymptomatic. It is generally found during the surgery because of the difficulty of preoperative diagnosis. Here, we report a case of LAMN diagnosed by magnetic resonance imaging (MRI) and surgical findings.

CASE PRESENTATION

Chief complaints

The patient presented with an adnexal mass found by physical examination more than 1 mo previously.

History of present illness

On August 23, 2020, a 70-year-old postmenopausal woman who presented with an adnexal mass found by physical examination 1 mo previously was admitted to the department of gynecology at our hospital. She did not complain of any clinical symptoms or discomfort.

History of past illness

The past medical history was unremarkable. One month prior, a right adnexal mass was found by ultrasonography at the local hospital.

Personal and family history

The patient had no remarkable personal or family history.

Physical examination

Upon arrival at our hospital, the patient was well-nourished, and without pain, pallor, or jaundice. Abdominal examination revealed distension without tenderness.

Laboratory examinations

Laboratory examination demonstrated found hemoglobin: 10.3 g/dL, leucocyte count: \(4.86 \times 10^{9}/L\), hematocrit: 31.7%, and platelet count: \(210 \times 10^{9}/L\). Liver and renal function tests, and the coagulation profile were all within normal ranges. Cancer antigen markers including carcinoembryonic antigen and carbohydrate antigen 19.9 were all within normal ranges.
**Imaging examinations**

B-ultrasound re-examination at our hospital showed a small amount of pelvic effusion (122 mm × 64 mm) in the right adnexal area (Figure 1A). No tenderness or rebound pain was found in the lower abdomen, and a mass of about 12 cm × 6 cm in the pelvic cavity with a tough texture and low mobility was detected by palpation. Whole abdomen computed tomography (CT) showed a small amount of effusion in the pelvic cavity, with lesions on the right (Figure 1B). The irregular cyst wall and thick soft tissue seen in the CT image might have resulted from tumor transformation. However the tumor markers were all normal. An MRI examination suggested a mucinous neoplasm in the right pelvic cavity (Figure 1C). It was not clear whether the neoplasm originated from abdominal mesodermal tissue or the appendix. The patient was transferred to the general surgery department. During laparoscopic exploration, a large amount of jelly-like mucosubstance was found in the right lower abdomen and pelvic cavity, and a huge cystic mass of about 10 cm × 7 cm originating from the apex of the appendix were found (Figure 2A).

**FINAL DIAGNOSIS**

Giant low-grade appendiceal mucinous neoplasm.

**TREATMENT**

An open appendectomy was performed, followed by peritoneal lavage and drainage. Postoperative pathological examination revealed a LAMN (Figure 2B). Anti-infective and symptomatic treatments were given after surgery; no obvious abnormalities was found on whole abdomen CT.

**OUTCOME AND FOLLOW-UP**

Tumor markers and a colonoscopy performed 3 mo after surgery were all normal. No disease recurrence or other conditions were found on follow-up in May 2021.

**DISCUSSION**

Appendiceal mucinous neoplasm accounts for 8%-10% of appendiceal tumors and 58% of malignant appendiceal tumors. The incidence is 0.2%-0.3% in patients who underwent appendectomy. LAMN is a borderline or low-grade malignant tumor, regardless of rupture, and is characterized by implantation metastasis and a rate of recurrence rate[2-4]. Its pathogenesis involves atypical hyperplasia of the glandular appendix epithelium that obstructs the appendix with a gradual accumulation of mucus resulting in increased pressure. Mucus penetrates the muscularis mucosa and produces mucinous masses around the appendix and in the retroperitoneum[5,6]. Most cases are asymptomatic, and in the absence of acute infection, the symptoms and signs of LAMN resemble those of chronic appendicitis. A correct diagnosis may be difficult, but on physical examination large tumors can be found as a complete oval mass with no surrounding adhesions. An appendiceal mucinous cyst that forms from an appendiceal lesion can easily be misdiagnosed as a common appendiceal abscess, right adnexal cyst, and so on[7,8]. A recent case report described a patient with LAMN that was initially diagnosed as an ovarian tumor[9]. As in this case, an appendiceal mucinous neoplasm should still be taken into consideration even if the tumor marker results are negative.

Abdominal ultrasound and CT are auxiliary diagnostic methods that can distinguish appendiceal mucinous cysts from other lesions before surgery[10,11]. Color Doppler ultrasound for mucinous cystadenoma of the appendix shows a dark liquid area in the appendix, with a small number of small flocculent light spots. Ultrasound exhibits better sound transmission, a round or oval shape, and smooth wall. There were no findings suggestive of LAMN by echo. CT is a more accurate imaging method for the diagnosis of appendiceal mucinous neoplasms, and shows a cystic mass closely adjacent to the cecum, with a round or long tubular shape, thin
Figure 1 Preoperative examination of the mass. A: Ultrasound; B: Computed tomography; and C: Magnetic resonance imaging.

Figure 2 Postoperative images. A: The macroscopic view the resected mass; and B: Microscopic pathology of the low-grade appendiceal mucinous neoplasm (Magnification × 4).

wall, and a smooth and regular outline, suggesting LAMN. When CT shows an irregular cyst wall and thick soft tissue, it is more likely to be malignant[10]. In this case, gynecologic ultrasonography revealed a cystic mass in the right adnexa, and CT showed a cystic mass in the pelvic cavity. However, there was still a possibility that it was an adnexal cyst. MRI performed with a variety of sequences and scanning methods, and high tissue resolution can clearly and consistently distinguish the wall and fluid of the appendiceal mucinous cyst, and more accurately show the integrity and boundary of the cyst wall. In this case, additional MRI evaluation showed typical manifestations of appendiceal cysts. The lesion was located in the right lower abdomen, had a with clear boundary, and was closely related to the cecum, which showed changes in external pressure. MRI had uniform long T1 and long T2 signals, and the cyst wall was thin and uniform, with similar signals to those of the intestinal wall. The cross section of the mass was round or elliptical, and the sagittal or coronal plane presented as a long tubular or gourd-shaped structure[12,13]. We thus successfully excluded the possibility of adnexal cyst by MRI. Subsequent surgery and pathological examination finally confirmed the diagnosis of LAMN.

Surgery is still the only treatment option for appendiceal mucinous neoplasms. Iatrogenic rupture of the tumor should be avoided during surgery to reduce the risk of implantation metastasis and disease recurrence. Unfortunately, preoperative abdominal ultrasound and CT examinations had shown effusion in the pelvic cavity. Spontaneous rupture of the tumor and the spread of mucus to the abdominal cavity were observed during laparoscopic exploration, indicating that the patient might have a relatively high risk of disease recurrence. Open surgery was performed after finding the spontaneous rupture of the tumor. Although appendectomy and peritoneal lavage and drainage were performed, and a negative incision margin was obtained, postoperative follow-up should be continued for a long time. Chen et al[14] reported a patient with recurrence of appendix mucinous adenocarcinoma at 26 mo after appendectomy.
CONCLUSION

LAMN is a rare clinical or imaging diagnosis. The female appendix is adjacent to the adnexa, which may lead to a misdiagnosis of either an appendiceal cyst or adnexal mass. The diagnosis and treatment of this patient suggested that for female patients who are clinically diagnosed with an adnexal mass at admission, we must broaden our minds and look further. Diagnosis should not be limited to the common diseases that we are familiar with. The physical examination should be done carefully, and the laboratory and imaging examination results should be comprehensively analyzed to reduce the possibility of misdiagnosis and to ensure prompt diagnosis and treatment, and to improve patient prognosis. MRI may be a better option for the diagnosis of appendiceal mucinous neoplasms.

REFERENCES

Thoracoscopic resection of a large lower esophageal schwannoma: A case report and review of the literature

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Abstract

BACKGROUND
Esophageal schwannomas originating from Schwann cells are extremely rare esophageal tumors. They commonly occur in the upper and middle esophagus but less frequently in the lower esophagus. Herein, we report a rare case of a large lower esophageal schwannoma misdiagnosed as a leiomyoma. We also present a brief literature review on lower esophageal schwannomas.

CASE SUMMARY
A 62-year-old man presented with severe dysphagia lasting 6 mo. A barium esophagogram showed that the lower esophagus was compressed within approximately 5.5 cm. Endoscopy revealed the presence of a large submucosal protuberant lesion in the esophagus at a distance of 32-38 cm from the incisors. Endoscopic ultrasound findings demonstrated a 4.5 cm × 5.0 cm hypoechoic lesion. Chest computed tomography revealed a mass of size approximately 53 mm × 39 mm × 50 mm. Initial tests revealed features indicative of leiomyoma. After multidisciplinary discussions, the patient underwent a video-assisted thoracoscopic partial esophagectomy. Further investigation involving immunohistochemical examination confirming palisading spindle cells as positive for S100 and Sox10 led to the final diagnosis of a lower esophageal schwannoma. There was no tumor recurrence or metastasis during follow-up.

CONCLUSION
The final diagnosis of esophageal schwannoma requires histopathological and immunohistochemical examination. The early appropriate surgery favors a remarkable prognosis.
INTRODUCTION

Schwannomas are neurogenic tumors that arise from proliferating Schwann cells; they grow slowly and are predominantly benign[1-3]. Schwannomas occur most commonly in the trunk, limbs, head, and neck but rarely in the gastrointestinal tract[4,5]. Most gastrointestinal schwannomas originate from the stomach or intestine; esophageal schwannomas are the rarest[3]. Esophageal schwannomas are the fewest esophageal submucosal tumors, accounting for less than 2% of all esophageal tumors[6,7]. They commonly occur in the upper and middle esophagus but less frequently in the lower esophagus[6]. This report presents the case of a 62-year-old man who had a lower esophageal schwannoma, which was misdiagnosed as leiomyoma. In addition, we performed a brief literature review of the lower esophageal schwannomas.

CASE PRESENTATION

Chief complaints
A 62-year-old man presented with severe dysphagia lasting 6 mo.

History of present illness
The patient suffered from severe dysphagia for 6 mo, with associated symptoms such as chest tightness, shortness of breath, chest pain, palpitations, and back pain.

History of past illness
The patient had an unremarkable medical history.

Personal and family history
The patient had no special personal or family history.

Physical examination
The patient’s temperature was 36.3 °C, heart rate was 83 beats per min, respiratory rate was 23 breaths per min, blood pressure was 118/81 mmHg, and oxygen saturation in room air was 95%. A heart murmur was heard in the apical area. Findings of his lungs and abdominal examinations were normal. Neurological examination showed no significant abnormalities. There was no edema in both lower extremities.

Laboratory examinations
Routine blood test results revealed the following: white blood cells $9.2 \times 10^9/L$, hemoglobin 133 g/L, and blood platelets $87 \times 10^9/L$. Tumor marker analysis showed a
slight increase in CY211 (6.46 ng/mL) and carcinoembryonic antigen (3.76 ng/mL). Routine urine tests and blood biochemistries were within normal limits. His feces showed normal findings in the routine test, and parasitological examination and occult blood tests yielded negative results.

**Imaging examinations**
A barium esophagogram (Figure 1) showed that the lower esophagus was compressed to a size of approximately 5.5 cm, with the mucosa appearing regular. Endoscopy (Figure 2A) revealed the presence of a large submucosal protuberant lesion in the esophagus at a distance of 32-38 cm from the incisors, with a smooth surface and normal color. Endoscopic ultrasound (EUS) (Figure 2B) findings demonstrated a 4.5 cm × 5.0 cm hypoechoic lesion with interior calcified areas, possibly originating from the muscularis propria. Subsequently, chest computed tomography (Figure 3) revealed a mass measuring approximately 53 mm × 39 mm × 50 mm, protruding from the lower esophagus; its features were suggestive of leiomyoma or gastrointestinal stromal tumor. Thus, for this patient, esophageal leiomyoma was suspected during the initial diagnosis.

**MULTIDISCIPLINARY EXPERT CONSULTATION**

**Cardiology expert opinion**
The patient complained of dysphagia and palpitation. Computed tomography indicated that the tumor oppressed the esophagus and left atrium. His cardiac ultrasound findings indicated rheumatic valvular heart disease. Considering that tumor compression had a serious impact on diet and cardiac function, resection surgery was recommended as the initial treatment, with strict limitations on the volume of liquid intake. The patient was recommended to wait 3 mo after this operation to undergo cardiac valve surgery.

**FINAL DIAGNOSIS**
Histopathological examination (Figure 4) findings revealed a fence-like structure formed by spindle-shaped cells, and immunohistochemical examination showed positivity for S100, Sox10 (Figure 5), vimentin, and TLE1 but negativity for CD34, desmin, CD117, actin, GFAP, h-caldesmon, STAT6, DOG-1, CD21, and SMA. Hence, a final diagnosis of esophageal schwannoma was made.

**TREATMENT**
The patient underwent a video-assisted thoracoscopic partial esophagectomy. During the operation, a 5.0 cm × 5.0 cm hard mass was noted, which had poor mobility and did not break through the adventitia, extending from the lower edge of the inferior pulmonary vein to the esophageal hiatus.

**OUTCOME AND FOLLOW-UP**
After surgery, the dysphagia disappeared, and the patient was relieved from other symptoms. Follow-up did not reveal local tumor recurrence or metastasis.

**DISCUSSION**
The most common submucosal tumors of the gastrointestinal tract are myogenic tumors such as leiomyomas and gastrointestinal stromal tumors[8]. Neurogenic tumors such as esophageal schwannomas are rare[9]. This case had several peculiarities. First, esophageal schwannomas commonly occur in middle-aged women[10]; however, the present case occurred in a male patient. Second, instead of the usual occurrence in the upper to mid-esophagus[6], this case involved the lower esophagus,
which was easily ignored. Finally, the patient experienced oesophageal schwannoma with rheumatic valvular heart disease, and the tumor was so large that it compressed the left atrium (Figure 3), leading to aggravated cardiac insufficiency.

We performed a statistical analysis of published cases about oesophageal schwannomas and found that there were fewer cases of lower oesophageal schwannomas (13) than upper to middle oesophageal schwannomas (57) (Table 1), which is similar to previous reports. However, the reason why lower oesophageal schwannomas are rare has not been clearly reported. Anatomically, the innervation of the striated muscle in the pharynx and the upper esophagus originates from the brain stem, but the nerve of the distal esophagus originates from the dorsal motor nucleus of the vagus nerve and ends at the ganglion of the myenteric plexus[11]. It has been shown that there are two peak areas of innervation in the cervical and thoracic regions of the esophagus in canines[12]. We speculate that the incidence of oesophageal schwannoma may be related to the origin and distribution of the nerve plexus; however, no study has confirmed it clearly at present. This makes it a significant study worthy of further exploration in the future.

To our knowledge, we are the first to conduct a statistical analysis of lower oesophageal schwannoma data, hoping to contribute to clinical diagnosis and treatment. We will discuss the characteristics of the clinical data, symptoms, diagnosis, differential diagnosis, and treatment of lower oesophageal schwannoma and compare them with those of upper/middle oesophageal schwannomas.

From the statistics (Table 2) on lower oesophageal schwannoma, we observed that the ages (years) with the highest prevalence were at 50-59 (38.5%)[8,13-16], followed by 20-29 (15.4%)[17,18], 40-49 (15.4%)[8,19], 60-69 (15.4%)[20], 30-39 (7.7%)[21], and 70-79 (7.7%)[22]. The mean age was 50.85 years, and the median age was 54 years, with a
Table 1 Clinical characteristics of lower schwannoma and upper/middle schwannomas

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Lower schwannoma, n (%)</th>
<th>Upper/middle schwannoma, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>13</td>
<td>57</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>9 (69.2%)</td>
<td>14 (24.6%)</td>
</tr>
<tr>
<td>Female</td>
<td>4 (30.8%)</td>
<td>43 (75.4%)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20–29 yr</td>
<td>2 (15.4%)</td>
<td>2 (3.5%)</td>
</tr>
<tr>
<td>30–39 yr</td>
<td>1 (7.7%)</td>
<td>7 (12.3%)</td>
</tr>
<tr>
<td>40–49 yr</td>
<td>2 (15.4%)</td>
<td>12 (21.1%)</td>
</tr>
<tr>
<td>50–59 yr</td>
<td>5 (38.5%)</td>
<td>13 (22.8%)</td>
</tr>
<tr>
<td>60–69 yr</td>
<td>2 (15.4%)</td>
<td>17 (29.8%)</td>
</tr>
<tr>
<td>70–79 yr</td>
<td>1 (7.7%)</td>
<td>6 (10.5%)</td>
</tr>
</tbody>
</table>

standard deviation of 14.536 years. These data are similar to those of total esophageal schwannoma. We also analyzed schwannomas in the upper to mid-esophagus, noting a mean age of 53.17 years and a median age of 55 years, with a standard deviation of 13.089 years. There was no significant difference in age when comparing the cases of schwannoma found in the lower esophagus and in the upper/middle esophagus.

With this disease, some patients show corresponding clinical symptoms. The occurrence of symptoms is related to the location and size of the tumor. We evaluated 13 patients on the lower esophageal schwannoma and found that the patients mainly showed dysphagia and esophageal reflux-like symptoms, which may be caused by the compression injury of the tumor to the esophagus-gastric junction. In addition, some patients had symptoms such as chest pain, palpitations, burning pain in the upper abdomen, back pain, chest tightness, shortness of breath, abdominal distention, loss of appetite, and so on. Three patients\cite{14,18,22} had weight loss, including two malignant esophageal schwannomas\cite{14,18} and one esophageal melanocytic schwannoma\cite{22}. In upper to middle esophageal schwannomas, dyspnea was the most common symptom after dysphagia, which was caused by the proximity of the upper/middle esophagus to the trachea that is being compressed by the tumor\cite{6,23}. It was reported that the tumor severely obstructed the trachea, resulting in dyspnea and disturbance of consciousness\cite{24}. After ineffective endotracheal intubation, emergency subtotal esophagectomy was performed in order to save the patient\cite{24}.

Esophageal schwannoma is easily misdiagnosed as esophageal leiomyomas before the biopsy. There is no specific abnormality in laboratory examination. Computed tomography, positron emission tomography, and magnetic resonance imaging examinations can be used for auxiliary diagnosis, but schwannoma shows no notable differences from other submucosal tumors. Simultaneously, it is difficult to diagnose esophageal schwannoma through endoscopic mucosal biopsy. Deep tissue biopsy may improve the accuracy of pathology, but it increases bleeding risk\cite{25}. Esophageal schwannoma is a hypoechoic mass with uneven echo and clear boundaries under EUS\cite{26}. Standard EUS aids in determining the exact location and origin of lesions in different esophageal layers, and the accuracy ranges from 30% to 66%\cite{27,28}. Rong et al\cite{29} reported that the diagnostic accuracy of EUS-guided fine needle aspiration for submucosal tumors is 85.2%; however, it may be misdiagnosed or missed due to insufficient sampling\cite{30}. Therefore, the final diagnosis often requires immunohistochemical examination after surgical removal of the lesion.

The resected tumor surface is gray-white and translucent. The histopathological features include that the tumor cells are arranged as fusiform to a fence-like structure or in a network to form a loose structure\cite{30}. The immunohistochemical staining is currently the only reliable method for diagnosis. Among the 13 patients with lower esophageal schwannomas, it was found that the S100 protein had strong immunohistochemical activity and characteristics and was stained positively in all the schwannomas. CD34, CD117, desmin, actin, DOG-1, SMA, DES, and AE1/AE3 were not found in all schwannomas analyzed. HMB45 and Melan A were positive in esophageal melanocytic schwannoma\cite{22}, and their expression was not found in other patients. Esophageal schwannomas are easily misdiagnosed as gastrointestinal stromal tumors.
<table>
<thead>
<tr>
<th>Case</th>
<th>Ref.</th>
<th>Age (yr)/Sex</th>
<th>Presenting symptom</th>
<th>Immunohistochemical studies</th>
<th>Location</th>
<th>Tumor size</th>
<th>Benign or malignant</th>
<th>Treatment</th>
<th>Postoperative complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Matteo et al [17]</td>
<td>22/Male</td>
<td>Dysphagia, chest pain, esophageal reflux-like symptom</td>
<td>Reactive with S100 protein and negative for desmin, DOG1, CD117, EMA, HM485, Melan A, synaptophysin and neurofilaments</td>
<td>34 to 41 cm</td>
<td>75 mm</td>
<td>Benign but locally advanced</td>
<td>A subtotal esophagectomy via a muscle sparing lateral thoracotomy</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>Mishra et al [18]</td>
<td>27/Female</td>
<td>Dysphagia, palpitations, weight loss, loss of appetite</td>
<td>Immunepositive for S100 and negative for DOG-1, CD117, CD34, and SMA</td>
<td>30 cm</td>
<td>120 mm × 100 mm × 100 mm</td>
<td>Low-grade malignant</td>
<td>Esophagectomy through a left thoraco-abdominal incision</td>
<td>Right recurrent laryngeal nerve palsy</td>
</tr>
<tr>
<td>3</td>
<td>Naus et al [21]</td>
<td>39/Male</td>
<td>Burning epigastric pain</td>
<td>Positive for S100 protein</td>
<td>34 cm</td>
<td>15 mm</td>
<td>Benign</td>
<td>Endoscopic removal</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>Zhang et al [19]</td>
<td>48/Female</td>
<td>Dysphagia</td>
<td>Positive for S100</td>
<td>30 cm</td>
<td>70 mm × 60 mm × 40 mm</td>
<td>Benign</td>
<td>Robot-assisted thoracoscopic excision</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>Li et al [8]</td>
<td>49/Male</td>
<td>Dysphagia</td>
<td>Positive staining of the tumor cells for S100, Lea-7, and PC0.5 protein, and negative staining for CD117, CD34, DOG-1, DES, and smooth muscle actin</td>
<td>35 cm</td>
<td>28 mm × 22 mm</td>
<td>Benign</td>
<td>STER: Submucosal tunneling endoscopic resection. The lesion was resected in a piecemeal fashion</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>Hsu et al [13]</td>
<td>54/Male</td>
<td>Dysphagia</td>
<td>Positive for S100 protein and negative staining for actin</td>
<td>35 cm</td>
<td>25 mm × 20 mm × 15 mm</td>
<td>Benign</td>
<td>Submucosal tumor enucleation via left thoracotomy</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>Sánchez et al [14]</td>
<td>54/Male</td>
<td>Dysphagia, weight loss</td>
<td>Positive for S100 and vimentin and negative for CD117</td>
<td>34 to 40 cm</td>
<td>60 mm</td>
<td>Malignant</td>
<td>Ivor-Lewis esophagectomy with gastric-tube reconstruction</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>Trindade et al [15]</td>
<td>54/Male</td>
<td>Esophageal reflux-like symptom</td>
<td>Positive for S100 and negative for smooth muscle markers</td>
<td>In the distal third of the esophagus</td>
<td>6 mm</td>
<td>Benign</td>
<td>Endoscopic mucosal resection</td>
<td>No</td>
</tr>
<tr>
<td>9</td>
<td>Shimamura et al [16]</td>
<td>56/Male</td>
<td>Esophageal reflux-like symptom</td>
<td>Strongly positive for S100 and not stain for CD117, SMA, CD68 and inhibit S100</td>
<td>Distal esophagus</td>
<td>5 mm</td>
<td>Benign</td>
<td>Endoscopic mucosal resection</td>
<td>No</td>
</tr>
<tr>
<td>10</td>
<td>Li et al [8]</td>
<td>59/Male</td>
<td>Upper abdominal distension, esophageal reflux-like symptom</td>
<td>Positive staining of the tumor cells for S100, Lea-7, and PC0.5 protein, and negative staining for CD117, CD34, DOG-1, DES, and smooth muscle actin</td>
<td>35 cm</td>
<td>14 mm × 5 mm</td>
<td>Benign</td>
<td>ESE: Endoscopic submucosal excision</td>
<td>No</td>
</tr>
<tr>
<td>11</td>
<td>Shichinohe et al [20]</td>
<td>61/Female</td>
<td>Dysphagia</td>
<td>Positive staining of S100, and negative staining of c-kit and α-SMA</td>
<td>In the lower thoracic esophagus</td>
<td>45 mm × 30 mm</td>
<td>Benign</td>
<td>Thoracoscopic esophageal submucosal tumor enucleation</td>
<td>No</td>
</tr>
<tr>
<td>12</td>
<td>Our case</td>
<td>62/Male</td>
<td>Dysphagia, chest pain, palpitations, chest tightness, shortness of breath, back pain</td>
<td>Positivity for S100, Sox10, vimentin, and TLE1, but negativity for CD34, desmin, CD117, actin, GFAP, h-caldesmon, STAT6, DOG-1, CD21 and SMA</td>
<td>32 to 38 cm</td>
<td>53 mm × 39 mm × 50 mm</td>
<td>Benign</td>
<td>Video-assisted thoracoscopic partial esophagectomy</td>
<td>No</td>
</tr>
<tr>
<td>13</td>
<td>Brown et al [22]</td>
<td>76/Female</td>
<td>Dysphagia, weight loss</td>
<td>Positive for S100, HM485, and Melan A and negative for CD34, epithelial membrane antigen, smooth</td>
<td>In the lower third of the esophagus</td>
<td>50 mm × 40 mm × 20 mm</td>
<td>Benign</td>
<td>Subtotal esophagectomy</td>
<td>No</td>
</tr>
</tbody>
</table>
muscle antigen, and desmin

Figure 3 Chest computed tomography revealed a mass approximately 53 mm × 39 mm × 50 mm protruding from the lower esophagus (arrowheads).

Figure 4 Histopathological examination revealed spindle-shaped cells arranged in interlacing fascicles (hematoxylin and eosin stain, × 200).

or esophageal leiomyomas. The immunohistochemical examination is the most accurate method for the differential diagnosis of esophageal tumors. The gastrointestinal stromal tumor is positive for CD34 and CD117, and the leiomyoma is positive for desmin and actin[6]. Furthermore, the upper schwannoma can be misdiagnosed as a thyroid tumor on ultrasonography[31]. Surgical exploration is
Immunohistochemical examination revealed SOX10 protein positivity (× 200).

However, Sox10 (Figure 5) was strongly positive in our case. To the best of our knowledge, we are the first to use Sox10 to detect esophageal schwannomas. It is worth noting that the Sox10 factor is expressed in Schwann cells and melanocyte lineages and is important for their development[32]. Recent studies have suggested that Sox10 is a potential molecular biological marker and can be used to diagnose and differentiate some tumors of the nervous system. Sox10 is consistently expressed in gastrointestinal schwannomas and can distinguish them from stromal tumors that are occasionally S100 protein positive[32]. As a molecular marker, Sox10 is superior to S100 in terms of sensitivity and specificity for the differential diagnosis of schwannoma and fibrous meningioma[33]. Studies also have shown that Sox10 has a higher specificity for tumors of neural crest origin than S100: Sox10 (specificity, 99%) and S100 (specificity, 91%)[34]. The combined use of Sox10 and S100 aids in improving the sensitivity and specificity for the diagnosis of schwannoma.

Esophageal schwannoma is insensitive to medical treatments such as radiotherapy and chemotherapy; hence, surgery is the only effective treatment, including endoscopic surgery and surgical resection. When the lesion is small, endoscopic treatment is a great choice. In the published literature on lower esophageal schwannomas, the tumor size in 6 patients was less than 3 cm; of these, 5 patients (83.3%) underwent endoscopic surgery. For larger lesions (≥ 3 cm) with suspicious features, endoscopic treatment may not be suitable[8], and surgical operation is required. The tumor size in 5 patients was between 3 cm and 7 cm, including 3 cases (60%) of thoracoscopic surgery. For tumors of size > 7 cm, thoracotomy is often the treatment of choice[35]. Statistically, 2 patients with tumors measuring > 7 cm underwent thoracotomy. For malignant esophageal schwannoma, surgical resection and lymph node dissection are necessary[18]. Thoracoscopy and thoracotomy incisions are related to the tumor location and anatomical rationality.

There are some differences in the choice of surgical incision between lower schwannoma and upper to middle schwannoma. Since the upper esophagus is partially posterior to the left subclavian artery and the middle thoracic esophagus is below the aortic arch, the left-side approach is generally not chosen for upper to middle esophageal schwannomas to avoid vascular damage[6,20]. Due to the esophageal hiatus position on the upper left of the aortic hiatus, surgery for lower schwannoma, which is located above the diaphragm, can be performed through the left chest wall without any anatomical obstacles[20]. Therefore, the surgeon chooses the left-side approach for the schwannoma on the left side of the lower thoracic esophagus[20]. The azygos vein arch is the only structure of the right thoracic mediastinum above the esophagus, and the vein is separable without any complications[20]. Due to this, both lower and upper to middle esophageal schwannoma can be approached from the right side. In the present case, the patient’s esophageal schwannoma was located on the right side of the lower esophagus, prompting the use of the right-side approach. At the same time, the patient was also experiencing cardiac insufficiency. Early appropriate resection surgery improved cardiac function and favored a great prognosis.
CONCLUSION

Briefly, esophageal schwannoma is an extremely rare disease that can be easily misdiagnosed. There is no differential laboratory examination for the disease. Initial imaging test findings are similar to those of leiomyoma cases before surgery. The definitive diagnosis of esophageal schwannoma requires histopathological and immunohistochemical examination of postoperative specimens. Studies revealed that Sox10 may be a potential molecular marker for esophageal schwannoma, but further studies with large samples for an in-depth investigation on Sox10 are required. Furthermore, if esophageal schwannoma is suspected, then early surgery is recommended to completely resect the tumor. When the patient is identified to have comorbidities, it is necessary to comprehensively evaluate the patient’s condition and choose the appropriate treatment method.

ACKNOWLEDGEMENTS

Thanks to the Pathology Department for helping us with histopathological images.

REFERENCES


Wang TY et al. Large lower esophageal schwannoma


Signet ring cell carcinoma hidden beneath large pedunculated colorectal polyp: A case report

Jia-Ning Yan, Yong-Fu Shao, Guo-Liang Ye, Yong Ding

Abstract

BACKGROUND
Large pedunculated colorectal polyps are not frequent among colonic polyps. We present a clinical case of a large pedunculated colorectal polyp with signet ring cell cancer infiltrating the submucosa and lymph node invasion in a patient who ultimately underwent additional surgery. Clinicians should attach importance to pedunculated colorectal polyps and choose the most appropriate therapy.

CASE SUMMARY
A 52-year-old female farmer underwent routine screening colonoscopy and denied constipation, diarrhea, hematochezia, or other gastrointestinal symptoms. Her past medical history and general biochemical examination results were unremarkable. During the colonoscopy, a 25-mm pedunculated polyp in the sigmoid colon was identified. The superficial epithelium was macroscopically congestive, rough, and granular, showing characteristic features of adenoma. We first ligated the root of the pedunculated polyp using nylon loops as well as a titanium clip. Histopathological examination revealed high-grade intraepithelial neoplasia of the tumor surface and a negative margin with signet ring cell adenocarcinoma infiltrating the submucosal layer. The deepest infiltration was approximately 0.9 cm from the tumor surface and 0.55 cm from the stratum basale. We performed radical resection of the left colon with lymph node dissection after two weeks. The lesion was completely resected, and pathological assessment revealed signet ring cell adenocarcinoma infiltrating the submucosal layer as well as lymph node invasion (stage PT1N1M0 and grade IIIA in pathological grading, NRAS-, BRAF V600E-, KRAS-).

CONCLUSION
This case highlights the importance of paying attention to the malignancy of large pedunculated polyps. Polyps or adenomas removed via endoscopy must be
INTRODUCTION

Colorectal cancer (CRC) is the third most common malignant tumor worldwide, most of which develop from polyps, and the transition of polyps to carcinoma is a vital process in CRC development[1]. Large pedunculated polyps are polyps ≥ 10 mm in head diameter, and the degree of malignancy is always low[2]. Herein, we present a clinical report of a patient with signet ring cell colorectal adenocarcinoma in a long pedunculated colorectal polyp that is easily confused with benign polyps.

CASE PRESENTATION

Chief complaints
A 52-year-old female farmer underwent routine screening colonoscopy at our hospital.

History of present illness
She denied constipation, diarrhea, hematochezia, or other gastrointestinal symptoms.

History of past illness
The patient’s previous medical history was uneventful.

Personal and family history
The patient and her family members had no previous episodes of similar diseases.

Physical examination
Her pulse rate, blood pressure, and respiratory rhythm were normal. No scleroma was observed on anal finger examination, and no positive nervous system signs were observed on physical examination.

Laboratory examinations
The general biochemical examinations were unremarkable.

Imaging examinations
Contrast-enhanced CT scans of the abdomen showed no specific abnormalities in the left colon in Figure 1. During colonoscopy, a 25-mm pedunculated polyp was identified in the sigmoid colon. The superficial epithelium was macroscopically evaluated histologically. Even if adenomas may be fragile, endoscopy doctors should still remove polyps as completely as possible and choose perpendicular sections through the stalk and base to fix by formaldehyde solution.

Key Words: Signet ring cell carcinoma; Colorectal cancer; Pedunculated colorectal polyp; Surgery; Pathology; Case report

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Contrast-enhanced computed tomography scans of the abdomen showed no specific abnormalities in the left colon. The mucosa was congestive, rough, and granular, showing characteristic features of adenoma (Figure 2).

**HISTOLOGICAL EXAMINATION**

Histopathological examination showed high-grade intraepithelial neoplasia of the tumor surface and a negative margin, but a signet ring cell adenocarcinoma was found to infiltrate the submucosal layer of the first biopsy during colonoscopy. The deepest infiltration was approximately 0.9 cm from the tumor surface and 0.55 cm from the stratum basale (Figure 3A and B).

The second histopathological examination after operation showed signet ring cell adenocarcinoma infiltrating the submucosal layer as well as lymph node invasion (stage PT1N1M0 and grade IIIA in pathological grading, NRAS-, BRAF V600E-, KRAS-) (Figure 3C and D).

**FINAL DIAGNOSIS**

The final diagnosis was signet ring cell adenocarcinoma (stage PT1N1M0 and grade IIIA in pathological grading, NRAS-, BRAF V600E-, KRAS-).

**TREATMENT**

We first ligated the root of the pedunculated polyp using nylon loops as well as a titanium clip and then performed polypectomy using a snare and fixed it at once (Figure 2D). The patient had a definite surgical indication and required additional surgery. We performed radical resection of the left colon with lymph node dissection after two weeks. This patient subsequently received a chemotherapy regimen with XELOX.

**OUTCOME AND FOLLOW-UP**

The patient was referred to the oncology department for the assessment of chemotherapy. The xelox chemotherapy regimen was well tolerated and established 8 times.

**DISCUSSION**

The incidence of signet ring cell carcinoma in the colon and rectum is low; most cases are usually detected only at an advanced stage[3]. Meanwhile, it is difficult to identify...
Figure 2 Multiangle photographs of the pedunculated polyp under colonoscopy. A-C: The pedunculated polyp shows the characteristic features of adenoma with unclear surface pattern; D: The pedunculated polyp was resected under colonoscopy.

the pit pattern because signet ring cell carcinoma produces a large amount of mucus, and the structure of the pits is always destroyed[4]. Recent studies have shown that signet ring cell adenocarcinoma is more frequently found in men in the left-sided colon with a more advanced tumor-node-metastasis stage and worse outcomes than in women; the median overall survival in patients with stage IV disease was found to be 14 mo, which was much shorter than the 23.4 mo at the same stage[5]. To the best of our knowledge, this is the first report of signet ring cell carcinoma with such a large pedunculated polyp.

It has been revealed that the incidence of carcinoma in flat and depressed lesions is higher than that in pedunculated polyps, and few studies have focused on the strategy for pedunculated polyps[6]. Although pedunculated polyps are generally considered to pose a lower risk of lymph node metastases, it is necessary to ascertain the distinction between the head and stalk in pedunculated polyps. The depth of invasion of the stalk is critical for estimating lymph node invasion, formulating therapeutic schemes, and determining distal prognosis. Factors such as the depth of submucosal invasion (SM invasion depth) and histological type (differentiated adenocarcinoma, signetring cell carcinoma) have been reported to be risk factors for regional lymph node metastasis in pT1 (SM) carcinoma[7]. It has been suggested that the long stalk may play a protective role and suppress the invasive progression of malignant cells because sessile polyps are closer, hence facilitating infiltration, but this has not been proven[2]. Haggitt et al[8] proposed a new method to distinguish the level of invasion in a pedunculated malignant polyp and summarized the methods as follows: Level 1, invasive adenocarcinoma limited to the polyp head; Level 2, neck involvement; Level 3, carcinoma cells in the stalk; and Level 4, carcinoma cells infiltrating the submucosa at the level of the adjacent bowel wall, in which levels less than 4 indicate a low risk of metastasis. The European Society of Gastrointestinal Endoscopy 2015 guidelines advocate using the Haggitt classification for pedunculated polyps, and the Japanese Society for Cancer of the Colon and Rectum 2016 guidelines suggest measuring from the Haggitt line only in pedunculated lesions[9,10]. The Japanese Society for Cancer of the Colon and Rectum 2019 indicates that the lymph node metastasis rate in patients with a depth of invasion of 1000 μm or greater is 12.5%[11]. Emerging cases have revealed associations among the Haggitt level, lymph node invasion risk, and long-term prognosis[12,13]. However, we could not define the Haggitt line clearly because in this case, the stem base and long, large stalk were smooth, lacking the typical
Figure 3 The pathologic results for pedunculated polyps and lymph nodes. A: The tumor was composed of signet ring cell carcinoma (dark rectangle, hematoxylin and eosin: 0.52 ×); B: The pathologic result in the rectangle clearly showed that the signet ring cells infiltrated the submucosa (hematoxylin and eosin: 40 ×); C: The lymph node was invaded by signet ring cell adenocarcinoma (blue rectangle, hematoxylin and eosin: 1.32 ×); D: The pathologic result in the rectangle clearly showed that the signet ring cells invaded a lymph node (hematoxylin and eosin: 40 ×).

characteristics of adenoma, such as swelling mucous and an unstructured or excavated surface according to Kudo’s pit pattern classification[14]. Finally, we ensured that the Haggitt level was 4; this theory still deserves further study in larger patient cohorts for validation.

The principle of pT1 carcinoma treatment is intestinal resection with lymph node dissection. We refer to the treatment strategies for cTis and cT1 colorectal cancer from the Japanese Society for Cancer of the Colon and Rectum Guidelines shown in Figure 4 [11]. In the present case, the lesion was obscure, hidden, and easy to overlook. Fortunately, our ligation position and polypectomy were thorough, and the deep lesion was suitable for surgery (depth of SM invasion ≥ 1000 µm and signet ring cell carcinoma)[11].

Polyps or adenomas removed via endoscopy must be sent for histopathology examination to be carefully evaluated by the pathologists keeping in their minds the possibility of underlying malignancy in a benign looking lesion, they should examine the lesion from the muscularis mucosae to the submucosa and describe the position precisely as well[15,16].

CONCLUSION

This case highlights the importance of paying attention to malignancy of large pedunculated polyps. Polyps or adenomas removed via endoscopy must be evaluated histologically. Even if adenomas may be fragile, endoscopy doctors should still remove polyps as completely as possible and choose perpendicular sections through the stalk and base to fix by formaldehyde solution.
Figure 4 The treatment strategies for cTis and cT1 colorectal cancer from the Japanese Society for Cancer of the Colon and Rectum Guidelines.

Acknowledgements

We are grateful to our colleagues from the Department of Imaging, Laboratory, Pathology, and Infection for providing diagnostic and therapeutic assistance.

References

Yan JN et al. Signet ring beneath pedunculated colorectal polyp


Double-mutant invasive mucinous adenocarcinoma of the lung in a 32-year-old male patient: A case report

Ting Wang

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Author contributions: Wang T is responsible for manuscript writing, data collection, and performing the analysis with constructive discussions.

Informed consent statement: Written consent to publish the clinical or possible personal information was obtained from the participant included in the study.

Conflict-of-interest statement: Dr. Wang has nothing to disclose.

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Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Abstract

BACKGROUND
Invasive mucinous adenocarcinoma of the lung, formerly known as mucinous bronchioalveolar carcinoma, is a rare category of lung tumors and radiologically characterized by dense pneumonic consolidation, ground-glass opacity, crazy paving, and nodules. However, early pleural effusion is uncommon in this malignancy.

CASE SUMMARY
The case of a 32-year-old male patient who visited our facility with symptoms of cough and gradually aggravated shortness of breath was reported. X-ray examination revealed a massive left hydrothorax. The patient underwent thoracentesis, and pleural fluid tumor markers, including carcinoembryonic antigen, carbohydrate antigen 19-9, neuron-specific enolase, and cytokeratin 21-1 fragment, were significantly elevated. A similar tendency was observed among the serum tumor markers. After draining the pleural effusion, the patient underwent chest computed tomography, and no obvious mass was found in the lung. Thoracoscopy revealed that the left visceral pleura was covered with nodular, cauliflower-like protrusions of various sizes. These histopathological results suggested cancerous cells, and the immunohistochemical findings were consistent with mucinous adenocarcinoma of pulmonary origin. It tested positive for cytokeratin, cytokeratin 5/6, carcinoembryonic antigen, and thyroid transcription factor-1.

CONCLUSION
The patient was diagnosed with a rare case of lung mucinous adenocarcinoma. Subsequent genetic testing was positive for epidermal growth factor receptor-21 mutations and echinoderm microtubule-associated protein-like 4-lymphoma anaplastic kinase fusion. This prompted treatment with alfatibin and crizotinib.

Key Words: Lung mucinous adenocarcinoma; Hydrothorax; Double mutant; Case report
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DOI: https://dx.doi.org/10.12998/wjcc.v9.i35.11078

INTRODUCTION
According to the global cancer statistics in 2018, lung cancer is the leading cause of cancer-related mortality, killing approximately 1761000 people worldwide[1]. Histologically, lung cancer is divided into non-small cell lung cancer and small cell lung cancer, with the former pathological type accounting for 80% of cases[2]. Invasive mucinous adenocarcinoma (IMA) of the lung was introduced as a new category in the 2015 World Health Organization classification of lung tumors. It accounts for 2%-5% of lung adenocarcinomas, the most common histologic subtype of non-small cell lung cancer[3,4]. IMA is diagnosed based on tall columnar cell morphology with abundant intracellular/extracellular mucus and invasive adenocarcinoma patterns, such as lepidic, acinar, papillary, and predominant patterns. Due to its pathological and growth characteristics, the typical computed tomography (CT) findings of IMA include consolidation, ground-glass opacity, and nodules.

In contrast, pleural IMAs are rare[5-7]. A case of IMA presenting as a massive pleural effusion in the left thoracic cavity in a 32-year-old male patient was reported. After drainage, multiple nodules on the left visceral pleura, instead of apparent pulmonary masses, were found on a chest CT scan. Gene testing showed that the biopsy tissue had a double mutation, namely positive epidermal growth factor receptor-21 (EGFR-21) mutations and echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (ALK) fusion. To the best of my knowledge, this is the first published report on dual-mutation IMA with early pleural invasion in a young patient.

CASE PRESENTATION
Chief complaints
A 32-year-old male chronic smoker (ten cigarettes a day for more than 10 years) was referred to our hospital’s respiratory department on June 25, 2020. He complained of shortness of breath and a cough.

History of present illness
The patient had a history of progressive shortness of breath and a cough for 20 d before consult.

History of past illness
He had no prior chronic diseases but recently lost 4 kg of his body weight.

Personal and family history
The patient denied having a family history of lung cancer, hypertension, and coronary heart disease.
**Physical examination**
Physical examination showed that respiratory sounds were absent in the patient’s left lung field.

**Laboratory examinations**
He was admitted to our department where he underwent thoracocentesis that resulted in the extraction of 700 mL of pleural effusion. Related laboratory results of the yellow turbid pleural fluid revealed an exudate with dramatically high tumor biomarkers and normal adenosine deaminase, which was unexpected. Detailed data are as follows: total cell count = 8015 × 10⁶/L, leukocyte count = 440 × 10⁶/L, positive Rivalta test, lactate dehydrogenase = 676 U/L, total protein 51 g/L, adenosine deaminase = 13 U/L, carcinoembryonic antigen = 34.6 ng/mL (normal range: 0-5), carbohydrate antigen 19-9 > 1000 U/mL (normal range: 0-37), neuron-specific enolase = 22.65 ng/mL (normal range: 0-18), and cytokeratin 21-1 fragment > 500 ng/mL (normal range: 0-3.3). The patient’s serum tumor biomarkers exhibited a less obvious upward trend than their counterparts in the pleural effusion, with carcinoembryonic antigen 7.96 ng/mL, carbohydrate antigen 19-9 204.2 U/mL, and cytokeratin 21-1 fragment 6.33 ng/mL. Cytological tests revealed allotype tumor cells in the hydrothorax. We then performed closed thoracic drainage because of the massive pleural effusion and apparent symptoms of this patient.

**Imaging examinations**
Chest X-ray showed a severe left hydrothorax (Figure 1), and the patient was hospitalized with a suspected diagnosis of tuberculous exudative pleurisy. After pleural effusion drainage, the patient underwent chest CT, demonstrating no evident pulmonary masses or nodules; however, multiple nodules were found in the left visceral pleura (Figure 2). Subsequent thoracoscopy revealed that the visceral pleura was filled with nodular, cauliflower-like protrusions of various sizes (Figure 3).

**FINAL DIAGNOSIS**
The initial pathological diagnosis was allotypic epithelioid cells, and immunohistochemical analysis showed tumor cell positivity for cytokeratin, cytokeratin 5/6, carcinoembryonic antigen, thyroid transcription factor-1, and Ki-67 (20%). The tumor tested negative for calretinin, cytokeratin 20, and p53, which were compatible with lung IMA (Figure 4). Genetic testing revealed positive EGFR-21 mutations and echinoderm microtubule-associated protein-like 4-ALK fusion. This prompted treatment with alfatinib and crizotinib.

**TREATMENT**
Considering the side effects of the two targeted drugs, we initially prescribed alfatinib alone with a daily dose of 40 mg. After 1 mo, re-examination showed decreased pleural nodules, no pleural effusion recurrence, and significantly reduced serum lung cancer biomarkers. Meanwhile, the patient had a long-standing unresolved left lateral chest pain. After 2 mo, the second follow-up showed no changes in serum lung cancer biomarkers. However, the number of pleural nodules increased, and small metastases were observed in the contralateral lung. We adjusted the therapeutic plan based on these findings. Both alfatinib and crizotinib were administered.

**OUTCOME AND FOLLOW-UP**
The patient’s left lateral chest pain resolved within 1 wk. Thus far, the patient has taken alfatinib 40 mg per day and crizotinib 250 mg twice per day for more than 10 mo, and side effects, such as mild diarrhea and skin rashes, have occurred. After 12 mo, chest CT scan re-examination showed apparent reductions in the pleural nodules and no recurrence of pleural effusion.
Figure 1 A chest radiograph showed severe left hydrothorax.

Figure 2 Chest computed tomography demonstrated multiple nodules on left visceral pleura (indicated by orange arrows) and part of atelectasis in the left lower lung (showed by the blue arrow).

DISCUSSION

Lung cancer, which is associated with high morbidity and mortality among all types of tumors, frequently occurs in the sixth to eighth decades of life. It is uncommon among people around 30 years of age\(^8\). A new and rare type of adenocarcinoma, IMA, was reclassified as a variant of invasive adenocarcinoma by the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society lung adenocarcinoma classification system because of its unique clinical, pathological, and radiological features as well as its unique genetic characteristics (lower prevalence of EGFR mutations)\(^9,10\).
IMA has a tall columnar morphology with abundant mucus inside or outside the tumor cells. It exhibits adenocarcinoma patterns, including acinar, papillary, micropapillary, and solid predominant patterns. Specifically, IMA is divided into two groups based on the mucinous percentage: pure mucinous (invasive mucinous component > 90%) and mixed mucinous/non-mucinous (non-mucinous invasive pattern > 10%)\[11\]. IMA, a classification with poor survival outcomes compared with other adenocarcinoma subtypes, frequently spreads aerogenously, forming satellite tumors. Lymph node involvement and distant metastasis are less common\[3,12\].

On CT, IMA presents as consolidation, nodules, or ground-glass opacity. In a study by Nie et al[13], 54 of 68 patients with IMA had solitary-type tumors on their chest CT scan. Nearly 80% of the imaging signs of IMA are solitary nodules or masses. The other 20% of CT findings are the pneumonic type, which is defined as consolidation without a defined shape, distributed along the lung lobe or lung segment, and sometimes with air bronchogram. In contrast, pleural effusion, as an early sign of IMA, is rare. In our case, immunohistochemical analysis showed that the tumor cells were of pulmonary origin. No clear pulmonary signs were observed on chest imaging after pleural effusion drainage. Instead, multiple nodules were observed in the left visceral pleura, which was more suggestive of pleural mesothelioma. Atelectasis was also observed in the left lower lung, which may have negatively influenced assessment and diagnosis.

Concerning the molecular features of IMA, several studies have linked IMA with frequent Kirsten rat sarcoma viral oncogene mutations and a lower prevalence of EGFR and ALK rearrangements, indicating a poor prognosis for target-specific drug treatment\[14,15\]. In our case, the EGFR-21 mutations and echinoderm microtubule-associated protein-like 4-ALK fusion were both positive, which is rare for IMA. This case emphasizes the significance of applying medicine to different targets in lung cancer. We will conduct a continuous follow-up of this young patient in the future.
Figure 4 Immunohistochemical analysis showed that the tumor cells were positive for cytokeratin, cytokeratin 5/6, carcinoembryonic antigen, thyroid transcription factor-1 and Ki-67. A: Cytokeratin; B: Cytokeratin 5/6; C: Carcinoembryonic antigen; D: Thyroid transcription factor-1; E: Ki-67.

CONCLUSION

In conclusion, atypical IMA is challenging to diagnose, especially in young patients. It is necessary to consider IMA in patients with unusual laboratory test results and radiological presentations.

ACKNOWLEDGMENTS

We are thankful to Dr. Mingwei Chen for his advice on writing this rare case as a report.

REFERENCES


Acute myocarditis presenting as accelerated junctional rhythm in Graves’ disease: A case report

Meng-Mei Li, Wei-Sheng Liu, Rui-Cai Shan, Jun Teng, Yan Wang

Abstract

BACKGROUND
Acute myocarditis is an acute myocardium injury that manifests as arrhythmia, dyspnea, and elevated cardiac enzymes. Acute myocarditis is usually caused by a viral infection but can sometimes be caused by autoimmunity. Graves’ disease is an autoimmune disease that is a rare etiology of acute myocarditis. Accelerated junctional rhythm is also a rare manifestation of acute myocarditis in adults.

CASE SUMMARY
A rare case of new-onset Graves’ disease combined with acute myocarditis and thyrotoxic periodic paralysis is reported. The patient was a 25-year-old young man who suddenly became paralyzed and felt palpitations and dyspnea. He was then sent to our emergency department (ED). Upon arrival, electrocardiography revealed an accelerated junctional rhythm and ST-segment depression in all leads, and laboratory findings showed extreme hypokalemia and elevated troponin I, with the troponin I level being 0.32 ng/mL (reference range, 0-0.06 ng/mL). Coronary computer tomography angiography was performed, and there were no abnormal findings in the coronary arteries. Subsequently, the patient was admitted to the ED ward, where further testing revealed Graves’ disease, along with continued elevated cardiac enzyme levels and B-type natriuretic peptide (BNP) levels. The troponin I level was 0.24 ng/mL after admission. All of the echocardiography results were normal: Left atrium 35 mm, left ventricle 48 mm, end-diastolic volume 102 mL, right atrium 39 mm × 47 mm, right ventricle 25 mm, and ejection fraction 60%. Cardiac magnetic resonance was performed on the fifth day of admission, revealing myocardial edema in the lateral wall and intramyocardial and subepicardial late gadolinium enhancement in the lateral wall.
Graves’ disease presenting as myocarditis

INTRODUCTION

Graves’ disease is an autoimmune disorder that affects the thyroid gland[1]. Hyperthyroidism affects 0.5%-2% of females[2] in geographical areas not featuring iodine deficiency. Males show a 10-fold lower prevalence. Graves’ disease is the most frequent cause and is more likely to occur in female populations[2]. Graves’ disease would seem to be more frequent in Asian populations and less frequent in sub-Saharan Africans[2]. Thyroid hormone (TH) receptors are present in the myocardium and vascular endothelial tissues, thereby allowing changes in circulating TH concentration to modulate end-organ activity[3]. Thus, Graves’ disease can present with cardiovascular manifestations. Usually misdiagnosed as myocardial infarction, Graves’ disease combined with acute myocarditis is a rare manifestation, and the etiology is due to an autoimmune process.

When the electrical activity of the sinoatrial node is blocked or is less than the automaticity of the atrioventricular node/His bundle, a junctional rhythm originates [4]. Numerous conditions can cause a junctional rhythm, among which myocarditis is a rare etiology [4]. Acute myocarditis should be diagnosed when several differential diagnoses are excluded, such as tachycardiomyopathy (TCMP), stress cardiomyopathy, and pericardial diseases. Acute myocarditis presents with junctional arrhythmia is reported in children and seldomly reported in adults. There have been a few reports about Graves’ disease combined with acute myocarditis[5-7]. However, the patient’s manifestations differ in these cases. None of these cases presents with junctional arrhythmia. In this case, the patient presented with an accelerated junctional rhythm and myocarditis, which is unique compared with other reported cases, so that clinicians can have a new understanding of the cardiovascular complications of Graves’ disease.

CONCLUSION

Acute myocarditis is a rare manifestation of Graves’ disease. Accelerated junctional rhythm is also a rare manifestation of acute myocarditis in adults. When the reason for hypokalemia and elevated cardiac enzymes in patients is unknown, cardiologists should consider Graves’ disease and also pay attention to accelerated junctional rhythm.

Key Words: Graves’ disease; Myocarditis; Thyrotoxic periodic paralysis; Accelerated junctional rhythm; Case report

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Core Tip: Junctional rhythm is a significantly rare occurrence in patients and is a manifestation of acute myocarditis. The etiology of junctional rhythm may be attributed to autoimmunity, and physicians should not ignore such arrhythmia. In addition to viruses, autoimmune diseases like Graves’ disease can also cause acute myocarditis. The present case highlights that those endocrine diseases should not be disregarded in patients who present with cardiovascular symptoms.


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CASE PRESENTATION

Chief complaints
Sudden paralysis, dyspnea, and vomiting for 1 d.

History of present illness
A 25-year-old young male realized that he was paralyzed when he woke in the morning. At the same time, the patient felt palpitations, dyspnea, and nausea, with one instance of vomiting gastric contents. The patient was then brought to the emergency department (ED) by ambulance. Upon arrival, electrocardiography revealed an accelerated junctional rhythm (heart rate 91 beats per minute, Figure 1) and ST-segment depression in all leads. The laboratory results showed potassium 1.7 mmol/L and troponin I 0.32 ng/mL (reference range, 0-0.06 ng/mL). Acute myocardial infarction or acute myocarditis and hypokalemic periodic paralysis were considered, and thus, the ED administered potassium supplements orally and intravenously, oxygen inspiration, aspirin, and clopidogrel. Metoprolol was administered to control the heart rate. Due to the young age of the patient and no risk factors contributing to acute myocardial infarction, the ED department suggested an emergent coronary computer tomography (CT) angiography and a brain computer tomography to rule out more dangerous diseases. The results showed no abnormal findings of the coronary artery and the brain. Accordingly, the patient was diagnosed with acute myocarditis. The patient was then admitted to the ED ward, in which he was diagnosed with suspected acute myocarditis and hypokalemic periodic paralysis (reason unknown). The next step was to determine the primary disease.

History of past illness
The patient had no previous health issues.

Personal and family history
The patient’s family history did not reveal anything significant to the present condition. The patient was healthy and had not taken any drugs previously. He also reported no recent changes in weight.

Physical examination
The patient was conscious and afebrile, and his blood pressure was 110/65 mmHg. He was agitated and sweating profusely. Muscle strength was grade 2. According to the patient’s high metabolic condition, hyperthyroidism was considered the most common cause of hypokalemic periodic paralysis in young males. We especially checked the thyroid gland. There was no exophthalmos of the patient’s eyes, and no restriction of eye movements. There were no hand tremors. Palpation of the thyroid showed II degree of swelling of the thyroid gland with no abnormal findings on the isthmus. There was no tenderness. On auscultation of the thyroid, a bruit could be heard. The lungs, heart, and abdomen were subsequently examined, all of which were normal.

Laboratory examinations
Thyroid function tests revealed a hyperthyroid state, and thus, Graves’ disease was considered: T3 17.51 pmol/L (3.1-6.8 pmol/L), T4 39.68 pmol/L (12-22 pmol/L), thyroid-stimulating hormone (TSH) 0.005 μIU/mL (0.27-4.2 μIU/mL), thyroglobulin 94.77 ng/mL, anti-thyroglobulin antibodies 18.35 IU/mL (normal), TSH receptor antibody (TSHR-AB) 13.76 IU/L (0-1.5 IU/L), and thyroid peroxidase antibody 77.67 IU/mL (0-34 IU/mL). Other significant laboratory findings revealed elevated troponin I and elevated B-type natriuretic peptide (BNP) [troponin I 0.24 ng/mL (reference range, 0-0.06 ng/mL) and BNP 196.24 pg/mL]. The troponin I level measurement was performed five times, and the trend is shown in Figure 2. The inflammatory markers C-reactive protein and erythrocyte sedimentation rate were also measured, which were elevated to 12.6 mg/L and 50.3 mm/h, respectively (the references were within 0.5 mg/L and 20 mm/h, respectively). Initially, viral myocarditis was considered. The nucleic acids of 13 common virus types were checked in throat swabs and no positive results were found. The 13 virus types were as follows: Adenovirus, influenza-a, influenza-b, parainfluenza virus, respiratory syncytial virus, Bocavirus, rhinovirus, influenza H1N1, chlamydia, metapneumovirus, influenza H3N2, coronavirus, and Mycoplasma pneumoniae. Since the belief was that autoimmunity might be the etiology, cardiac magnetic resonance (CMR) and endocardial myocardial biopsy (EMB) were suggested.
Figure 1 Electrocardiography showed an accelerated junctional rhythm. No sinus P waves were found, the heart rate was 91 beats per minute, within 60-100 beats per minute, and ST-segment depression was seen in all leads. Accelerated junctional rhythm could be seen in patients with acute myocarditis.

Figure 2 Troponin I level.

Imaging examinations
CMR was performed on the fifth day of admission. The results showed myocardial edema in the lateral wall and intramyocardial and subepicardial late gadolinium enhancement in the lateral apex, anterolateral, and inferior lateral segments of the ventricle (Figure 3 and 4). Said results suggested acute myocarditis. The patient refused to undergo an EMB examination, but echocardiography was performed, with the results being normal: Left atrium 35 mm, left ventricle (LV) 48 mm, end-diastolic volume 102 mL, right atrium 39 mm × 47 mm, right ventricle 25 mm, and ejection fraction (EF) 60%. Thyroid ultrasonography was performed to confirm the diagnosis of Graves’ disease, which showed an enlarged thyroid gland and rich blood flow signal, and no tumor was found. Thyroid static imaging was then performed to exclude subacute thyroiditis, which showed bilateral lobe swelling and increased function. Such examinations confirmed the diagnosis of Graves’ disease.

FINAL DIAGNOSIS
Acute myocarditis presenting as an accelerated junctional rhythm in Graves’ disease.

TREATMENT
An endocrinologist was consulted, who suggested that the patient should undergo radioactive iodine therapy. However, the patient expressed a preference for taking medicine. Thus, according to recommendations, methimazole 20 mg/d was administered to treat hyperthyroidism, while trimetazidine 60 mg/d, metoprolol 50 mg/d, and calcium dibutyryl adenosine cyclophosphate 40 mg/d were administered for myocarditis.
OUTCOME AND FOLLOW-UP

The patient’s symptoms were relieved within 6 d, and troponin I, BNP, and electrocardiography tests were performed. All tests showed normal results (Figure 5). The patient was discharged from the hospital and was instructed to continue taking methimazole, trimetazidine, and metoprolol.

A 6-mo follow-up process was performed in the emergency clinic and by phone calls, and the patient continued taking metoprolol, trimetazidine, and thiamazole. The patient was asymptomatic aside from several symptoms of thyrotoxicosis, and subjected to thyroid function, liver function, kidney function, troponin I, and electrocardiograph routine tests for medicine adjustments. After 45 d, all of the patient’s symptoms disappeared and thyroid function improved: T3 12.26 pmol/L (3.1-6.8 pmol/L), T4 28.37 pmol/L (12-22 pmol/L), and TSH 0.07 μIU/mL (0.27-4.2 μIU/mL). After 80 d, the euthyroid state was restored, and the patient’s liver and kidney functions were in good condition. Electrocardiography and troponin I levels were also normal. Methimazole was adjusted to 5 mg/d and metoprolol was adjusted to 23.75 mg/d.

DISCUSSION

Acute myocarditis is an acute injury of the myocardium that manifests as arrhythmia, dyspnea, and elevated cardiac enzymes. Acute myocarditis is usually caused by a viral infection but can sometimes be caused by autoimmunity. An autoimmune state is always triggered in patients with acute autoimmune myocarditis, such as systemic lupus erythematosus, rheumatoid arthritis, and others[5]. Graves’ disease is also an autoimmune disease and can manifest as acute autoimmune myocarditis. However, acute autoimmune myocarditis is rarely observed in patients with Graves’ disease. Despite a previous case report in which acute autoimmune myocarditis could have
been a manifestation of Graves’ disease[5], the patient did not manifest with junctional arrhythmia and was not suffering from new-onset Graves’ disease. Thus, there are several significant differences in comparison with the present case report. The rarity and diagnosis of this case are further clarified in Tables 1 and 2[8].

The present patient’s electrocardiograph, elevated troponin I, normal coronary arteries, symptoms, and CMR results were consistent with acute myocarditis[8]. However, several differential diagnoses, such as TCMP, stress cardiomyopathy, and pericardial diseases, had to be excluded. If there is evidence of persistent or frequently occurring tachycardia or frequent premature ventricular complexes, the possibility of TCMP should be considered when eliciting a history of any new diagnosis of LV dysfunction. The traditional clinical presentation includes symptoms and signs of congestive heart failure and dilated cardiomyopathy. Other factors that point to a diagnosis of TCMP include: (1) Evidence of a previously normal EF and a degree of LV dysfunction out of proportion to other comorbidities; (2) no other cause of non-ischemic cardiomyopathy (e.g., hypertension, alcohol or drug use, and stress (3) absence of left ventricular hypertrophy; (4) relatively normal LV dimensions (LV end-diastolic dimension below 5.5 cm); (5) recovery of LV function after control of tachycardia (by rate control, cardioversion or radiofrequency ablation within 1-6 mo); and (6) rapid decline in LV ejection fraction following the recurrence of tachycardia in a patient with recovered LV function after previous control of tachycardia[9]. The patient had no previous health issues and had no history of tachycardia. Moreover, the patient’s heart rate was 91 bpm initially, which could not be defined as tachycardia. Hence, there was no evidence of persistent tachycardia. Echocardiography and CMR did not reveal any LV dysfunction. The ejection fraction was normal, and there were no significant abnormalities in the cardiac structure. No dilation of the atrium and ventricles was observed, and no hypertrophy was observed. The results above could exclude the possibility of TCMP[9]. The patient did not meet the criteria for stress cardiomyopathy listed in the guidelines of the Heart Failure Association-European Society of Cardiology Criteria and the Revised Mayo Clinic Criteria[10]. The patient did not have left ventricular dysfunction, wall motion abnormalities, or emotional disorders, and echocardiography was normal. The patient’s CMR confirmed the diagnosis of myocarditis, which excluded the probability of stress cardiomyopathy[10]. According to the latest diagnostic criteria[11], acute pericarditis could be excluded in the patient. The patient did not have chest pain, and a pericardial friction rub was not heard. There was no new ST-segment elevation or PR segment depression in the patient, and CMR results did not suggest pericardial involvement. Since myopericarditis has myocardial involvement, the clinical presentation thereof is considerably similar to that of myocarditis. Myopericarditis was diagnosed when the patient had both acute pericarditis and elevated myocardial injury biomarkers. As aforementioned, acute pericarditis was excluded in the patient, and CMR did not show pericardial involvement. As the primary disease in this patient was myocarditis, myopericarditis could also be excluded[11]. According to the latest diagnostic criteria, EMB should be performed, but the patient refused this procedure. The patient’s myocarditis was deduced to be attributed to autoimmunity. Treatment of primary diseases is of vital importance. The differential diagnostic process of this case is further clarified in Table 3.
Junctional arrhythmia, including accelerated junctional rhythm and junctional tachycardia, is rarely seen in patients with myocarditis. If the patient’s heart rate does not exceed 100 bpm, such conditions can be referred to as an accelerated junctional rhythm. No related reports on acute myocarditis and accelerated junctional rhythm were found, but there were reports on junctional tachycardia, usually seen in infants and children. Junctional tachycardia is also known as junctional ectopic tachycardia (JET), and the mechanism thereof is the same as accelerated junctional rhythm. Junctional tachycardia is thought to arise from the atrioventricular node and the His bundle area[12]. The incessant form of junctional ectopic tachycardia with 1:1 ventriculoatrial conduction, is a regular, short RP, narrow complex tachycardia and similar to typical Atrial Ventricular Nodal Reentry Tachycardia[12]. The patient’s electrocardiography findings were consistent with an accelerated junctional rhythm, which is rarely seen in children with acute viral myocarditis and even rarer in adults. There has been one report of junctional tachycardia in a child[13]. The etiology of accelerated junctional rhythm in the present patient could be attributed to autoimmunity (Table 3).

Graves’ disease manifests as a hyperthyroid state but is also an autoimmune process. Based on the patient’s thyroid function tests, hyperthyroidism was diagnosed. Measurements of the serum levels of TRAb and thyroid ultrasonography are the most important diagnostic tests for Graves’ disease. Following the latest guidelines[14], the patient had high TSHR-AB, and thyroid static imaging further confirmed the diagnosis of Graves’ disease. Graves’ disease treatment includes radioactive iodine (RAI),

### Table 1 Uniqueness of this case

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Setting</th>
<th>Main findings</th>
<th>Correlation and difference compared with this case</th>
</tr>
</thead>
<tbody>
<tr>
<td>[6]</td>
<td>A 29-year-old male presents with hyperthyroidism and chest pain</td>
<td>The patient is diagnosed with new-onset of Graves’ disease combined with myocarditis</td>
<td>The manifestation in the study is similar to this case report. However, that patient has already known that he had hyperthyroidism, which reduces the difficulty of the diagnosis. That patient does not present with hypokalemic periodic paralysis. Withal, the patient presents with sinus tachycardia on the electrocardiograph instead of a junctional rhythm</td>
</tr>
<tr>
<td>[5]</td>
<td>A 40-year-old male presents with refractory hyperthyroidism and chest pain</td>
<td>The patient is diagnosed with Graves’ disease combined with myocarditis</td>
<td>The study is similar to the above research. The patient is finally diagnosed with refractory Graves’ disease combined with myocarditis. No other manifestations are observed</td>
</tr>
<tr>
<td>[7]</td>
<td>A 31-year-old woman with 2-mo pregnancy with hyperthyroidism complained of palpitation and excessive sweating</td>
<td>The patient is diagnosed with Graves’ disease combined with myocarditis</td>
<td>The patient has reduced ejection fraction in the study. Besides, the patient does not present with other combinations except for myocarditis, which is different from this case</td>
</tr>
</tbody>
</table>

### Table 2 Diagnostic criteria for myocarditis[8]

<table>
<thead>
<tr>
<th>Examinations and presentations</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECG/Holter/stress test</td>
<td>Newly abnormal 12 lead ECG and/or Holter and/or stress testing, any of the following: I to III degree atrioventricular block, or bundle branch block, ST/T wave change (ST elevation or non-ST elevation, T wave inversion), sinus arrest, ventricular tachycardia or fibrillation and asystole, atrial fibrillation, reduced R wave height, intraventricular conduction delay (wided QRS complex), abnormal Q waves, low voltage, frequent premature beats, supraventricular tachycardia</td>
</tr>
<tr>
<td>Myocardiocytolysis markers</td>
<td>Elevated TnT/TnI</td>
</tr>
<tr>
<td>Functional and structural abnormalities on cardiac imaging (echo/angio/CMR)</td>
<td>New, otherwise unexplained LV and/or RV structure and function abnormality (including incidental finding in apparently asymptomatic subjects): regional wall motion or global systolic or diastolic function abnormality, with or without ventricular dilatation, with or without increased wall thickness, with or without pericardial effusion, with or without endocardial thrombi</td>
</tr>
<tr>
<td>Tissue characterization by CMR</td>
<td>Oedema and/or LGE of classical myocarditic pattern</td>
</tr>
<tr>
<td>Clinical presentations</td>
<td>Acute chest pain, pericarditic, or pseudo-ischaemic (1) New-onset (days up to 3 mo) or worsening of: Dyspnea at rest or exercise, and/or fatigue, with or without left and/or right heart failure signs; (2) Subacute/chronic (&gt; 3 mo) or worsening of: dyspnea at rest or exercise, and/or fatigue, with or without increased wall thickness, with or without pericardial effusion, with or without endocardial thrombi, with or without other combinations except for myocarditis, which is different from this case</td>
</tr>
</tbody>
</table>

*If the patient is asymptomatic, ≥ 2 diagnostic criteria should be met. Clinically suspected myocarditis if ≥ 1 clinical presentation and ≥ 1 diagnostic criteron from different categories, in the absence of: (1) Angiographically detectable coronary artery disease (coronary stenosis ≥ 50%); (2) known pre-existing cardiovascular disease or extra-cardiac causes that could explain the syndrome (e.g., valve disease, congenital heart disease, and hyperthyroidism) (see text). Suspicion is higher with higher number of fulfilled criteria. ECG: Electrocardiography; CMR: Cardiac magnetic resonance; LV: Left ventricle; RV: Right ventricle; LGE: Late gadolinium enhancement; TnI: Troponin I; TnT: Troponin T.
Correlation with this study

The clinical diagnosis of pericarditis can be made with two of the following criteria: (1) Chest pain (>85%-90% of cases)—typically sharp and pleuritic, improved by sitting up and leaning forward; (2) pericardial friction rub (≤ 33% of cases)—a superficial scratchy or squeaking sound best heard with the diaphragm of the stethoscope over the left sternal border; (3) electrocardiogram changes (up to 60% of cases)—with new widespread ST elevation or PR depression in the acute phase; and (4) pericardial effusion (up to 60% of cases, generally mild). Additional signs and symptoms may be present according to the underlying etiology or systemic disease (i.e., signs and symptoms of systemic infection such as fever and leukocytosis, or systemic inflammatory disease or cancer). Diagnosis of predominant pericarditis with myocardial involvement, or “myopericarditis”, can be clinically established if patients with definite criteria for acute pericarditis show elevated biomarkers of myocardial injury (troponin I or T, CK-MB fraction) without newly developed focal or diffuse impairment of left ventricular function in echocardiography or CMR.

The revised Mayo Clinic Criteria: (1) Transient hypokinesis, akinesis, or dyskinesis of the left ventricular midsegments with or without apical involvement; the regional wall motion abnormalities extend beyond a single epicardial vascular distribution; a stressful trigger is often, but not always present; (2) absence of obstructive coronary disease or angiographic evidence of acute plaque rupture; (3) new electrocardiographic abnormalities (either ST-segment elevation and/or T-wave inversion) or modest elevation in cardiac troponin; and (4) absence of pheochromocytoma or myocarditis CMR is a useful tool to confirm the diagnosis, and the pattern of DGE at CMR is useful to distinguish myocarditis from stress cardiomyopathy. The patient’s clinical presentation and CMR did not meet these criteria. Thus, stress cardiomyopathy was excluded in this patient.

The electrocardiography of a junctional rhythm shows a narrow complex QRS wave, along with retrograde P waves, sometimes are overlapped in the QRS waves. The RP interval is lower than 200 ms. Treatment of a junctional rhythm primarily depends on the underlying cause of the rhythm. If the heart rate is within 60 to 100 beats per min, accelerated junctional rhythm is considered. Aetiology-based treatment is recommended.

Diagnosis of Graves’ disease is now usually based on anti-TSH-receptor antibody assays and thyroid ultrasonography. The patient’s electrocardiography was consistent with accelerated junctional rhythm. Treatment of Graves’ disease is fundamental.

TSHR-Ab is a specific biomarker for Graves’ disease. In addition to thyroid function and TSHR-Ab determination, most clinicians would request thyroid ultrasound and less often isotope scanning. A color-flow or power Doppler examination characterizes vascular patterns and quantifies thyroid vascularity. Beta-adrenergic blockade is recommended in all suitable patients with Graves’ hyperthyroidism. The patient’s positive TSHR-Ab and ultrasound examination results were consistent with Graves’ disease. Moreover, the patient’s thyroid static imaging further proved the diagnosis of Graves’ disease. The patient was diagnosed with new-onset Graves’ disease. The ATD must be initiated. Thus, methimazole 20 mg/d was administered. The patient was combined with thyrotropic periodic paralysis, which was suitable for RAI. However, he refused this treatment method. The patient was combined with acute myocarditis, beta-blocker was administered.

Hypokalemia is present in most patients. Abnormal thyroid hormones like elevated T4, or elevated T3 and low TSH might be present. The thyroid uptake scan might show increased uptake. The goal for treatment is to supplement potassium quickly along with the reduction of thyroid hormones. Non-selective beta-blockers have been shown to improve neuromuscular symptoms by reducing the intracellular shift of phosphate and potassium. The patient was administered with potassium supplements, ATD and a beta-blocker, all of which met the treatment criteria.

The core principles of treatment in myocarditis are optimal care of arrhythmia and heart failure and, where supported by evidence, aetiology-targeted therapy. For patients with autoimmune diseases, treatment of primary disease is of vital importance. The patient did not have heart failure, and a beta-blocker was administered to treat his arrhythmia. The treatment of Graves’ disease is significant for his myocarditis.

For the present patient, thyroidectomy was not suitable. The patient had acute myocarditis and thyrotropic periodic paralysis, and RAI was more suitable for rapidly controlling the patient’s hyperthyroid state. Attempts were made to persuade the patient to accept RAI, but he and his family opted for treatment by medicine. Thus, in accordance with the guidelines and the endocrinologist’s suggestions, methimazole was administered, and the thyroid function was routinely checked. The patient was advised to accept radioactive iodine therapy if methimazole could not control his hyperthyroid state. The diagnosis and treatment of the diseases are further clarified in Table 3.

A limitation of the present case is that EMB was not performed. Current guidelines recommend EMB only in a limited number of clinical scenarios that do not include some common presentations of myocarditis, particularly pseudo-infarction[8]. The guidelines give the highest levels of recommendations for EMB in life-threatening antithyroid drugs, and thyroidectomy[15,16]. For the present patient, thyroidectomy was not suitable. The patient had acute myocarditis and thyrotropic periodic paralysis, and RAI was more suitable for rapidly controlling the patient’s hyperthyroid state. Attempts were made to persuade the patient to accept RAI, but he and his family opted for treatment by medicine. Thus, in accordance with the guidelines and the endocrinologist’s suggestions, methimazole was administered, and the thyroid function was routinely checked. The patient was advised to accept radioactive iodine therapy if methimazole could not control his hyperthyroid state. The diagnosis and treatment of the diseases are further clarified in Table 3.

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clinical manifestations[8]. The patient’s symptoms of myocarditis were atypical. Therefore, he met the indications for EMB according to the guidelines. Although the patient was advised to accept EMB, the patient still refused. EMB could have provided a definite diagnosis for the patient and been especially beneficial in defining the type of myocarditis. According to the latest guidelines[8], since CMR has a good correlation with EMB, the patient could be diagnosed with myocarditis according to CMR, and other diseases could be excluded. The main issue is that EMB can be beneficial in defining the type of myocarditis, in terms of being autoimmune or viral. However, the treatment of the patient was not primarily affected. According to the latest guidelines of myocarditis, conventional therapy is the same in all types of myocarditis. New treatment methods include anti-viral therapy or immunosuppressive therapy, but the patient did not show any sign of viral infection. Hence, anti-viral treatment was not necessary. The patient was diagnosed with Graves’ disease, and autoimmune myocarditis could not be excluded. Thus, the treatment of primary disease was of vital importance. The patient recovered quickly after his symptoms of hyperthyroidism were controlled. EMB was beneficial for the patient, but the patient did not accept this procedure. EMB would be better for diagnosis but would not have primarily affected this case. As such, the decision of the patient was ultimately accepted after failing to persuade him.

In the present case, the patient had an accelerated junctional rhythm, which is significantly rare in adults and is a manifestation of acute myocarditis. The etiology may be attributed to autoimmunity, and cardiologists should not ignore such arrhythmia. From the present patient, autoimmune diseases such as Graves’ disease may be attributed to autoimmunity, and cardiologists should not ignore such endocrine diseases.

CONCLUSION

Usually seen in young males, Graves’ disease can manifest as thyrotoxic periodic paralysis, in which sudden paralysis and extreme hypokalemia will be experienced. The correction of hypokalemia and hyperthyroidism will relieve the symptoms. The electrocardiograph of an accelerated junctional rhythm usually shows an absence of P waves and a heart rate within 60-100 rates per minute. Accelerated junctional rhythm is a manifestation of acute myocarditis. Clinicians should not ignore such endocrine diseases when facing patients with cardiac manifestations.

REFERENCES

Li MM et al. Graves’ disease presenting as myocarditis


CASE REPORT

Lingual nerve injury caused by laryngeal mask airway during percutaneous nephrolithotomy: A case report

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Abstract

BACKGROUND
Lingual nerve injury (LNI) is a rare complication following the use of laryngeal mask airway (LMA). The occurrence of this unexpected complication causes uncomfortable symptoms in patients and worsens their quality of life. We present an unusual case of LNI caused by the use of an LMA in percutaneous nephrolithotomy (PCNL).

CASE SUMMARY
A 49-year-old man presented to our hospital with a 3-year history of intermittent left lower back pain. Abdominal computed tomography showed a 25 mm × 20 mm stone in the left renal pelvis. PCNL surgery using LMA was performed to remove the renal stone. The patient reported numbness on the tip of his tongue after the operation, but there were no signs of swelling or trauma. The patient was diagnosed with LNI after other possible causes were ruled out. The symptom of numbness eventually improved after conservative medical therapy for 1 wk. The patient completely recovered 3 wk after surgery.

CONCLUSION
This is the first case report describing LNI with the use of LMA in PCNL. In our case, an inappropriate LMA size, intraoperative movement, and a specific surgical position might be potential causes of this rare complication.

Key Words: Lingual nerve injury; Laryngeal mask airway; Percutaneous nephrolithotomy; Case report

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Core Tip: This is the case report of a 49-year-old male patient who reported numbness on the tip of his tongue after a percutaneous nephrolithotomy surgery. A diagnosis of lingual nerve injury caused by laryngeal mask airway (LMA) was made after ruling out other possible causes. The occurrence of this rare complication may be associated with several factors, such as inappropriate LMA size, intraoperative movement, and special surgical position. The patient completely recovered after 3 wk of conservative medical therapy.

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INTRODUCTION
Lingual nerve injury (LNI) is an extremely rare complication after general anesthesia and is mostly related to the use of airway devices[1]. LNI commonly manifests as paresthesia, including unilateral or bilateral numbness, altered taste sensation, and loss of gustatory function. Compression of the surrounding tissues due to overinflation of the mask cuff is considered to be the most likely cause of LNI[2]. We report a rare case of LNI after laryngeal mask airway (LMA) use in a kidney stone patient and present a literature review. The patient underwent percutaneous nephrolithotomy (PCNL) to remove stones from the left kidney and reported tongue tip numbness after the surgery. The numbness symptom was thought to be associated with the use of LMA and disappeared after 5 wk of drug therapy.

CASE PRESENTATION

Chief complaints
A 49-year-old male patient was admitted to our clinic with a chief complaint of left lower back pain.

History of present illness
The patient experienced intermittent lower back pain on the left side that worsened when tired. He had a 3-year history of this symptom.

History of past illness
The patient had a history of hypertension that was well controlled by medicine.

Personal and family history
The patient was a heavy smoker and smoked at least two packs of cigarettes a day for 30 years. His family history did not reveal anything of significance to the present illness.

Physical examination
The patient’s vital signs were within normal limits. Physical examination revealed percussion tenderness over the left kidney region.

Laboratory examinations
Routine urinalysis revealed a white blood cell count of 61/µL, and the result of the urine culture was negative.

Imaging examinations
An abdominal computed tomography scan showed a 25 mm × 20 mm stone in the left renal pelvis (Figure 1).
The patient underwent PCNL in a prone position to remove left renal calculi. The operation was performed by a surgeon who had previously performed thousands of PCNL surgeries. The preoperative airway evaluation was normal and revealed a Mallampati class I and a full set of normally arranged teeth. After intravenous anesthesia induction, a size 4 LMA (Shanyou Ltd., Hangzhou, Zhejiang Province, China) was successfully inserted and fixed on the first attempt. Continuous intravenous infusion of propofol (6-10 mg/kg/h) was used to maintain anesthesia. Then, the patient was turned over to the prone position, and his head was held in a right-side position during the entire surgical procedure.

The surgery was uneventful and lasted for 80 min. The LMA was removed successfully in the recovery room. The patient found numbness at the tip of his tongue when he returned to the ward. There was no marked swelling, hematoma, or sign of trauma to the tongue or oral cavity (Figure 2). A brain magnetic resonance imaging scan was performed on day 2 postoperatively and showed no abnormalities. We consulted with a neurologist, and no organic disease was found.

**FINAL DIAGNOSIS**

According to the patient’s presentation and clinical examinations, the most likely diagnosis was LNI secondary to compression by LMA.

**TREATMENT**

To the best of our clinical judgment, nerve injury in the patient was mild (Sunderland grade I) in severity, and conservative treatment was elected. Neurotrophic drugs could promote the biosynthesis of phospholipids and proteins, which are beneficial for neurological recovery. The patient was treated by oral administration of methylcobalamin and vitamin B1. We communicated with the patient extensively to relieve his anxiety.

**OUTCOME AND FOLLOW-UP**

The numbness symptom gradually improved after 1 wk. The patient was subsequently discharged to his home and received weekly telephone calls for follow-up. The numbness resolved completely 3 wk after discharge.

**DISCUSSION**

Supraglottic airway devices, including classic LMA and other variants, are widely used in general anesthesia surgery. LNI following LMA is an extremely rare complication after general anesthesia. This unexpected complication can cause bothersome symptoms that worsen patients’ quality of life. A retrospective matched
case-control study showed that the incidence rate of LNI among patients receiving general anesthesia with airway devices is 0.066%[3]. We found 18 cases of lingual nerve injuries correlated with different LMAs over the last 20 years in the literature (Table 1). The symptoms of LNI appeared immediately after anesthesia to 24 h after surgery. Most patients recovered from their symptoms spontaneously within 6 mo.

The lingual nerve is distributed in the sublingual region, sublingual gland, and anterior two-thirds of the tongue, the latter of which is its main area. It provides taste and tactile sensations to the anterior two-thirds of the tongue through its branches. This nerve originates from the mandibular branch of the trigeminal nerve and carries taste fibers from the chorda tympani. It is superficially located on the distal medial side of the mandibular third molar, with only a thin layer of mucosal tissue covering the surface. It is in front of the inferior alveolar nerve, arching downward along the outside of the hyoglossus muscle to the tongue's inferior surface, which lies directly under the mucosa of the tongue[4]. It is vulnerable to injury when the lingual nerve is located in these superficial positions. LNI presents as paresthesia in the anterior two-thirds of the tongue, including unilateral numbness, altered taste sensation, and loss of gustatory function. Due to the particularity of the lingual nerve distribution area, patients with LNI may also have difficulty chewing and speaking, causing social and psychological complications. It is necessary to differentiate LNI from glossopharyngeal nerve injury, the primary symptom of which is sensory disturbance at the rear of the tongue.

Several risk factors for LNI after general anesthesia have been reported in the literature, including the selection of a small laryngeal mask, the use of nitrous oxide (N\textsubscript{2}O), and mechanical forces generated by surgical manipulation[1,2,5]. It is necessary to consider the shape and size of the patient's oropharynx when selecting the LMA size. Using a larger mask in which the cuff is not visible in the back of the mouth and the cuff volume is inflated to the minimum necessary level seems to be an appropriate technique[1]. Using an inappropriate LMA size prevents satisfactory sealing, and too much gas is injected into the mask cuff. The lingual nerve might be compressed and injured by the overfilled cuff. Because of the special physical properties of N\textsubscript{2}O, it diffuses into the cuff and causes the cuff pressure to increase gradually. It is important to monitor the cuff pressure if N\textsubscript{2}O is used during surgery. The traction forces resulting from surgical procedures on the head and neck regions place additional stress on the tongue tissue through the airway device, potentially causing LNI.

The diagnosis of LNI mainly depends on a detailed invasive manipulation history and clinical symptoms and signs. Basic neurological assessments such as light touch, pin prick, and two-point discrimination may assist in LNI diagnosis and monitoring. Determining the grade of nerve injury before treatment is the key to successful treatment. Similar to most lingual nerve injuries following LMA, the injury that our patient experienced was considered a grade I injury according to the Sunderland classification[6]. Conservative medication is the most commonly used treatment for LNI following LMA. After 3 wk of drug therapy, the patient achieved complete remission of tongue tip numbness. Most patients fully recover within 4 wk, and no case of permanent nerve injury has been reported in the literature.

Several strategies are suggested to prevent this rare complication. It is vital to select LMA size in the context of not only sex but also other factors, such as oropharynx space, physical stature, and body mass index. The LMA should be inserted gently and carefully fixed. Attention should be given to whether the LMA is displaced when moving the patient; if so, the LMA should be adjusted in time. During the operation,
<table>
<thead>
<tr>
<th>Ref.</th>
<th>Age (yr)</th>
<th>Gender</th>
<th>Weight (kg)</th>
<th>Position</th>
<th>Size of device (min)</th>
<th>N₂O used</th>
<th>Location</th>
<th>Symptoms</th>
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<td>Taste disturbance</td>
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<td>3</td>
<td>120</td>
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<td>Bilateral</td>
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<td>1 h</td>
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<tr>
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<td>NR</td>
<td>Supine</td>
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<td>Numbness; Taste disturbance</td>
<td>Few hours</td>
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<td>150</td>
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<td>75</td>
<td>Prone</td>
<td>4</td>
<td>80</td>
<td>No</td>
<td>Unilateral</td>
<td>Numbness</td>
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<td>LMA Supreme</td>
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<td>Numbness</td>
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<td>Conservative</td>
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<tr>
<td>I-gel</td>
<td>Renes et al[16], 2011</td>
<td>69</td>
<td>M</td>
<td>78</td>
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<td>Numbness</td>
<td>24 h</td>
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<td>NR</td>
<td>Unilateral</td>
<td>Numbness</td>
<td>Few hours</td>
<td>Conservative</td>
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</table>

N₂O: Nitrous oxide; LMA: Laryngeal mask airway; F: Female; M: Male; NR: Not recorded; PACU: Post-anaesthesia care unit.
the cuff pressure must be monitored to keep it less than 44 mmHg[7]. If the operation time is long, the LMA should be deflated for 2 min every 1-2 h to improve regional circulation. However, before deflating the LMA, it is necessary to clean up the pharynx secretions and ensure airway patency.

PCNL is an effective surgical method for the treatment of kidney stones. The prone position has been the most widely used position in PCNL surgery, but low comfort and complications are the major drawbacks of this special position. Anesthesia-related complications after prone positioning are associated with many factors, such as changes in heart functions, malposition of airway devices, and excessive movement of the head and neck. To the best of our knowledge, this is the first report describing LNI caused by using an LMA during PCNL. We suspect that there are three possible causes associated with this infrequent complication. First, the size 4 LMA selected may not have been suitable for the patient. For a better sealing effect, excessive gas was injected into the cuff, causing the cuff to excessively expand and compress surrounding tissues. Second, the patient was passively moved from the supine position to the prone position under general anesthesia for surgery. Prolonged retraction of the nerve from positional changes of the body and head is a potential cause of LNI. Third, due to the influence of gravity, the pressure of the pharynx on the LMA in the prone position is greater than that in the supine position. This causes additional inflation of the cuff, which consequently leads to compression of the lingual nerve.

CONCLUSION

As LMA is widely used during general anesthesia, it is necessary to be aware of this potential rare complication and try to avoid it. In addition to inappropriate LMA size, intraoperative movement and special surgical position may increase the potential for LNI. The nerve injury symptoms usually disappear on their own, and no surgery is needed. Telephone follow-up is necessary, and patients should be reassured that they can recover from their injury completely in a short period.

REFERENCES


14 **Dhillon SS**, O’Leary K. Lingual nerve paralysis after endobronchial ultrasound utilizing laryngeal mask airway. *J Bronchology Interv Pulmonol* 2012; **19**: 72-74 [PMID: 23207270 DOI: 10.1097/LBR.0b013e318231414a]


Ventricular fibrillation and sudden cardiac arrest in apical hypertrophic cardiomyopathy: Two case reports

Yae Min Park, Albert Youngwoo Jang, Wook-Jin Chung, Seung Hwan Han, Christopher Semsarian, In Suck Choi

Abstract

BACKGROUND
Apical hypertrophic cardiomyopathy (HCM) is considered to have a benign prognosis in terms of cardiovascular mortality. This serial case report aimed to raise awareness of ventricular fibrillation (VF) and sudden cardiac death (SCD) in apical HCM.

CASE SUMMARY
Here we describe two rare cases of apical HCM that presented with documented VF and sudden cardiac collapse. These patients were previously not recommended for primary prevention using implantable cardioverter-defibrillator (ICD) therapy based on current guidelines. However, both received ICD therapy for the secondary prevention of SCD.

CONCLUSION
These cases illustrate serious complications including VF and aborted sudden cardiac arrest in apical HCM patients who are initially not candidates for primary prevention using ICD implantation based on current guidelines.

Key Words: Apical hypertrophic cardiomyopathy; Ventricular fibrillation; Implantable cardioverter-defibrillator; Case report

Core Tip: Apical hypertrophic cardiomyopathy (HCM) is a rare form of non-obstructive
HCM. It has a benign prognosis in terms of cardiovascular mortality. Here we describe two rare cases of apical HCM that presented as documented ventricular fibrillation (VF) and sudden cardiac collapse. Although apical HCM has a typically benign prognosis, clinicians must consider that VF can occur and lead to sudden cardiac arrest.

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INTRODUCTION

Apical hypertrophic cardiomyopathy (HCM) is considered clinically benign, with an estimated annual mortality rate of 0-0.1% and no reports of sudden cardiac death (SCD) during follow-up[1]. Case reports of patients developing ventricular tachycardia (VT), mainly due to an apical aneurysmal segment and sudden cardiac collapse, have been reported[2,3]. However, documented ventricular fibrillation (VF) with sudden cardiac arrest without apical aneurysm is extremely rare in patients with apical HCM.

Here we report two cases of apical HCM who presented with documented VF and sudden cardiac collapse who were previously not candidates for implantable cardioverter-defibrillator (ICD) therapy based on current guidelines.

CASE PRESENTATION

Chief complaints
Case 1: A 41-year-old man was brought to the emergency department after sudden cardiac collapse.
Case 2: A 29-year-old man was brought to the emergency department after sudden cardiac collapse.

History of present illness
Case 1: The patient had known apical HCM; however, he did not receive regular follow-up or management. He presented to the emergency department after sudden cardiac collapse during sleep.
Case 2: The patient had known apical HCM, and he had received regular follow-up at the cardiology department for apical HCM and paroxysmal atrial fibrillation (AF) over the preceding 5 years. He was brought to the emergency department after sudden cardiac collapse while working.

History of past illness
Case 1: The patient visited the cardiology outpatient department with palpitations and chest discomfort 3 years prior. Echocardiography at that time revealed apical HCM (18.7 mm thickness at the apex) with a normal left ventricular ejection fraction (LVEF; 58%) and diastolic relaxation impairment with an elevated e/e’ ratio of 22 and enlarged left atrium (51 mm) (Figure 1A). Holter monitoring did not demonstrate relevant arrhythmia, and no paradoxical blood pressure response was observed during the exercise tolerance test at that time. He was prescribed a β-blocker; however, the patient did not complete follow-up.
Case 2: The patient was diagnosed with apical HCM and paroxysmal AF 5 years prior when he presented with chest discomfort. Echocardiography revealed apical HCM (20.1 mm thickness at the apex) without apical aneurysm and a normal LVEF (59%) and a diastolic relaxation impairment with an elevated e/e’ ratio of 16 and an enlarged left atrium (57 mm) (Figure 1B). Over the preceding 5 years, he had received regular follow-up at the cardiology department and was treated with aspirin and amiodarone.
Personal and family history
Cases 1 and 2: Family history was unremarkable for structural heart disease, syncope, or SCD.

Physical examination
Cases 1 and 2: On admission, the patients were unconscious and pulseless.

Laboratory examinations
Case 1: The patient’s troponin I level (0.36 mg/mL) was within the normal range, while the CK-MB level (23.42 ng/mL) was remarkably elevated. His electrolyte levels were within the normal ranges.
Case 2: Troponin I level (1.78 mg/mL) and CK-MB level (9.77 ng/mL) were slightly elevated. His electrolyte levels were within the normal ranges.

Imaging examinations
Case 1: Initial electrocardiography (ECG) revealed VF (Figure 2A). Biphasic 200-J defibrillation restored sinus rhythm, and his cardiopulmonary function recovered without neurologic sequelae. ECG performed after stabilization showed sinus rhythm with deep T-wave inversion (Figure 2B). Coronary angiography revealed no significant stenosis in the epicardial coronary arteries.
Case 2: Initial ECG revealed VF (Figure 3A). Biphasic 150-J defibrillation restored sinus rhythm, and his cardiopulmonary function recovered without neurologic sequelae. His ECG after stabilization was similar to that before the cardiac collapse, showing sinus rhythm with a tri-fascicular block and T-wave inversion (Figure 3B). Coronary angiography revealed no significant stenosis in the epicardial coronary arteries.

FINAL DIAGNOSIS
Cases 1 and 2: The final diagnosis was VF and aborted sudden cardiac arrest in the apical HCM.

TREATMENT
Case 1: The patient was treated with carvedilol 6.25 mg twice daily and underwent ICD implantation for the secondary prevention of SCD.
Case 2: The patient underwent ICD implantation for the secondary prevention of SCD while maintaining his current medications.
Figure 2 The initial rhythm strip and electrocardiogram in case 1. A: The initial electrocardiogram (ECG) revealed ventricular fibrillation; B: The ECG after stabilization showed sinus rhythm with deep T-wave inversion.

OUTCOME AND FOLLOW-UP

Case 1: The patient was discharged uneventfully and remained free of VF for 3 years.

Case 2: The patient was subsequently discharged uneventfully. He experienced an inappropriate shock due to paroxysmal AF; however, he has remained free of VF for 10 years.

DISCUSSION

Apical HCM is considered clinically benign with an estimated annual mortality rate of 0-0.1% with no reports of SCD during follow-up[1]. Case reports have detailed patients developing VT mainly due to an apical aneurysmal segment and sudden cardiac collapse[2-5]. However, documented VF with sudden cardiac arrest without apical aneurysm is extremely rare in patients with apical HCM.

ICD implantation is recommended in HCM patients at high risk of SCD based on current guidelines[6,7]. Neither of our patients had any established risk factors, risk modifiers, or high-risk features. Neither met the criteria for ICD implantation according to the current guidelines. However, VF and sudden cardiac arrest occurred later despite the apical HCM, which is known to be clinically benign.

Although the risk factors for VF and SCD in apical HCM are rarely evaluated because of its significantly low incidence, several parameters affecting poor outcomes were reported previously. Patients of advanced age with hypertension, diabetes, or baseline AF have poor prognosis or decreased survival[2,8]. Patients with apical HCM and poor clinical outcomes have more advanced diastolic dysfunction, increased left atrial volume, reduced myocardial contraction/relaxation properties, and increased
Figure 3 The initial rhythm strip and electrocardiogram in case 2. A: The initial electrocardiogram (ECG) revealed ventricular fibrillation; B: The ECG after stabilization was similar to that before cardiac collapse showing sinus rhythm with a trifascicular block and T-wave inversion.

LV filling pressure at presentation[2]. Impaired LV diastolic function is a proposed mechanism for progressive left atrial enlargement and subsequent AF development[1, 9]. Apical aneurysm and late gadolinium enhancement extent on cardiac magnetic resonance imaging (MRI) are also independent predictors of a poor outcome[10]. However, the association between VF and these parameters has not been evaluated until now.

The hypertrophied LV apex could predispose the myocardium to ischemia due to a limited coronary blood flow reserve. The foci of cellular disarray throughout the hypertrophied LV wall might impair the transmission of normal electrophysiological impulses and predispose that region to a disordered pattern of depolarization and repolarization, thereby serving as an arrhythmogenic substrate[11]. Our second patient had a trifascicular block and inverted T-waves on ECG in addition to LV hypertrophy prior to VF development. These findings indicate that adverse electrical remodeling had already progressed in the myocardium and may have predisposed the patient to developing VF.

CONCLUSION

Although apical HCM has a typically benign prognosis, VF can occur and lead to sudden cardiac arrest. Our case reports support the concept that clinical outcomes in patients with apical HCM are not always as benign as previously thought. We should be aware of serious complications, including VF, and aborted sudden cardiac arrest in apical HCM patients who are initially not candidates for primary prevention ICD implantation based on current guidelines. Risk factors such as diastolic dysfunction, late gadolinium enhancement on cardiac MRI, or electrical remodeling on ECG should be evaluated further for risk stratification for VF and SCD in cases of apical HCM.
REFERENCES


Rhizopus microsporus lung infection in an immunocompetent patient successfully treated with amphotericin B: A case report

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Abstract

BACKGROUND
Rhizopus microsporus (R. microsporus) lung infection is an invasive fungal disease with high mortality that is increasingly common in immunocompromised patients. However, it is very rare in immunocompetent patients. Here, we present the case of a 19-year-old girl who developed R. microsporus lung infection without any known immunodeficiency.

CASE SUMMARY
The patient presented to our hospital because of hemoptysis and irritative cough without expectoration. She was first treated for community-acquired pneumonia until the detection of R. microsporus in bronchoalveolar lavage fluid by metagenomics next-generation sequencing (mNGS). After a combination therapy of intravenous inhalation and local airway perfusion of amphotericin B, she eventually recovered, with significant absorption of lung infections.

CONCLUSION
Early diagnosis and treatment are very important for pulmonary mucormycosis. Compared to fungal culture, mNGS is a relatively precise and convenient method to obtain pathogenic results. A combination therapy of intravenous inhalation and local airway perfusion of amphotericin B may be a promising strategy for the treatment of pulmonary mucormycosis in the future.

Key Words: Rhizopus microsporus; Immunocompetent patient; Pulmonary mucormycosis; Amphotericin B; Case report

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A 19-year-old girl was admitted on January 26, 2021 because of hemoptysis for 15 d. The girl started coughing blood for no apparent reason 15 d ago, and the maximum amount of hemoptysis was approximately 100 mL at one time. She also had irritating coughs without expectoration. The patient did not complain of other symptoms, including fever, chest pain, respiration difficulties, headache, or vomiting. Seven days before admission, she received intravenous cefotaxime (2 g, twice daily) and an unknown hemostatic medication for 7 d at a local hospital.

### History of past illness
The patient’s history was unremarkable, without previous contact with infectious agents.

### Personal and family history
The patient was living on campus and had no contact with animals or fungus exposure, with no history of smoking or drinking, denying a history of drug abuse.

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**Core Tip:** We present the case of a 19-year-old girl who developed *Rhizopus microsporus* (*R. microsporus*) lung infection without any known immunodeficiency. Due to the early detection of the *R. microsporus* in bronchoalveolar lavage fluid by metagenomics next generation sequencing, promptly anti-mucor therapy was started. A new attempt of a combination therapy of intravenous, inhalation, and local airway perfusion of amphotericin B was then performed, which showed a good therapeutic effect.

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**Introduction**

Due to advancements in the diagnosis and treatment of immunosuppressed diseases, an increasing number of clinicians are aware of *Rhizopus microsporus* (*R. microsporus*) lung infection in immunocompromised patients. *Rhizopus* belongs to the zygomycotina and is also the most common species that causes pulmonary mucormycosis[1,2]. *R. microsporus* lung infection is more common in people with immunodeficiency diseases, especially in diabetic patients with poor blood sugar control and patients with hematological malignancies. It is also common in patients using immunosuppressive agents after transplantation to prevent transplant rejection. If not treated in time, the mortality rate is as high as 70%-100%[3]. A retrospective study in 2019 revealed 851 patients with mucormycosis from 2000 to 2017[4]. In that study, diabetes was the most common underlying disease (340/851, 40%), and pulmonary mucormycosis (172/851, 20%) was the third most common clinical manifestation. A total of 447 (53%) cases of certain Mucorales organisms were identified by culture, and *R. microsporus* (213/447, 48%) was the most common pathogen.

Mucormycosis in immunocompetent patients is rare and is easily ignored by clinicians. In the current study, we report a rare case of pulmonary *R. microsporus* infection in an immunocompetent young patient. Depending on the early pathological results via percutaneous lung puncture and pathogenic conclusions from metagenomics next-generation sequencing (mNGS), we avoid misdiagnosis and buy much time for the subsequent successful treatment of the patient.

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**Case presentation**

**Chief complaints**
Hemoptysis for 15 d.

**History of present illness**
A 19-year-old girl was admitted on January 26, 2021 because of hemoptysis for 15 d. The girl started coughing blood for no apparent reason 15 d ago, and the maximum amount of hemoptysis was approximately 100 mL at one time. She also had irritating coughs without expectoration. The patient did not complain of other symptoms, including fever, chest pain, respiration difficulties, headache, or vomiting. Seven days before admission, she received intravenous cefotaxime (2 g, twice daily) and an unknown hemostatic medication for 7 d at a local hospital.

**History of past illness**
The patient’s history was unremarkable, without previous contact with infectious agents.

**Personal and family history**
The patient was living on campus and had no contact with animals or fungus exposure, with no history of smoking or drinking, denying a history of drug abuse.
There was no history of infectious disease in her family.

**Physical examination**

On admission, the patient’s temperature was 36.5 °C, pulse rate was 86/min, respiration rate was 20/min, and blood pressure was 92/68 mmHg. Except for diminished vocal fremitus, dulls on percussion, and moist rales being found in her lower right lung, no other remarkable abnormalities were observed.

**Laboratory examinations**

Relevant laboratory examinations were as follows: White blood cell count: 12.74 × 10^9/L (reference interval: 4.0-10.0 × 10^9/L); hemoglobin: 82 g/L (115-150 g/L); neutrophils%: 53% (50%-70%); lymphocytes%: 22% (20%-50%); hypersensitive C-reactive protein: 36.1 mg/L (< 4 mg/L); and D-dimer: 12.94 mg/L (< 0.5 µg/mL). No obvious abnormalities were found on an electrocardiogram or for the rheumatic immune system, routine urine and liver function, electrolytes, renal function, HbAlc, and HIV tests.

According to the China Community Acquired Pneumonia Treatment Guidelines (2016), the patient was given intravenous piperacillin-tazobactam (4.5 g, 3 times daily). No abnormalities were found in sputum culture or smear. The serum (1-3)-beta-D-glucan (G test) and galactomannan assays (GM test) were negative. Percutaneous lung biopsy with the right lower lobe was performed 2 d after admission, and positive staining of hexamine silver indicated pulmonary mycosis with granulomatous inflammation and necrosis. The histopathological features of thick and scattered hyphae were in line with mucormycosis (Figure 1). PCR test of tuberculosis was negative.

Three days after admission, the patient received electronic bronchoscopy. Purulent secretions and a swollen mucosa were observed in the basal segment of the right lower lobe (Figure 2A). An analysis of bronchoalveolar lavage fluid (BALF) was quickly performed by mNGS (VISION MEDICALS, Wuhan, Hubei Province, China). The mNGS results were obtained after 2 d, suggesting *Rhizopus* microspore infection. No bacteria, viruses, mycoplasma, chlamydia, *Mycobacterium tuberculosis* complex, or other pathogenic microorganisms were detected. The G test and GM test of BALF were negative. A diagnosis of *Rhizopus* microspore lung infection was made.

**Imaging examinations**

Chest computed tomography (CT) suggested bilateral pulmonary infection with cavitation involving the pulmonary right lower lobe (Figure 3A).

**FINAL DIAGNOSIS**

*Rhizopus* microspore lung infection.

**TREATMENT**

Surgical resection is indeed one of the important therapies to deal with *Rhizopus* infection. We made consultation with the thoracic experts. Considering that the operation may be traumatic, and the patient’s parents disagreed with the lobectomy. Therefore, we started medical treatment. According to the Chinese guidelines for the diagnosis and treatment of invasive fungal disease in patients with hematological disorders and cancers (the 6th revision), amphotericin B (AmB) for injection (5 mg intravenous daily, then gradually increased to 120 mg daily) was administered as antifungal treatment 5 d after admission, and intravenous antibiotics were stopped. As a result, after 12 d of antifungal treatment (intravenous AmB for 120 mg daily), the hemoptysis and cough of the patient were suspended, and the white blood cell count decreased to 8.26 × 10^9/L (reference interval: 4.0-10.0 × 10^9/L). Although lung symptoms seemed improved, the patient began to experience severe nausea and vomiting with hypokalemia. Considering both the effectiveness and safety, a treatment combining intravenous and inhaled AmB was performed. The intravenous dose of AmB was adjusted to 60 mg daily, combined with inhalation of AmB 10 mg twice a day. After administering antiemetic therapy and potassium supplementation at the same time, the patient’s digestive symptoms gradually improved.

On March 3, 2021, after 30 d of antifungal treatment, chest CT showed a decrease in lung inflammation and an absorption of cavitation in the right lower lobe (Figure 3B).
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Figure 1 Histology. A: A needle biopsy of the pathological tissue of the right lower lung showed granulomatous inflammation, necrosis, and inflammatory cells (hematoxylin-eosin staining, 100 ×); B and C: The hyphae indicated mucormycosis that lacked regular septa and was paucisepitate, marked with white arrows by periodic acid-Schiff fungal staining (B, 400 ×) and hexamine silver staining (400 ×, C).

Figure 2 Images in electronic bronchoscopy. A: The anterior basal branch was swollen, accompanied by a deformed and narrowed lumen of the anterior basal branch; B: Perfusion with amphotericin B (10 mg dissolved in 10 mL saline) on the anterior basal segment of the right lower lobe was performed through a microtube in an electronic bronchoscope. Perfusion with AmB (10 mg dissolved in 10 mL saline) on the basal segment of the right lower lobe was then tried three times through a microtube in an electronic bronchoscope on March 4, March 11, and March 21 (Figure 2B). A slight improvement of the swollen mucosa of the right lower lobe was observed after the treatment, and no secretions were found in the local airway. Prior to discharge, the patient received an alternative therapy to posaconazole oral solution (400 mg twice daily) according to a Chinese expert consensus on the clinical use of posaconazole.

OUTCOME AND FOLLOW-UP
Significant absorption of lung infections was observed at the chest CT follow-up on April 15, 2021 (+ 80 d) (Figure 3C).

DISCUSSION
R. microsporus lung infection is rare in immunocompetent patients and seldom reported[5-11]. In a study in 2009, 24 patients with proven or probable pulmonary mucormycosis at Peking Union Medical College Hospital from January 2005 to December 2018 were retrospectively analyzed, and seven patients (29.2%) had no obvious predisposing risk factors[12]. Although some of these patients had normal immune function, they shared an environmental exposure history with mucor spores such as decaying food, soil, and animal excrement[1], which might be the diagnostic basis for pulmonary mucormycosis. In contrast, in the case that we reported, the patient was a 19-year-old young female student who usually lived on campus without any underlying diseases, weakened immune function, or mucor-related environmental exposure history. The patient was treated at another hospital for a period of time,
accompanies a prolonged course and nonabsorbable lung lesions. Invasive examinations, such as percutaneous lung puncture and electronic bronchoscopy, were tried promptly. The pathologic findings of mucor hyphae and the mNGS results both resulted in the conclusion of *R. microsporus* pulmonary infection. Commonly, pulmonary mucor infection lacks specificity in imaging and is variable. Techniques to determine infection by Aspergillus or Mucor based on the histopathological features of hyphae are not completely reliable\[13\]. Other clinical clues that suggest pulmonary mucormycosis rather than aspergillosis include concurrent sinus, previous voriconazole therapy, the presence of more than ten lesions, and the presence of pleural effusion for imaging findings\[14\]. None of the above abnormal manifestations were observed in this patient. On chest radiography, lobar and segmental consolidation is the most common imaging finding, and imaging in some patients shows a multilobar distribution\[15\], which is consistent with our case.

Prompt initiation of appropriate therapy is critical for patients with pulmonary mucomycosis\[16\]. A study also found that early intervention may lead to better outcomes\[17\]. Although histopathology will probably remain the gold standard for the diagnosis of mucormycosis\[18,19\], obtaining a biopsy specimen is not always feasible in most vulnerable populations. Moreover, the distinction between aspergillosis and scedosporiosis and between aspergillosis and fusariosis and certain mucormycosis from tissue sections may be difficult or impossible\[20\]. However, the clinical distinction between aspergillosis and mucormycosis is crucial since there is an increased incidence of mucormycosis in patients treated with voriconazole for suspected aspergillosis\[21\]. In recent years, mNGS methods have been used to try to improve the detection and identification of pathogens and have become a topic of concern as routine pathogen identification tools\[22\]. In our case, the identification of *Rhizopus* microspores in BALF by mNGS was achieved in the early stage. Considering that antibiotic treatment was ineffective in this patient and mNGS did not indicate other bacterial or viral infections, we made a final diagnosis of lung infection of *Rhizopus* microspores for the young immunocompetent patient. Unfortunately, we failed to obtain positive culture results from lung puncture specimens, which might be related to insufficient amounts or redundant necrotic contents of the specimens. However, early anti-mucor treatment was started immediately, which eventually led to an overall good therapeutic effect.

AmB is commonly used for the treatment of mucormycosis of the lung, and other optional drugs include posaconazole and isaconazole\[17,23\]. In addition to intravenous use of AmB, inhalation of AmB has been used in the clinic\[24\] and has the
advantages of high local concentration and low systemic side effects. For the application of AmB in the local airway through bronchoscopy, there is still a lack of clinical reports. We initiated treatment with AmB in the early stage, with a combination therapeutic strategy of intravenous inhalation and local airway perfusion, followed by sequential posaconazole oral administration, which eventually brought about a satisfactory therapeutic effect with the absorption of lung lesions. However, there is not enough evidence for perfusion by AmB through the local airway. The disadvantage is that it is limited by the patient's conditions and technical conditions of the medical team, and the patient is required to treat through bronchoscopy repeatedly, which means the requirement of a certain degree of compliance. To date, perfusion with AmB in the local airway might be safe and feasible, accompanied by small adverse effects. It can be used in combination, alternately or sequentially, with intravenous and inhalation therapy, although the prognostic efficacy needs further follow-up.

CONCLUSION

*R. microsporus* lung infection in immunocompetent patients is rare, which reminds clinicians to be alert to the potential risk of *Rhizopus* infection in these patients. Considering the high mortality rate of the disease, early diagnosis and treatment are very important for the prognosis of patients. In our clinical practice, a combination strategy of intravenous inhalation and local airway perfusion of AmB may be a new strategy for the treatment of pulmonary mucormycosis.

REFERENCES

Chen L et al. R. microsporus infection in an IC patient


17 van Burik JA, Hare RS, Solomon HF, Corrado ML, Kontoyiannis DP. Posaconazole is effective as salvage therapy in zygomycosis: a retrospective summary of 91 cases. *Clin Infect Dis* 2006; 42: e61-e65 [PMID: 1651748 DOI: 10.1086/500212]


Spermatocytic tumor: A rare case report

Mei-Ling Hao, Chun-Hui Li

Abstract

BACKGROUND
Spermatocytic tumor is a rare, malignant neoplasm of the testes. Since the prognosis for this tumor type is favorable, accurate diagnosis and differentiation from other malignant testicular neoplasms (classic seminoma and lymphoma) are crucial. To add to the existing literature on the diagnosis of spermatocytic tumor, herein we report the detailed clinical and histopathologic findings for a case that we encountered.

CASE SUMMARY
A 60-year-old Chinese man presented with a solid mass in the right scrotum. The mass was surgically removed and spermatocytic tumor was diagnosed. On microscopy, the tumor cells displayed an unusual arrangement in lobules, presenting a pseudo-glandular appearance. To summarize and compare the diagnostic features of this tumor and those of the differential diagnoses, we report our case findings and those mentioned in the literature for various testicular tumors. Although imaging methods can detect masses early in development, their diagnostic capabilities are limited. Biopsy, histopathology, and immunohistochemistry are necessary for confirmatory diagnosis.

CONCLUSION
It is important to identify and review the key diagnostic features of spermatocytic tumor.

Key Words: Spermatocytic tumor; Germ cell tumor; Immunohistochemistry; Pseudo-glandular; Case report
this disease is not comprehensive enough. Here we report a case of spermatocytic tumor, emphasizing the morphological features of spermatocytic tumor and the key points of differentiation from classic seminoma and lymphoma, so as to avoid misdiagnosis.

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**INTRODUCTION**

Spermatocytic tumor is a rare malignancy that accounts for 0.61% of testicular germ cell tumors[1]. Tumor development is independent of ethnicity and a history of cryptorchidism. Older men with an average age of 52 years are often the most affected [2]. At present, as spermatocytic tumors are extremely rare, there is a paucity of data for clinicians and pathologists to make differential diagnosis. Herein, we present a case of spermatocytic tumor, and review and consult the relevant literature. We summarize the morphological characteristics of spermatocytoma, hoping to provide clinicians and pathologists with more reliable diagnostic data and diagnostic ideas to help them serve patients better, reduce patients' pain, and avoid unnecessary, if not harmful, treatments.

**CASE PRESENTATION**

**Chief complaints**

A 60-year-old Chinese male farmer presented with a 3-mo history of right scrotal enlargement.

**History of present illness**

The patient presented with right scrotal enlargement and had no scrotal tenderness, chills, fever, or other discomfort. No abnormality of the left testis, epididymis, or spermatic cord was discerned. The patient did not self-medicate or seek alternative therapies. He reported no lumbar or abdominal pain and no increased frequency, urgency, or pain associated with urination, but had a slight weight loss.

**History of past illness**

The patient had no history of trauma, tuberculosis, or other relevant infectious disease.

**Personal and family history**

The patient denied any family history.

**Physical examination**

A 4 cm × 5 cm, slightly moveable, solid mass was palpated in the right scrotum, which dropped and was pale in color. No normal testicular or epididymal structures were palpated in the affected testis. No abnormality of the left testis, epididymis, or spermatic cord was discerned.

**Laboratory examinations**

The results such as routine hematological testing, blood sedimentation rate, vascular endothelial growth factor, human chorionic gonadotropin (HCG), serum carbohydrate antigen (CA)199, CA125, CA153, alpha-fetoprotein (AFP), thymidine kinase 1, and carcinoembryonic antigen (CEA) were normal.

**Imaging examinations**

Within 1 wk from presentation, the patient underwent scrotal ultrasound showing a 4.5 cm × 2.7 cm × 3.7 cm oval-shaped hypoechoic mass, with uneven internal
echogenicity in the right testicle (Figure 1A). Color Doppler showed scattered color blood flow signals within the lesion. Meanwhile, the patient underwent computed tomography (CT), which revealed an enlarged right testis, with indistinct contour, uneven density, and uniform nodular change (Figure 1B). No normal testicular or epididymal structures were palpated in the affected testis.

**FINAL DIAGNOSIS**

Spermatocytic tumor.

**TREATMENT**

The patient agreed and voluntarily underwent orchiectomy after 1 wk. The testicular specimens were fixed with 4% formalin for 24 h. Gross examination of the right testis identified a well-demarcated, solid, lobulated, expansile, yellow-gray nodule that was 3 cm × 3 cm × 2 cm in size. The mass contained multiple areas of myxoid degeneration. The postoperative specimens were made into wax blocks and observed after hematoxylin-eosin staining. Microscopy revealed a pseudo-glandular appearance of the tumor tissue, in which aggregates of tumor cells were arranged in an edematous stroma containing scant fibrous tissue (Figure 2A and C). The tumor cells formed diffuse sheets and nests (Figure 2B). Large, small, and medium-sized tumor cells were identified. The medium-sized cell type predominated and was characterized by eosinophilic cytoplasm, suggesting decreased glycogen, round nuclei, and a filamentous chromatin pattern similar to that of spermatocytes (Figure 2A and C). The small cells resembled lymphocytes and had no obvious cytoplasm (Figure 2A and C). The large mononuclear tumor cells had round, oval, or indented nuclei, with thick chromatin and multiple nucleoli (Figure 2A and C). No mitotic figures were observed. Mucinous degeneration was observed in some areas (Figure 2D). No lymphocyte infiltration or granulomatous inflammatory response was noted. Thereafter, we performed indirect immunohistochemical staining and used mouse anti-human primary antibody and rabbit anti-mouse secondary antibody. The results revealed: CD117(+) (Figure 3A), PLAP(-) (Figure 3B), CD30(-), HCG(-), SOX-2(-), CK(-), CD45RO(-), CD3(-), D2-40(-), CK8/18(-), AFP(-), and GPC3(-). The proliferation index (Ki-67) was 80%.

**OUTCOME AND FOLLOW-UP**

The patient only underwent orchiectomy without radiotherapy or chemotherapy. No recurrence or metastasis has been observed till date (12 mo post surgery).
**DISCUSSION**

The theory that spermatocytic tumor precursor cells originate in embryogenesis is disputed[3]. Some scholars[1] believe that spermatocytic tumor develops from mature cells such as pachytene spermatocytes. A recent study found that these tumor cells express reproductive cell-specific markers[4]. Morphological and immunohistochemical features of the tumor cells suggest derivation from spermatogonial stem cells [5].

Clinical symptoms associated with spermatocytic tumor include painless and slowly progressive testicular swelling[6,7] and low back pain in cases with a poor prognosis due to retroperitoneal metastasis. Spermatocytic tumors range from 2 cm to 20 cm in diameter, with an average diameter of 7 cm. Grossly, Hu et al[7] reported that these lobulated tumors have a homogeneous parenchymal appearance and most tumors were pink-tan, brown-tan, or white-tan and typically soft and lobulated, mucinous. They often contain areas of edema, hemorrhage, and necrosis. The majority of these
tumors are contained within the testis and do not breach the testicular sheath to infiltrate surrounding tissues[8-10]. The histomorphologic spectrum of spermatocytic tumor[11] is characterized by several points as follows: (1) At low magnification, the tumors are mainly multinodular or diffuse. All tumors have typical cell populations of three different sizes; (2) spermatocytic tumors often show edematous or myxoid degeneration with edematous stroma forming slit like structures and follicular like or irregular patterns, which are seen in some classical seminomas and rare in lymphomas; (3) tumor nodules focally show fibrous margins, and closely anastomosing connected island like structures; and (4) there is marked lymphocytic infiltration with granulomatous inflammation. It is important to recognize all the above characteristics, which will help the pathologist to diagnose and make a differential diagnosis[5]. Notably, its immunohistochemical markers are also very special. Although it belongs to germ cell tumors of the testis, it does not express useful markers in other germ cell tumors, such as OCT3/4, PLAP, AFP, HCG, and CD30. It often shows positive or weak positive expression of a key marker, CD117, and the proliferation index (Ki-67) tended to be very high. This adds challenges to our diagnostic work and requires pathologists to constantly expand their diagnostic ideas.

Spermatocytic tumor must be distinguished from classic and anaplastic seminoma. Classic seminoma is characterized by an earlier average age of onset (30 years)[2] and tumor cells that are often rich in glycogen with clear cytoplasm. The tumor cells form nests that are rimmed by fibrous tissue bands. Lymphocytic infiltration and a granulomatous inflammatory response are seen in the stroma. Classic seminoma tumor cells are positive for the immunohistochemical markers such as PLAP, CD117, vimentin, LDH, ferritin, and germ cell antigen, but usually negative for high molecular weight keratin. Spermatocytic tumor cells display obvious heteromorphism and increased mitotic rate, but do not stain positively for the abovementioned immunohistochemical markers[12]. Some experts proposed that classic seminoma and anaplastic seminoma are variants of the same tumor[13]. An elevated serum HCG level and/or tumor features, such as hemorrhage, necrosis, and vascular infiltration, are seen in patients with invasive, late clinical stage anaplastic seminoma that has a poor prognosis[14]. The spermatocytic tumor we identified in our patient contained small, medium, and large tumor cells that were slightly separated within an edematous stroma, creating a pseudo-glandular tissue appearance. The lack of lymphocytic infiltration, granulomatous inflammatory response, increased level of mitosis, and sarcomatous components were features of our patient’s tumor that were consistent with this diagnosis. The tumor in our patient’s case lacked markers (OCT3/4, AE1, AE3, and CD30) that are absent in spermatocytic tumor, but present in other germ cell tumors. Moreover, immunohistochemical staining for CD117 was positive in our patient’s tumor; this marker is a key feature for identifying spermatocytic tumor.

The clinical features and imaging findings of testicular spermatocytic tumor are not distinct from those of classic spermatoplasm cytomaspermatocytic tumor and other types of testicular tumors. Laboratory test results for serum LDH, HCG, and AFP levels are usually not elevated. Ultrasound is useful for early testicular tumor detection and is a preferred imaging method due to its non-invasive nature[14-18]. CT provides more information regarding features such as tumor boundary, internal architecture, involvement of surrounding structures, and lymph node metastasis, and is useful for establishing a preoperative presumptive diagnosis and for postoperative follow-up[19-22]. However, biopsy and histopathology are required to confirm the diagnosis. Currently, orchietomy is the preferred treatment for testicular spermatocytic tumor. The scope of surgical resection should include the testicular epididymis and a portion of the spermatic cord to ensure complete excision for the 10%-15% of testicular tumors that invade these structures[23-26]. Most spermatocytic tumors exhibit benign behavior, with a low potential for invasion and metastasis. Given the favorable prognosis for this tumor type, no adjuvant therapy is usually required following excision by orchietomy[27,28]. However, tumors that are larger than 4 cm in diameter, involve the epididymis or spermatic cord, or have sarcomatous features may have an increased risk for malignant behavior and recurrence. Long term follow-up is necessary in such cases.

CONCLUSION

In summary, we report a typical case of spermatocytic tumor, review its epidemiology and various examined features, as well as pathological features such as three typical cellular morphologies and interstitial mucinous degeneration, and make a differential
Hao ML et al. Spermatocytic tumor diagnosis with its similar counterpart. The first line of therapy for spermatocytic tumor is orchietomy, which does not require other adjuvant therapy unless there is an incomplete or spermatic cord, or recurrent features. Long-term follow-up may be recommended to identify potential postoperative recurrence.

REFERENCES


