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REVIEW

Controversies in the management of acute pancreatitis: An update

Manish Manrai, Saurabh Dawra, Anupam K Singh, Daya Krishna Jha, Rakesh Kochhar

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Abstract

This review summarized the current controversies in the management of acute pancreatitis (AP). The controversies in management range from issues involving fluid resuscitation, nutrition, the role of antibiotics and antifungals, which analgesic to use, role of anticoagulation and intervention for complications in AP. The interventions vary from percutaneous drainage, endoscopy or surgery. Active research and emerging data are helping to formulate better guidelines. The available evidence favors crystalloids, although the choice and type of fluid resuscitation is an area of dynamic research. The nutrition aspect does not have controversy as of now as early enteral feeding is preferred most often than not. The empirical use of antibiotics and antifungals are gray zones, and more data is needed for conclusive guidelines. The choice of analgesic is being studied, and the recommendations are still evolving. The position of using anticoagulation is still awaiting consensus. The role of intervention is well established, although the modality is constantly changing and favoring endoscopy or percutaneous drainage rather than surgery. It is evident that more multicenter randomized controlled trials are required for establishing the standard of care in these crucial management issues of AP to improve the morbidity and mortality worldwide.

Key Words: Acute pancreatitis; Fluid resuscitation; Antibiotics; Analgesia; Anti coagulation; Intervention

Core Tip: The controversies in the management of acute pancreatitis are an area of dynamic research, and emerging data is assisting in guideline formulation. The current evidence favors crystalloids, although the choice and type of fluid resuscitation is an evolving research area. The empirical use of antibiotics and antifungals are gray zones and lack guidelines. The choice of analgesic lacks definite recommendations. The role of anticoagulation lacks agreement. The role of intervention is well established and favors endoscopy or percutaneous drainage rather than surgery. It is obvious that more evidence is essential for effective guidelines in these critical management issues of acute pancreatitis.

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INTRODUCTION

Acute pancreatitis (AP) is an acute inflammatory process involving the pancreas, frequently affecting the peripancreatic tissue and less commonly the remote organ systems. It represents a spectrum of diseases ranging from a mild, self-limited course needing only brief hospitalization to moderate disease with increased morbidity and a rapidly progressive, severe illness culminating into multiorgan dysfunction, as categorized by the revised Atlanta Classification[1].

In 2019, the countries with the greatest number of incident cases of AP were India followed by China and the United States. The global estimate of AP incidence in 2019 was 33.7/per 100000 population and is rising in the Western world. The global burden of disease estimation is 1.4 deaths per 100000[2]. Therefore the disease burden is significant and requires more data and research in optimizing therapy. Although the revised Atlanta Classification has standardized the disease severity classification, there are a few controversies in the management of AP that are still evolving and are areas of active research.

In this review, we summarized the current controversies in the management of AP. The controversies are in the following areas: (1) Fluid resuscitation; (2) Nutrition; (3) Antibiotics and antifungals; (4) Analgesics; (5) Role of anticoagulation; (6) Endoscopic retrograde cholangiopancreatography (ERCP); and (7) Drainage in local complications. Certain issues like intra-abdominal hypertension (IAH) and persistent ascites also confound the management. Therefore, despite active research in many of these areas, the consensus is lacking. The data are still emerging, and guidelines are evolving.

FLUID MANAGEMENT IN AP

The pathophysiology of AP can broadly be classified into an early phase of systemic inflammatory response syndrome (SIRS), lasting 1-2 wk followed by a late phase characterized by disease sequelae and infection. There is a paucity of pharmacological options in the initial acute inflammatory phase; hence, treatment by and large remains supportive. Fluid management in the initial acute inflammatory phase becomes particularly important.

Which fluid? Crystalloids vs colloids

Our understanding of this vital management aspect is based on our understanding of altered pancreatic microcirculation in animal models. Studies have focused on using crystalloids as well as colloids to offset circulatory alterations. However, none of these studies conclusively established the superiority of one over the other[3,4].

Colloids (albumin, dextran, hexastarch) in animal studies have been shown to have better optimization of hemodynamic response. They have a larger molecular size and are better retained in the intravascular compartment. Their osmotic effect draws the fluid from the interstitium into the vascular compartment, thus maintaining better circulatory flow. These benefits, however, come at the cost of anaphylactic reactions, intravascular volume overload and renal impairment. Hypertonic saline, in particular, has shown promising results in animal models especially in modulating cytokine expression [5,6]. The use of balanced solutions like Ringer's lactate (RL) has demonstrated an inflammasome-mediated anti-inflammatory effect by acting on G-protein-coupled receptor 81, which is a cell surface lactate receptor[7]. The use of colloids in human studies include a combination of dextran with albumin in varying concentrations. A study using albumin after dilution with dextran has demonstrated reduced mortality (7.7%) and reduced progression of pancreatic necrosis (15.0%)[8]. The use of hydroxyethyl starch has not shown any benefit in reducing the risk of organ failure (OF) or mortality in AP[9]. Trials combining the colloids and crystalloids in different concentrations have also shown promising results

Table 1 Randomized controlled trials comparing resuscitation with Ringer's lactate *vs* normal saline in the initial acute phase of acute pancreatitis

Ref.	RL	NS	SIRS			CRP		
Wu *et al*[15], 2011	19	21	RL	84% at 24 h	$P = 0.035$	RL	Mean CRP 51 mg/L	$P = 0.018$
			NS	0% reduction at 24 h		NS	Mean CRP 104 mg/L	
de Madaria *et al*[13], 2018	19	21	RL	Median no of SIRS criteria at 48 h: 01 (0-1)	$P = 0.060$	RL	Mean CRP at 48 h: 28 mg/L	$P = 0.037$
			NS	Median no of SIRS criteria at 48 h: 01 (1-2)		NS	Mean CRP at 48 h: 166 mg/L	
Choosakul *et al*[14], 2018	23	24	RL	Reduction in SIRS at 48 h: 26.1%	$P = 0.02$	No difference in CRP		
			NS	Reduction in SIRS at 48 h: 26.1% 4.2%				
Karki *et al*[16], 2022	26	25	RL	SIRS at 24 h: 15.4%	$P = 0.025$	Median CRP at 72 h: 14.2 mg/L		$P < 0.001$
			NS	SIRS at 24 h: 44.0%		Median CRP at 72 h: 22.2 mg/L		

CRP: C-reactive protein; NS: Normal saline; RL: Ringer's lactate; SIRS: Systemic inflammatory response syndrome.

[10]. The American Gastroenterology Association recommends crystalloids as the initial fluid of choice for resuscitation in the acute inflammatory phase of AP, while it does not recommend the use of colloids like hydroxyl ethyl starch[11].

Which is better as the initial fluid of choice? RL vs normal saline

Traditionally, normal saline (NS) is the crystalloid of choice for critical illnesses like trauma or sepsis. Studies, however, have highlighted the adverse effects of NS therapy notably acute kidney injury (AKI) and non-anion gap acidosis. The landmark SMART trial provided valuable insight supporting the role of balanced crystalloids, *i.e.* RL and Plasma-Lyte A over NS alone in critically ill patients. Out of a total of 15802 adults admitted to intensive care units (ICUs), those receiving balanced crystalloids ($n = 7942$) had a lower incidence of major adverse kidney events (14.3%) *vs* 15.4% in patients receiving NS ($n = 1211$). Other notable benefits were reduced requirement of renal replacement therapy (2.5% *vs* 2.9%), persistent renal dysfunction (6.4% *vs* 6.6%), and 30 d in-hospital mortality (10.3% *vs* 11.1%) in the RL group compared to the NS group, respectively[12].

Researchers have strived hard to critically analyze the effects of RL *vs* NS in patients with AP. de Madaria *et al*[13] showed favorable anti-inflammatory effects of using RL *vs* NS in AP. Choosakul *et al* [14] showed a beneficial effect of using RL in reducing SIRS in the first 24 h of pancreatic injury as compared to those receiving NS. This beneficial effect, however, was not reciprocated at 48 h with no effect on disease-related mortality. This is in contrast to an earlier randomized controlled trial (RCT) by Wu *et al*[15] who demonstrated a statistically significant reduction in SIRS after 24 h of pancreatic injury in patients receiving RL *vs* those receiving NS. Karki *et al*[16] in their recent paper provided evidence of reduced systemic inflammation at 72 h in patients who received initial resuscitation with RL *vs* those who received NS (Table 1).

Four recent meta-analyses including the above-mentioned RCTs have drawn conflicting conclusions varying from reduced severity of AP, laparoscopic cholecystectomy and risk of ICU admission to no statistically significant benefit of resuscitating with RL compared to NS (Table 2)[17-20].

Which strategy of fluid resuscitation? Aggressive vs restricted fluid resuscitation

Recent human studies in AP have focused on two distinct aspects of fluid management, namely the aggressiveness of fluid therapy and the optimal fluid required for resuscitation.

Early aggressive resuscitation proposes to transfuse one-third of the body's 72-h fluid requirement within the first 24 h of presentation. This hypothesis was subsequently challenged by other investigators. Garg *et al*[21] aptly described that this clinical dilemma may require the services of an 'alchemist.' This clinical aspect thus required critical review. RCTs comparing aggressive *vs* restricted fluid resuscitation in the inflammatory phase of AP have been summarized in Table 3[22-26].

Recent systemic reviews and meta-analyses that included both RCTs and cohort studies on the use of aggressive *vs* restricted intravenous fluid resuscitation in the early acute phase (within the first 24 h from presentation) have weighed in favor of restrictive intravenous transfusion. This has shown that restricted intravenous fluid administration decreases the risk of AKI, pulmonary edema and the need for mechanical ventilation[27].

The recent 'waterfall trial' has provided valuable evidence supporting 'moderate resuscitation, *i.e.* up to 1.5 mL/kg/h and bolus of 10 mL/kg only in the presence of hypovolemia[28].

Table 2 Recent meta-analyses comparing resuscitation with Ringer's lactate *vs* normal saline in patients with acute pancreatitis

Ref.	Inclusion	Conclusion
Zhou *et al*[17], 2021	4 RCT, 7964 abstracts, 57 full-text documents	Patients resuscitated with RL were less likely to develop moderately severe/severe AP (OR: 0.49; 95%CI: 0.25-0.97), had reduced requirement of ICU admission (OR: 0.33; 95%CI: 0.13-0.81) and had reduced local complications (OR: 0.42; 95%CI: 0.20-0.88)
Aziz *et al*[18], 2021	4 RCT, 2 cohort studies	Patients resuscitated with RL had a lower rate of ICU admission (RR: 0.43; 95%CI: 0.22-0.84), a lower length of hospital stay (MD: 0.77 d; 95%CI: 1.44-0.09 d) and no difference in overall mortality and SIRS at 24 h
Vedantam *et al*[19], 2022	6 studies	Patients resuscitated with RL had a decreased need for ICU admission and no statistical difference in the risk of developing SIRS at 24 h (pooled OR: 0.59; 95%CI: 0.22-1.62, $P = 0.31$)
Chen *et al*[20], 2022	4 RCT	Patients resuscitated with RL had a reduced incidence of ICU admission (RR: 0.39; 95%CI: 0.18-0.85; $P = 0.02$), no significant reduction in SIRS at 24 h, 48 h and 72 h and no reduction in risk of mortality, severe disease or local complications

AP: Acute pancreatitis; CI: Confidence interval; ICU: Intensive care unit; MD: Mean difference; OR: Odds ratio; RCT: Randomized controlled trial; RL: Ringer's lactate; RR: Relative risk; SIRS: Systemic inflammatory response syndrome.

Table 3 Randomized controlled trials comparing aggressive *vs* restricted fluid resuscitation in the inflammatory phase of acute pancreatitis

Ref.	No. of patients	Disease severity	Aggressive resuscitation	Non-aggressive resuscitation
Mao *et al*[22], 2009	Aggressive: 36	SAP	Mortality: 94.4%	Mortality: 10.0%
	Non-aggressive: 40		Mechanical ventilation: 30.6%	Mechanical ventilation: 65.0%
Mao *et al*[23], 2010	Aggressive: 56	SAP	Mortality: 33.9%	Mortality: 15.3%
	Non-aggressive: 59		Sepsis: 78.6%	Sepsis: 57.6%
Wu *et al*[15], 2011	Aggressive: 19		Reduction in SIRS: 58%	Reduction in SIRS: 42%
	Non-aggressive: 21			
Buxbaum *et al*[24], 2017	Aggressive: 27	Mild AP	Clinical improvement: 70%	Clinical improvement: 42%
	Non-aggressive: 33		SIRS: 7.4%	SIRS: 21.1%
Cuellar-Monterrubeo *et al*[25], 2020	Aggressive: 43	Mild, moderately severe and severe AP	SIRS at day 7: 13.3%	SIRS at day 7: 13.9%
	Non-aggressive: 45			
Li *et al*[26], 2020	Total number ($n = 912$)	Hemoconcentration hematocrit > 44% *vs* < 44%	In hematocrit > 44%: increased NPPV	In hematocrit < 44%: reduced risk of NPPV

AP: Acute pancreatitis; NPPV: Non-invasive positive pressure ventilation; SAP: Severe acute pancreatitis; SIRS: Systemic inflammatory response syndrome.

To conclude, there is considerable heterogeneity in the study designs amongst various studies, the rate and type of fluids studied, study population and outcome measures. There is a paucity of evidence to recommend aggressive *vs* restrictive intravenous fluid administration. Most guidelines recommend RL as the initial fluid of choice intending to maintain urine output > 0.5 mL/kg[28,29]. The need of the hour is to incorporate non-invasive methods to assess the patient's hydration status before commencing intravenous fluid administration and dynamic hemodynamic monitoring and to determine a patient-centric treatment strategy.

NUTRITIONAL ASPECTS IN THE MANAGEMENT OF AP

There has been a paradigm shift in the management of AP from surgical management to conservative support. While judicious fluid therapy is imperative in the initial inflammatory phase, the concept of

Table 4 Meta-analysis on early enteral nutrition *vs* delayed enteral nutrition/total parenteral nutrition in acute pancreatitis

Ref.	Inclusion	Conclusion
Li *et al*[35], 2013	6 studies	Early EN *vs* delayed EN: reduced incidence of all infections (OR: 0.38; 95%CI: 0.21–0.68, P < 0.05); reduced incidence of catheter-related sepsis (OR: 0.26; 95%CI: 0.11–0.58, P < 0.05); reduced pancreatic infection (OR: 0.49; 95%CI: 0.31–0.78, P < 0.05); reduced risk of hyperglycemia (OR: 0.24; 95%CI: 0.11–0.52, P < 0.05); reduced length of hospitalization (mean difference: -2.18; 95%CI: -3.48-(-0.87); P < 0.05); reduced mortality (OR: 0.31; 95%CI: 0.14–0.71, P < 0.05); and no difference in pulmonary complications (P > 0.05)
Feng *et al*[36], 2017	4 RCTs, 2 retrospective studies	Early EN (within 48 h) *vs* delayed EN (after 48 h): reduced risk of multiple organ failure (RR: 0.67; 95%CI: 0.46-0.99; *P* = 0.04); decreased systemic inflammatory response syndrome but not significant (RR: 0.85; 95%CI: 0.71-1.02; *P* = 0.09); and no significant difference in mortality (RR: 0.78; 95%CI: 0.27-2.24; *P* = 0.64)
Qi *et al*[37], 2018	8 studies (727 patients)	Early EN *vs* late EN and TPN: risk of mortality (OR: 0.56; 95%CI: 0.23-1.34); multiple OF (OR: 0.40; 95%CI: 0.20-0.79); infectious complications: (OR: 0.57; 95%CI: 0.23-1.42); adverse events (OR: 0.45; 95%CI: 0.17-1.21); and pancreatitis-related infections (OR: 0.83; 95%CI: 0.59-1.18)
Zeng *et al*[38], 2019	17 RCTs	Early EN *vs* delayed EN: lower mortality (9.21% *vs* 11.22%) but no statistical significance between the two groups (RR: 0.86; 95%CI: 0.60-1.23; *P* = 0.42); reduced risk of complications (RR: 0.81; 95%CI: 0.70-0.93; *P* = 0.002); reduced incidence of infections (RR: 0.68; 95%CI: 0.51-0.91, *P* = 0.009); and no difference in risk of multi OF (RR: 0.82; 95%CI: 0.59-1.14; *P* = 0.23)

CI: Confidence interval; EN: Enteral nutrition; OF: Organ failure; OR: Odds ratio; RCT: Randomized controlled trial; RR: Relative risk; TPN: Total parenteral nutrition.

Table 5 Summary of the meta-analysis highlighting the feasibility of nasogastric feeding in acute pancreatitis

Ref.	Inclusion	Conclusion
Zhu *et al*[40], 2016	4 RCTs	NG *vs* NJ feed: mortality (RR: 0.71; 95%CI: 0.38-1.32; *z* = 1.09; *P* = 0.28); infectious complications (RR: 0.77; 95%CI: 0.45-1.30; *z* = 0.99; *P* = 0.32); digestive complications (RR: 1.02; 95%CI: 0.57-1.83; *z* = 0.08; *P* = 0.93); achievement of energy balance (RR: 1.00; 95%CI: 0.97-1.03; *z* = 0.00; *P* = 1.00)
Dutta *et al*[41], 2020	5 RCTs	NG *vs* NJ feed: mortality (RR: 0.65; 95%CI: 0.36-1.17; no difference in the rate of OF, procedure-related complications, the requirement of surgical intervention and the requirement of PN

CI: Confidence interval; NG: Nasogastric; NJ: Nasojejunal; OF: Organ failure; PN: Parenteral nutrition; RCT: Randomized controlled trial; RR: Relative risk.

"nutritional support'' to prevent malnutrition is widely gaining acceptance. Inflammatory cytokines, higher ''resting energy expenditure," protein catabolism, ongoing pain, poor oral intake and complications like gastric outlet obstruction and ileus in combination with micronutrient deficiency have all been postulated as contributing factors that precipitate a state of malnutrition in AP[30].

When to initiate enteral nutrition? Early enteral nutrition vs delayed enteral nutrition

The earlier concept of "pancreatic rest" (*i.e.* initiation of enteral feeding on the complete resolution of pain abdomen) has given way to the concept of "early enteral nutrition (EN)". This concept is based on experimental evidence demonstrating that pancreatic enzyme secretion reduces with increased severity of AP. Thus, injured acinar cells may not respond to an increased physiological stimulus[31].

Early EN has shown a reduced incidence of bacterial translocation thus reducing systemic inflammation and maintaining gut integrity and gut microbiota composition[32-34]. The benefits of early EN have been confirmed in a meta-analysis and systemic reviews[35-38].

Table 4 highlights the meta-analysis demonstrating the benefits of early EN in AP. The newer concept of "immediate EN" *vs* early EN has been shown to decrease the length of hospital stay and intolerance of feeding but with no statistically significant decrease in the rate of progression to severe pancreatitis or incidence of complications[39].

Which modality of EN? Nasogastric vs nasojejunal feed

Oral nutritional support is the preferred mode of feeding in mild AP[37]. The traditional approach of nasojejunal feeding is based on the premise that it bypasses the inflamed pancreas. On the other hand, it was believed that nasogastric (NG) nutrition stimulates pancreatic secretion, thereby causing an exacerbation of the inflammatory process and increasing the risk of developing aspiration pneumonia. However, there is growing evidence that establishes the safety, feasibility and tolerability of NG feeding in AP (Table 5)[40,41]. Whether NG feeding affects disease mortality or morbidity is debatable.

The ESPEN guidelines recommend early initiation of oral feeding in predicted mild AP and EN in preference to parenteral nutrition in those who are unable to take an oral feed with an initial energy requirement of 15-20 kcal/kg/d and protein requirement of 1.2-1.5 g/kg/d.

Table 6 Guidelines on the use of antibiotics in acute pancreatitis

Societies	Prophylactic antibiotics	Indications of therapeutic antibiotics	Probiotics
ACG, 2013[50]	Not recommended	Extrapancreatic infections. Cholangitis, catheter-acquired infections, bacteremia, urinary tract infection, pneumonia. Infected pancreatic necrosis	Not recommended
IAP/APA, 2013[46]	Not recommended	Infected pancreatic necrosis	No recommend-ations
Japanese guidelines, 2021 [51]	Not recommended	Not addressed	No recommend-ations
AGA, 2018[11]	Not recommended	Not addressed	No recommend-ations
ESGE, 2018[52]	Not recommended	Infected pancreatic necrosis	Not recommended
World Society of Emergency Surgery, 2019[53]	Not recommended	Infected pancreatic necrosis	No recommend-ations

ACG: American College of Gastroenterology; AGA: Androgenetic Alopecia; APA: American Pancreatic Association; ESGE: European Society of Gastrointestinal Endoscopy; IAP: International Association of Pancreatology.

ANTIBIOTICS IN AP

Diagnosis of infection in AP and judicious use of antimicrobials is a challenge faced by clinicians with very limited tools available for decision-making. Infections and OFs are critical determinants of outcome in cases of AP[42].

What is the origin of the infection? Pancreatic vs extrapancreatic

Infections can be of pancreatic [infected pancreatic necrosis, infected pseudocyst and infected walled-off necrosis (WON)] or extrapancreatic origin (pneumonia, bacteremia, urinary tract infection or indwelling catheters). Etiologically, infections may be of bacterial origin, fungal origin or both may coexist. Bacterial infections can complicate 30%-50% of severe AP (SAP), and the presence of infected necrosis increases the risk of mortality by 50% *vs* those with sterile necrosis[43]. Bacterial infections are monomicrobial in 60%-87% of patients. Infected necrosis may harbor polymicrobial infection in 10%-40% of patients, with Gram-negative anaerobes being the most common[44].

The use of antibiotics for extrapancreatic infections is less contested. Extrapancreatic infection can complicate almost one-third of patients. Respiratory infections are the commonest; however, their impact on mortality is less clear[45,46].

When to use antibiotics for patients with OF in AP?

Patients with SAP or moderate SAP who manage to tide over the initial onslaught of the inflammatory response may later develop an infection. This timing is variable and unpredictable; however, the incidence peaks during weeks 2 to 4 of illness, presumably secondary to increased gut translocation of bacteria and reduced immunity[47]. Tools that are readily available for diagnosis of infection are based on cultures, pancreatic necrotic aspirate or drainage samples. Cross-sectional imaging may demonstrate the presence of air in the collection. However, none provides absolute certainty. Recently there has been great emphasis on procalcitonin in guiding antibiotic treatment due to ease of applicability. Procalcitonin levels directly correlate with levels of microbial toxins and indirectly to cytokine-mediated host inflammatory response. However, cutoff values indicating infection are not standardized[48]. Recently procalcitonin-directed deescalation of antibiotics has shown efficacy in the management of infections in the setting of AP. Although, further RCTs may be required before definite conclusions can be drawn [49].

The use of antibiotics may be considered empirically in a subset of patients with pancreatic or extrapancreatic necrosis specifically in those patients who fail to improve or develop new onset OF after 7-10 d of initial hospitalization[50]. Empirical antibiotics should cover Gram-negative, Gram-positive and anaerobic microorganisms effectively, giving adequate cognizance to nosocomial infections and local antibiotics policy. The role of prophylactic antibiotics is contested routinely in clinical practice, with most of the guidelines and evidence recommending against its usage except for Japanese guidelines, which recommend prophylactic antibiotics in SAP and necrotizing pancreatitis within 72 h (Table 6)[11,46,50-53]. Prophylactic antibiotics increase the risk of multidrug resistant organisms and pancreatic fungal infection.

When to use antifungals in AP?

In critically ill patients with pancreatic fungal infection, echinocandins and liposomal amphotericin are the first-line drugs. However, differentiating invasive fungal infection from colonization can be perplexing[54]. Modalities available for diagnosing fungal infection are histological (aspirate samples or perioperative samples), cultures (drain catheters or blood cultures) and biomarkers[55]. Clinical judgment should be exercised when starting antifungals based on the likely diagnosis of invasive fungal infection, whereas it should be started in all cases with a definitive diagnosis[55]. Antifungals may be added considering clinical profile and risk factors for pancreatic fungal infection, such as prolonged intensive care, antibiotic administration, total parenteral nutrition and indwelling catheters[55].

In conclusion, antibiotics in AP should be initiated whenever a definite indication exists along with source control. However, there is no role for prophylactic antibiotics. Prophylactic antifungals especially with new-onset OF requires further evaluation.

ANALGESICS IN AP

Pain is a cardinal symptom and one of the diagnostic criteria for AP[1]. It not only contributes significantly to patient distress but also prognosticates the course of disease[56,57]. Alleviation of pain is an essential component in the management of the early phase of AP. We will be restricting our discussion to the management of inflammatory pain. Most, but not all, guidelines on AP remain noncommittal on analgesic management due to the paucity of high-quality evidence[11,46,50,58]. Japanese guidelines recommend that if pain associated with AP is severe and persistent, then it requires sufficient pain control; however, they remain noncommittal on the choice of analgesic[51]. The World Society of Emergency Surgery guidelines for the management of SAP provide no evidence or recommendation about any restriction in available pain medications except that nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided in cases with AKI[53]. None of the above guidelines provide sufficient recommendations on the type, route, dose, frequency and duration of analgesics in AP.

Which is preferred? NSAIDs vs opioids

NSAIDs and opioids are the most frequently prescribed analgesic for pain in AP. Thirteen RCTs and multiple meta-analyses have failed to provide any conclusive data on the analgesic management of AP, which hinges on the World Health Organization analgesic ladder (Figure 1, Table 7)[59-61]. Opioids have been the most studied analgesic for AP in RCTs, establishing good efficacy, and are the agent of choice for rescue analgesia in all of the trials. NSAIDs have been reported to be beneficial in mitigating the inflammatory cascade thus improving outcomes. However, their analgesic potency as compared to opioids remains controversial[62]. NSAIDs have been studied in only a few RCTs where it was found to be better than placebo but similar efficacy to weak opioids[63-65].

NSAIDs and opioids have different safety profiles. Opioids are known to cause bowel dysfunction and ileus, which may induce or exacerbate ileus in AP[66]. There is some evidence that opioid use is associated with sphincter of Oddi dysfunction as well as the risk of overuse and addiction[67]. The problem with NSAIDs is a risk of AKI and peptic ulcer disease, which should be avoided in AP with AKI[53]. Based on the better safety profile and comparable efficacy, NSAIDs may be preferred as first-line analgesia in patients with mild AP, keeping opioids as a reserve in refractory pain[62]. Monitoring of response using a visual analog scale and the need for rescue analgesia should be monitored regularly before consideration for escalation of therapy[21,68]. Lack of relevant and high-quality data on analgesics in cases of moderately SAP and SAP warrants further studies before any clear-cut recommendations can be made.

Newer modalities? Patient-controlled analgesia and epidural analgesia

Patient-controlled analgesia (PCA) and epidural analgesia are emerging therapies in AP. PCA allows adequate pain control allowing patients to control their medication doses. Intravenous protease inhibitor nafamostat mesilate is one of the newer agents that has been used in an open label RCT. The analgesic effect was analyzed based on 24 h cumulative dose of fentanyl required and any administration of intravenous PCA. Results showed encouraging analgesic effect. An ongoing clinical trial is studying the use of PCA in AP[69,70]. Epidural analgesia has been used infrequently in patients with SAP and has shown a beneficial effect on mortality and pancreatic arterial perfusion[71,72]. However, it bears the risk of catheter-related hypotension and epidural abscess and is presently not recommended for mild to moderate AP. Further studies assessing the efficacy and safety of epidural analgesia in SAP are needed to make a definite conclusion.

In conclusion, we would suggest using the World Health Organization analgesic ladder for the management of pain in AP keeping in mind the safety profile of drugs[59-61,73]. It begins with low-potency NSAIDs (*e.g.*, paracetamol, indomethacin and diclofenac), which is usually sufficient in mild to moderate AP. If NSAIDs are not sufficient for pain relief, then upgrading to weak opioids (*e.g.*, tramadol and codeine) or strong opioids (*e.g.*, pentazocine, fentanyl and buprenorphine) appears logical. PCA and

Table 7 Important randomized controlled trials on analgesics in acute pancreatitis

Ref.	Country	Comparison drugs	Study design	Patients, *n*	Rescue agent	Primary outcome	Results	Conclusion
Blamey *et al*[74], 1984	United Kingdom	IM buprenorphine *vs* IM pethidine	RCT, blinding not mentioned	32	Pethidine	Pain relief at 24 h	No significant difference in pain relief at 24 h and no significant difference in pain-free period	No superiority established
Ebbehøj *et al*[75], 1985	Denmark	Indomethacin suppository *vs* placebo	Placebo-controlled, double-blind RCT	30	Opiate not specified	Pain relief using VAS; Pain-free days	Indomethacin provided better pain control, a lesser number of painful days and lesser need for rescue analgesia	Indomethacin suppository favored over placebo
Jakobs *et al* [76], 2000	Germany	IV buprenorphine *vs* IV procaine	Open-label RCT	39	Procaine group–pethidine; buprenorphine group–pethidine	Pain relief: VAS ever 8 hr for 3 d; rescue demand	Buprenorphine provided better pain relief on days 1 and 2 with lesser need for rescue analgesia; comparable side effects, complications, mortality	Buprenorphine favored
Stevens *et al*[77], 2002	United States	Transdermal fentanyl IM pethidine *vs* placebo and IM pethidine	Double-blind placebo-controlled RCT	32	IM pethidine	Pain relief: Self-reported 0-5 scale; self-reported satisfaction 1-5 at discharge	Fentanyl provided no significant difference in pain relief at 24 h but better pain relief at 36 h and a shortened hospital stay	Fentanyl favored
Kahl *et al* [78], 2004	Germany	Infusion procaine *vs* IV pentazocine	Open RCT	101	IM pethidine	Pain relief based on VAS and rescue analgesia	Pentazocine provided better pain relief until day 3 and required fewer rescue doses	Pentazocine favored
Peiró *et al* [79], 2008	Spain	IV metamizole *vs* SC morphine	Open RCT	16	Pethidine	Pain relief based on VAS and time to pain relief	Metamizole showed better pain relief at 24 h and faster pain relief, which was nonsignificant	A favorable trend towards metamizole but a small sample size
Wilms *et al* [80], 2009	Germany	IV procaine *vs* IV placebo	Double-blind placebo-controlled RCT	42	Buprenorphine	Pain relief and need for rescue analgesia over 3 d	Failed to show better pain relief as compared to placebo, and the need for rescue analgesia was similar in both groups	Procaine is not superior to placebo
Layer *et al* [81], 2011	Germany	IV procaine *vs* IV placebo	Double-blind placebo-controlled RCT	44	Metamizole or buprenorphine	Pain relief at 3 d; rescue analgesia; proportion achieving > 67% drop in VAS	Procaine showed higher analgesic superiority with greater pain relief at 72 h, lesser need for rescue analgesia and more patients achieving VAS drop > 67%	Procaine favored over placebo
Sadowski *et al*[82], 2015	Switzerland	Epidural analgesia *vs* PCA	Open RCT	35	Not applicable	Safety and efficacy of EA; pancreatic perfusion on CT; pain relief VAS	EA was safe, provided faster pain relief and increased pancreatic perfusion	EA favored over PCA
Gülen *et al* [83], 2016	Turkey	Tramadol *vs* paracetamol + dexketoprofen	Single-blind RCT	90	Morphine	Pain relief at 30 min	No significant drop in VAS at 30 min for both agents and a similar need for rescue analgesia for both groups	No superior analgesia
Mahapatra *et al*[84], 2019	India	IV pentazocine *vs* IV diclofenac	Double blind RCT	50	Fentanyl PCA	Pain relief; pain-free period; rescue analgesia	Higher rescue analgesia needed with diclofenac; longer pain-free period and lower need for PCA with	Pentazocine favored

							pentazocine	
Kumar *et al*[85], 2019	India	IV diclofenac *vs* IV tramadol	Double-blind RCT	41	IV morphine	Pain relief VAS over 7 d; painful days; rescue demand; time for significant VAS drop	No significant difference among both groups except time to a significant drop in VAS was quicker with diclofenac	No superior agent
Chen *et al* [86], 2022	China	Hydromorphone PCA *vs* IM pethidine	Open-label RCT	77	IM dezocine	Change in VAS score over 72 h; rescue analgesia; organ failures; local complic-ations; ICU admission LOH; mortality	No significant difference in VAS score deduction was noted with PCA as compared to pethidine, but a higher dose of hydromorphone needed for similar pain relief; need for rescue analgesia similar	No superior agent

CT: Computed tomography; EA: Epidural analgesia; ICU: Intensive care unit; IM: Intramuscular; IV: Intraveneous; LOH: Loss of heterozygosity; PCA: Patient-controlled analgesia; RCT: Randomized controlled trial; SC: Synovial chondromatosis; VAS: Visual analog scale.

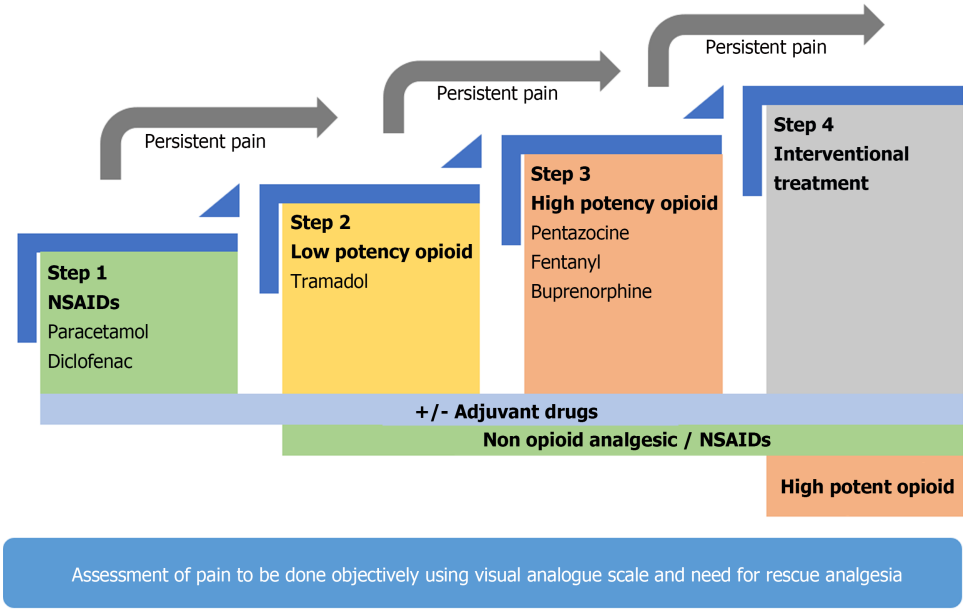

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Figure 1 Pain management in acute pancreatitis. NSAIDs: Nonsteroidal anti-inflammatory drugs.

epidural analgesia are promising therapies but need validation in larger cohorts and may be suited best as individualized therapy due to cost and limited availability (Figure 1). Table 7 summarizes the RCTs evaluating the role of different analgesics in management of pain in AP[74-86].

ANTICOAGULATION IN AP

The use of anticoagulation in AP is perhaps the least studied in the literature. This is because the disease can give rise to two different complications: Splanchnic thrombosis and retroperitoneal bleeding. Management of these two opposing complications poses a unique challenge for a clinician. Pancreatitis is an acute inflammatory condition coupled with systemic response to inflammation, fluid shifts and subsequent hypovolemia. These pathophysiological mechanisms in unison precipitate a prothrombotic milieu. Thrombosis involving the splanchnic vasculature may involve the portal vein (PV), superior mesenteric vein (SMV) and splenic vein either separately or in combination.

Splanchnic vein thrombosis in AP, with a reported incidence of 1%-2%, has been poorly studied in clinical trials[87] partly because thrombosis in splanchnic vasculature is often incidentally detected on

imaging. Clinical presentation of splanchnic vein thrombosis may overlap with that of AP. Our understanding of the natural history of splanchnic vein thrombosis in AP is still evolving. Some of these patients may have underlying prothrombotic risk factors that have just been unmasked because of pancreatitis. Understanding this rare complication is important because of prominent life-threatening manifestations, namely bowel gangrene, chronic portal hypertension and hepatic failure.

Thus, should we use anticoagulation in patients presenting with splanchnic vein thrombosis? Experience gained from the use of anticoagulation in patients without cirrhosis who present with acute PV thrombosis has been summarized in the European network of vascular diseases of the liver study. This study has shown the recanalization of the PV in 39% of those who were initiated on anticoagulation in the acute phase of PV thrombosis. Gastrointestinal bleeding and intestinal infarction occurred in 9.4% and 2.1% of anticoagulated patients, respectively[88]. This has led to some researchers advocating the use of anticoagulation in those with documented thrombosis of splanchnic vasculature in AP.

However, the benefits of giving anticoagulation have to be weighed in light of another potentially life-threatening complications (*i.e.* pseudoaneurysm-related bleeding from large vessels and retroperitoneal bleeding). Moreover, many of these patients with SAP undergo interventions (percutaneous/endoscopic drainage of collections or surgical interventions). Thus, from a clinician's point of view, using therapeutic anticoagulation in patients with AP may be a risky proposition. The lack of RCTs on the efficacy of anticoagulation in AP needs special attention. Then splenic vein lies in close anatomical proximity to the inflamed pancreas. Researchers have shown a direct correlation between the degree of peripancreatic inflammation, direct venous compression by collections and the incidence of splanchnic vein thrombosis. Thus, drainage of collections has been postulated to be the most ideal way of treating and preventing splanchnic vein thrombosis in AP[89].

Systematic reviews have been attempted to address this pertinent management dilemma. Hajibandeh *et al*[90] in their systemic review of 5 observational studies and 252 patients demonstrated no significant difference in the rate of resolution of thrombus or formation of varices/collaterals. The study had a major drawback of low study heterogeneity between the anticoagulation and no anticoagulation groups. Another systemic review by Norton *et al*[91] included 16 studies (9 case reports, 2 case series and 5 single-center studies); among the total of 198 affected patients, 46.5% received anticoagulation therapy. The rate of venous recanalization was 14% in the anticoagulated group *vs* 11% in the untreated group, while 16% and 5% of patients had bleeding manifestations, respectively.

The most recent meta-analysis included 7 retrospective cohort studies (233 AP patients suffered from splanchnic venous thrombosis). Splanchnic vein thrombosis was seen in 33%-82%, PV thrombosis in 4%-32% and SMV thrombosis in 5%-9% of all patients with splanchnic vein thrombosis. A combination of splanchnic vein thrombosis, PV thrombosis and/or SMV thrombosis has also been reported in variable combinations. Moderate AP to SAP was resent in 89% of patients who had some evidence of splanchnic vein thrombosis. Several drawbacks of these systemic reviews and meta-analysis include the absence of RCTs and the serious risk of bias, imprecision and indirectness[92].

There are no guidelines on the management of splanchnic vein thrombosis in AP. Management issues have been extrapolated from existing guidelines on pulmonary embolism, extrahepatic PV obstruction and deep vein thrombosis. Low molecular weight heparin followed by vitamin K antagonist, fondaparinaux and apixaban have been used in different studies. Approximately 47% of affected patients who received therapeutic anticoagulation showed no statistically significant rate of recanalization[92-95].

INTERVENTIONS IN AP

Interventions in AP could be an emergency or may be delayed. The emergency interventions in AP include ERCP to relieve the biliary obstruction. Non-emergency or delayed interventions include percutaneous catheter drainage or endoscopic drainage of necrotic or walled-off collections.

When to consider ERCP?

ERCP is an invasive intervention with a complication rate of 5% to 15%[90]. The current use of ERCP in AP is limited to relief of biliary obstruction. In patients with AP who present with acute cholangitis, emergency ERCP (within 24 h) is the recommended first-line treatment[46,50]. However, the role and timing of ERCP in biliary obstruction without cholangitis in AP is not clear[46].

Multiple studies have looked at the role and timing of ERCP in these patients of acute biliary pancreatitis (ABP) without cholangitis[96]. Neoptolemos *et al*[97] showed that patients with predicted SAP had fewer complications with an early ERCP (within 72 h of admission) (24% *vs* 61%, $P < 0.05$). On the other hand, Fölsch *et al*[98] reported that early ERCP was not beneficial in patients with ABP without obstructive jaundice. Furthermore, a meta-analysis showed no significant difference in mortality rate according to the timing of ERCP (< 24 h *vs* < 72 h) in patients with persistent biliary obstruction without cholangitis[6]. Fölsch *et al*[98] also compared urgent ERCP with a conservative approach in patients with predicted severe ABP. This study showed that urgent ERCP with sphincterotomy did not reduce the major complication or mortality [38% *vs* 44%, risk ratio: 0.87; 95% confidence interval (CI): 0.64–1.18].

The available studies suggest that emergency ERCP (within 24 h) is indicated in patients with ABP with cholangitis or persistent cholestasis. For the rest of the patients with ABP, the role of urgent ERCP is controversial, and a conservative approach should be considered.

What are the options for interventions for drainage?

The management of the pancreatic and peripancreatic collections has evolved over the last two decades. The indications to drain (peri-) pancreatic collections in AP are the presence of infection and symptomatic sterile necrosis (Table 8). The choice of interventions includes percutaneous, endoscopic, minimally invasive surgery or a combined approach. The approach depends on multiple factors including the time elapsed since the onset of the disease, condition of the patient, anatomy of the collection and expertise available. An open surgical approach is no longer the preferred strategy due to the higher risk of mortality and major complications[99].

Across the world, the step-up approach remains the standard of care for the management of collections in AP. The approach involves initial conservative management, and then either percutaneous drainage or endoscopic transluminal drainage can be selected.

Is there an ideal time for drainage?

There are multiple dilemmas while contemplating the drainage of necrotic collection. Should the drainage be performed early (*i.e.* before encapsulation of the collection) or should it be delayed? Most guidelines suggest delaying drainage as much as possible and preferably until 4 wk after the disease onset to allow liquefaction and encapsulation of the collection[46,100]. The cutoff of 4 wk is arbitrary, and studies have shown variable results for early and delayed drainage.

Various studies have reported a widespread time window, varying from a median of 9 d to 75 d, between the onset of the disease and the first drainage procedure. The older studies suggested that delaying percutaneous drainage until encapsulation may improve the outcome[101-106]. Other recent studies have suggested the usefulness of early drainage in improving outcomes[107]. However, a recent multicenter randomized study (POINTER trail), which compared early *vs* delayed drainage in AP, did not show the superiority of early drainage[108]. The study showed similar rates of mortality (13% *vs* 10%, relative risk: 1.25; 95%CI: 0.42-3.68) and adverse events (76% *vs* 82%, relative risk: 0.94; 95%CI: 0.77-1.14) in early and delayed drainage. Studies have shown that early drainage required a higher number of reinterventions compared to a delayed strategy[108]. Trikudanathan *et al*[109] demonstrated that early endoscopic drainage (< 4 wk) required higher percutaneous drainage compared with patients with walled-off collections. Navalho *et al*[110] demonstrated the benefits of early drainage of infected pancreatic collections in patients in ICU settings[110,111]. Table 9 summarizes the studies highlighting timing of first catheter drainage and outcome in various studies of AP[99,101,103-104,110,112-122].

The available literature suggests that the correct timing of intervention in AP requires careful clinical judgment. A subset of patients with infected collections, sepsis and persistence or new onset OF may require early drainage.

Which modality of drainage? Percutaneous drainage vs endoscopic drainage

Percutaneous drainage: Percutaneous catheter drainage is an important treatment modality for acute necrotizing pancreatitis. The percutaneous procedure could be done safely under ultrasound (US) or computed tomography guidance. Percutaneous catheter drainage is important in patients where early drainage is required and the necrotic collection is not well encapsulated. Freeny *et al*[112] for the first time demonstrated the safety and efficacy of percutaneous drainage in AP in 1998 with a successful outcome in 47% of patients with percutaneous drainage only. Subsequently, Mortelé *et al*[113] and Baril *et al*[114] also confirmed the success of percutaneous drainage in AP.

In 2010 van Santvoort *et al*[99] (PANTER trial) performed an RCT of the step-up approach and primary surgery and found a significant success rate of percutaneous drainage. The first step in the step-up approach is percutaneous drainage, and it remains the standard of care for early drainage. Several studies have also confirmed the safety of early percutaneous catheter drainage in sick patients[109,110]. Table 10 summarizes the important studies and outcomes after percutaneous catheter drainage in AP.

Endoscopic drainage: Endoscopic drainage involves the internal drainage of collection by creating a temporary fistula and placing a stent between the collection and the gastrointestinal lumen. Internal drainage carries the advantage of a lower risk of infection of collections and eliminates the risk of pancreatic-cutaneous fistula. However, these benefits come with a risk of anesthesia-related complications. Internal drainage could be completed using conventional endoscopic drainage or under endoscopic US (EUS) guidance. Though the studies have established the efficacy and safety of the conventional technique, its use is limited by a visible bulge in only 40%-50% of patients, and most endoscopists prefer EUS-guided drainage.

As with percutaneous drainage, the appropriate timing of drainage for endoscopic drainage is a matter of research. Though few studies have suggested the safety and efficacy of early endoscopic drainage for necrotic collections, most of the guidelines and reviews suggest the endoscopic drainage of collections with a well-defined wall[46,100].

Table 8 Indications of drainage of collection in acute pancreatitis

Clinical suspicion or documented infected pancreatic collection
Presence of gas in the fluid collection on imaging
Systemic signs of infections
Increasing leucocytes and worsening clinical condition
Persistent or new onset organ failure
Pressure symptoms
Gastric outlet obstruction
Intestinal obstruction
Biliary obstruction
Persistent symptoms (*e.g.*, pain, persistent unwellness)
Disconnected pancreatic duct (*i.e.* full transection of the pancreatic duct) with ongoing symptoms

Which modality to choose? Percutaneous drainage vs endoscopic drainage vs combined approach

The percutaneous method is a time-tested method of drainage of infected pancreatic collections. Endoscopic drainage is an alternative approach to draining such collections in AP. Compared to percutaneous drainage it carries less risk of secondary infection and pancreatic-cutaneous fistula. Recent American Gastroenterology Association guidelines also suggest that an endoscopic approach may be preferred. However, the choice of drainage method should be individualized and guided by multiple factors including the time elapsed since the onset of disease, encapsulation of the collection, location of the collection, solid contents of the collection, hemodynamic condition of the patient and available expertise. In early pancreatic collection with an ill-defined wall, sicker patients and peripherally located collections or when expertise is not available, percutaneous drainage should be considered. Endoscopic drainage is preferable for centrally located pancreatic collections in patients with a well-defined wall. A combined approach can be used for larger central collections extending into the periphery or when a single modality fails.

Which stent should be used? Plastic stent vs metal stent

Endoscopic drainage of a collection could be performed with multiple plastic stents or metal stents. Historically, plastic stents were the mainstay of endoscopic drainage. However, their placement is time-consuming and challenging when multiple stents are required. On the other hand, the insertion of transmural metal stents ensures a short procedure time and wider transmural fistula and provides a more efficient way of drainage compared to plastic stents. Though the larger diameter of metal stents allows rapid drainage and facilitates endoscopic necrosectomy through the stent, the metal flanges may increase the risk of pseudoaneurysm formation[123]. Table 10 summarizes the studies for the outcome of endoscopic drainage with plastic and metal stents[123-128].

The retrospective studies comparing metal and plastic stents showed that the biflanged metal stent performed better than multiple plastic stents for draining WON[127,129]. On the other hand, two RCTs showed similar clinical efficacy with metal and multiple plastic stents for WON[123,124]. Furthermore, a meta-analysis concluded no differences in clinical success and adverse events between lumen- apposing metal stents and multiple plastic stents for symptomatic WON[130]. A recent study of EUS-guided drainage of infected WON identified that the use of metal stents was associated with higher clinical success (96.2% *vs* 81.8%, $P = 0.04$) and shorter hospital stays (6 d *vs* 10 d)[128].

The current evidence suggests that the choice of a stent for draining the collection is a matter of ongoing research and depends on multiple factors including the hemodynamic condition of the patients, size of the collection, solid contents of the collection and cost associated with metal stents. In patients with pseudocysts and limited solid contents, multiple plastic stents can be considered. While in patients with large collections, significant solid contents and peripherally extending collections metal stents should be preferred.

What is the role of irrigation?

The concept of irrigating the collection to remove the solid necrotic debris is a less popular and debatable approach. It is based on the principle of chemical debridement using necrolytic agents to accelerate the drainage of pancreatic necrosis. The irrigation technique has been used for either percutaneous or endoscopic transmural drainage[43,131]. Studies have shown variable results with the use of different agents. Agents used for irrigation include NS, antibiotics, hydrogen peroxide and streptokinase. Werge *et al*[43] showed that local instillation of antibiotics in infected pancreatic necrosis improves the eradication of infection. Similarly, LarinoNoia *et al*[131] showed that the addition of local

Table 9 Timing of first catheter drainage and outcome in various studies of acute pancreatitis

Ref.	Number of days after the onset of the disease when PCD was performed, mean (range)	Patients, *n*	IPN, %	Mortality, %
Infected necrotic collection				
Freeny *et al*[112], 1998	9 (1-48)	34	100	12
Navalho *et al*[110], 2006	18	30	100	17
Mortelé *et al*[113], 2009	12 (2-33)	13	100	17
Baril *et al*[114], 2000	24 (18-30)[a]	7	100	0
Bala *et al*[115], 2009	26 (18-88)	8	100	13
Baudin *et al*[116], 2012	19.8 ± 15.7	48	100	29
Tong *et al*[101], 2012	PCD only = 30.74 ± 5.67; PCD + surgery = 27.80 ± 6.00	34	100	0 and 7
Pascual *et al*[117], 2013	28 ± 17	13	100	23
Wroński *et al*[102], 2013	PCD only = 33 (27-46); surgery = 35 (8-116)	18	100	0 and 17
Wang *et al*[118], 2016	11.7 ± 8.1	59	100	18.6
Infected or sterile necrotic collection				
Lee *et al*[103], 2007	10 (1-58)[a]	23	12	4
Bruennler *et al*[119], 2008	3.5 (median 7)	80	65	23
van Santvoort *et al*[99], 2010	30 (11-71)[a]	43	91	19
Kumar *et al*[104], 2014	36.4 ± 7	12	67	8
Bellam *et al*[120], 2019	Median: 20 d	51	33.3	29.4
Gupta *et al*[121], 2020	Median: 22 d (range: 3–267 d)	146	47.9	20.5
Lu *et al*[105], 2020	15.26 ± 7.08	43	86	13.9
	50.86 ± 19.58	55	56.3	10.9
Sterile necrotic collection				
Walser *et al*[122], 2006	NR	22	0	9.1

[a]Some patients underwent endoscopic transluminal drainage.
IPN: Infectious pancreatic necrosis; NR: Not reported; PCD: Percutaneous catheter drainage.

Table 10 Outcome on endoscopic drainage of a pancreatic collection with various types of stents

Ref.	Collection	*n*	Success
Lee *et al*[124], 2014	WON and pseudocyst	PS = 25; FCMS = 25	PS: 90%; FCMS: 87%
Mukai *et al*[125], 2015	WON	PS = 27; BFMS = 43	PS: 90.6%; FCMS: 97.7%
Siddiqui *et al*[126], 2017	WON	PS = 106 FCMS = 121; LAMS = 86	PS: 81%; FCMS: 95%; LAMS: 90%
Bapaye *et al*[127], 2016	WON	PS = 61; BFMS = 72	PS: 73.7%; BFMS: 94.0%
Bang *et al*[123], 2019	WON	PS = 29; LAMS = 31	PS: 96.6%; LAMS: 93.5%
Muktesh *et al*[128], 2022	WON 108	PS = 45; BFMS = 53	PS: 81.8%; BFMS: 96.2%

BFMS: Biflanged metal stent; FCMS: Fully covered self-expandable metal stent; LAMS: Lumen-apposing metal stent; PS: Plastic stent; WON: Walled-off necrosis.

infusion of antibiotics avoids the need for necrosectomy in half of the patients with infected pancreatic necrosis not responding to drainage and systemic antibiotics. Hydrogen peroxide and streptokinase are other adjunctives for the management of necrotic collections.

Though such agents have been used with modest success to improve the outcome of AP and collections, the optimal dose, volumes, concentration and timing for use of these agents are still not known. A recent review by Trikudanathan *et al*[132] suggested that these agents can be used in the management of necrotic pancreatitis if there is no clinical and imaging improvement after drainage alone.

When to contemplate and what role is played by direct endoscopic necrosectomy?

The term direct refers to the access of necrotic collection directly by endoscope through the gastric or duodenal wall. The direct endoscopic necrosectomy (DEN) forms the last step of the endoscopic step-up approach and involves direct access to the collection and debridement of the necrotic material. The step-up approach includes declogging of the blocked stent lumen, placement of a nasocystic tube and irrigation (chemical necrolysis) and DEN. Lakhtakia *et al*[133] showed that after initial drainage with a biflanged metal stent, 74.6% of patients had clinical success. Reintervention with a step-up approach improved the overall clinical success to 96.5% with DEN required in only 9.2% of the patients.

Several studies have confirmed the safety and efficacy of DEN in patients with infected pancreatic collections[134,135]. The PENGUIN trial compared DEN and surgical necrosectomy [video-assisted retroperitoneal debridement (VARD) or open] in patients with infected WON and showed significantly lower IL-6 levels and lower rates of complication (20% *vs* 80%) in the DEN group[136]. Subsequently, the TENSION trial compared the endoscopic step-up approach (EUS-guided stent placement followed by DEN) with the surgical step-up approach (percutaneous catheter drainage followed by VARD)[137]. The major complications and mortality rates were similar in both groups. However, the incidence of pancreatic fistula formation was higher with the percutaneous approach.

Though DEN has been shown to improve the outcome with a reduced need for surgical intervention. A relevant point of discussion is the timing of DEN after initial drainage. It was initially thought that performing DEN after 3-7 d would allow maturation of the cystogastrostomy/cystoenterostomy tract. However, with the advent of lumen-apposing metal stents, DEN can be performed immediately after the placement of the stent. Yan *et al*[138] in a multicentric study compared immediate and delayed DEN for WON. The study showed no difference in clinical success and adverse events. The study also showed the mean number of necrosectomy sessions for WON resolution was significantly lower in the immediate DEN group compared to the delayed DEN group (3.1 *vs* 3.9, $P < 0.001$).

The studies suggest that DEN remains the cornerstone of the endoscopic step-up approach with similar or lower complication rates than the percutaneous step-up approach. After initial endoscopic drainage, DEN can be performed immediately post-drainage, or delayed DEN can be considered depending on the clinical status of the patients. Post-endoscopic drainage of collection, a step-up approach of initial chemical necrolysis followed by DEN or upfront DEN can be considered depending on the available expertise, clinical status of the patient and residual collection.

When to consider a minimally invasive approach and surgery?

The indications of surgery are limited in the setting of AP. Surgery is usually required for necrosectomy and rarely for acute compartment syndrome. As a general rule of thumb, any surgical intervention should not be done before 4 wk of the onset of the disease to enable the walling-off of the collections.

The approach for surgical necrosectomy could be minimally invasive, laparoscopic or open. In 2010 van Santvoort *et al*[99] (PANTER trial) compared the step-up approach with primary open surgical necrosectomy surgery. The study concluded that a minimally invasive step-up approach reduced the rate of major complications and mortality in patients with infected pancreatic necrosis. In the step-up approach, initial drainage is followed by debridement and necrosectomy using minimally invasive surgical methods. Several minimally invasive approaches are described and popularly utilized including minimally invasive retroperitoneal percutaneous necrosectomy and VARD[139,140]. Both minimally invasive retroperitoneal percutaneous and VARD retroperitoneal techniques are modifications of the open lateral approach initially described in the 1980s by Fagniez *et al*[141]. The aim of these minimally invasive approaches is not complete necrosectomy but to remove loosely adherent pieces of necrosis, thus minimizing the risk of hemorrhage. Open surgical necrosectomy is only indicated when a minimally invasive approach fails or in the absence of expertise.

MISCELLANEOUS ISSUES

Certain issues like the management of IAH and persistent ascites may require a multipronged approach predominantly revolving around timely drainage.

How to manage IAH

In AP, high intra-abdominal pressures (IAPs) are a common finding and occur through multiple mechanisms (*i.e.* pancreatic and/or peri-pancreatic inflammation, third space fluid loss and retention in the abdominal cavity and ileus). The pressure can reach the extent to produce IAH or abdominal compartment syndrome. IAH is defined as sustained IAP above 12 mmHg and occurs frequently in AP

[51]. Several studies have observed poor outcomes in patients with IAH[142,143].

The management of increased abdominal pressure should follow the standard algorithm proposed by the various societies irrespective of the etiology[144,145]. The management includes the frequent monitoring of IAP, evacuation of intraluminal contents using NG or rectal tubes, improving abdominal wall compliance by use of adequate analgesia and sedation, goal-directed use of fluid and release of intra-abdominal fluid or collection using percutaneous drainage.

Singh *et al*[143] in a retrospective study showed that the presence of IAH increases the risk of development of multiple OF and was associated with higher mortality. At 48 h post-percutaneous drainage, the mean reduction in IAP was significantly higher (6.87 mmHg *vs* 3.21 mmHg, $P < 0.001$) in patients with baseline IAH than in patients without IAH. The study also identified that post-percutaneous drainage a pressure reduction of > 40% was associated with better survival.

How to manage persistent ascites?

Ascites are commonly described in patients with AP, but its association and effect on outcome are poorly understood. Samanta *et al*[146] identified that the presence of ascites was associated with higher rates of OF and increased mortality in AP. Mortality rates were four times higher in the presence of ascites compared to non-ascites patients (34.1% *vs* 8.4%, $P = 0.001$). The study showed that the presence of moderate to gross ascites was associated with IAH and higher rates of OF. Though the presence of ascites increases IAP, several unidentified mechanisms could contribute to the poor outcome in the presence of ascites in AP. Serum ascites albumin gradient (SAAG) can be used to differentiate the underlying pathophysiological process in addition to history and diligent physical examination. SAAG > 1 may indicate underlying portal hypertension, while pancreatic ascites (SAAG < 1) may require drainage and/or endoscopic placement of transpapillary pancreatic duct stent. Hence, the decision of drainage of persistent ascites should be considered before drainage of the collection.

CONCLUSION

The management of AP is still a work in progress. Even though there are several guidelines, there is a lack of consensus on certain issues. The choice and type of fluid resuscitation are still evolving. The nutrition aspect is settled with ample evidence for early enteral feeding. The judicious use of antibiotics is always debatable, and the ideal analgesic is unknown. The intervention is tending towards endoscopy or percutaneous drainage rather than surgery. With the progressive development of technology and expertise, more data is likely to emerge that may help in the formulation of more conclusive indications and guidelines.

FOOTNOTES

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REVIEW

Classification of osteogenesis imperfecta: Importance for prophylaxis and genetic counseling

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Abstract

Osteogenesis imperfecta (OI) is a genetically heterogeneous monogenic disease characterized by decreased bone mass, bone fragility, and recurrent fractures. The phenotypic spectrum varies considerably ranging from prenatal fractures with lethal outcomes to mild forms with few fractures and normal stature. The basic mechanism is a collagen-related defect, not only in synthesis but also in folding, processing, bone mineralization, or osteoblast function. In recent years, great progress has been made in identifying new genes and molecular mechanisms underlying OI. In this context, the classification of OI has been revised several times and different types are used. The Sillence classification, based on clinical and radiological characteristics, is currently used as a grading of clinical severity. Based on the metabolic pathway, the functional classification allows identifying regulatory elements and targeting specific therapeutic approaches. Genetic classification has the advantage of identifying the inheritance pattern, an essential element for genetic counseling and prophylaxis. Although genotype-phenotype correlations may sometimes be challenging, genetic diagnosis allows a personalized management strategy, accurate family planning, and pregnancy management decisions including options for mode of delivery, or early antenatal OI treatment. Future research on molecular pathways and pathogenic variants involved could lead to the development of genotype-based therapeutic approaches. This narrative review summarizes our current understanding of genes, molecular mechanisms involved in OI, classifications, and their utility in prophylaxis.

Key Words: Osteogenesis imperfecta; Heterogeneity; Classification; Molecular mechanism; Genetic counseling; Prophylaxis

Core Tip: Osteogenesis imperfecta (OI) is a genetically heterogeneous systemic collagenous disorder with high phenotypic variability. Recent discoveries of new genes and molecular mechanisms underlying the disease have led to revisions of classical classification. Identifying the causative gene and molecular mechanisms allows a personalized management strategy, accurate family planning, and pregnancy management decisions including options for mode of delivery, or early antenatal OI treatment.

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INTRODUCTION

Osteogenesis imperfecta (OI) is a rare monogenic disorder with an incidence estimated at about 1 per 10000 individuals[1]. It is a genetically and clinically heterogeneous disease characterized by decreased bone mass and bone fragility. This generates susceptibility to fractures with minimal or no trauma, vertebral compressions, variable skeletal deformities, and growth deficiency. Bone tissue is characterized by alterations of trabecular architecture, thin cortex, high bone turnover, and hypermineralized matrix. Patients with OI have a broad phenotypic spectrum ranging from prenatal fractures and pre and perinatal lethal outcome to mild forms with few fractures and normal stature. This phenotypic variability is only partially explained by the type of mutation or causative gene. Patients with the same pathogenic variant may present variable degrees of phenotype expression. The basic mechanism is a collagen-related defect, not only in structure or production, but also in folding, posttranslational processing, bone mineralization or osteoblast differentiation[2]. The disorder is a systemic collagen disorder and it also has extra-skeletal manifestations like blue-gray sclera, dentinogenesis imperfecta, conductive or sensory hearing loss, ligamentous laxity, muscle weakness, respiratory impairment, increased fragility of vessels, and cardiac valve abnormalities[1,3-5].

COLLAGEN SYNTHESIS

Collagen is a major component of the extracellular matrix, with essential roles in mechanical resistance and regulation of several signaling pathways. Type I collagen is a crucial skin, bone, tendons, lungs, heart, and blood vessels constituent. This collagen is a heterotrimer synthesized in a precursor form, procollagen, containing two proα1(I) and one proα2(I) chains. The procollagen has a rod-like central triple-helical domain with globular extensions at the N- and C- ends. The helical core contains repeating Gly-Xaa-Yaa tripeptides, where X is often proline and Y hydroxyproline. Type I procollagen synthesis is a complex process, involving numerous phases and many proteins necessary for post-translational modifications, folding, transport, and secretion. The proα1(I) and proα2(I) polypeptide chains, encoded by the *COL1A1* and *COL1A2* genes, are translated in the rough endoplasmic reticulum (ER). The post-translational modifications include 4hydroxylation of most prolines in the Yaa position – essential for triple helical stability. The complex formed by P3H1 – CRTAP – PPIB and the FKBP10 protein have an important role in triple helix formation. Serpin H1 is involved in the stabilization of the triple helix and transport to the Golgi apparatus. The terminal procollagen extensions are cleaved by specific proteases: Disintegrin, metalloproteinase with thrombospondin motifs 2 (ADAMTS2) and bone morphogenetic protein 1 (BMP1). Three specific regions, relevant to the interaction of collagen with other collagen molecules or extracellular matrix proteins, were identified along the α1chain - major ligand-binding regions (MLBRs), which are very important for matrix quality[6-9]. Pathogenic variants in gene-encoding key players in these processes lead to collagen defects and OI phenotype.

CLASSIFICATION

Lately, OI classification has been the subject of extensive debates and has been revised several times. In 1979, Sillence proposed a classification based on clinical/radiological characteristics and mode of inheritance: OI type I - autosomal dominant (AD) with blue sclerae, OI type II - perinatal lethal form with radiographically broad, crumpled femora and beaded ribs, OI type III - progressively deforming,

and OI type IV – dominant with normal sclerae[10] (Figure 1). This classification included only patients with defects in the primary structure of collagen. The discovery of pathogenic variants in new genes with clinical overlap with previous types has caused many debates. In 2014, Van Dijk and Sillence suggested the addition of OI type V – a form with calcification in the intraosseous membranes[11]. The revised nosology and classification of genetic skeletal disorders recognizes these five clinical types (but Arabic numerals are used), with subclasses based on inheritance patterns and genes involved[12]. Some types (*e.g.* 3 or 4) have many genes and different inheritance (dominant/ recessive) resulting in challenges for genetic counseling. An alternative functional classification based on the metabolic mechanism was also proposed: Group A - defects in collagen synthesis, structure, or processing, group B - defects in collagen modification, group C - collagen folding and cross-linking defects, group D - compromised bone mineralization, and group E - defects in osteoblast development with collagen insufficiency[8,13]. The Online Mendelian Inheritance in Man database uses a mixed-genetic classification, with types I–IV according to the Sillence classification and pathogenic variants in *COL1A1* or *COL1A2*, and the new gene-classified type[1] (Table 1). The advantages of genetic classification are the identification of the inheritance pattern for counseling, prophylaxis, and the possibility of grouping for etiology-based therapies research.

GENES AND PROTEINS INVOLVED IN OI

COL1A1 and COL1A2

Over 85% of OI cases are associated with pathogenic variants in *COL1A1* and *COL1A2* genes, which lead to quantitative or qualitative alterations of collagen. These mutations generate OI types I - IV. Pathogenic variants (mostly nonsense mutations) lead to haploinsufficiency and reduce the amount of normal collagen, thus generating a milder phenotype. In contrast, pathogenic variants leading to structural collagen defects cause a more severe phenotype. The most common mutations are single-nucleotide variants resulting in the substitution of a glycine residue. Substitutions in gene regions that encode branched-chain or charged amino acids interfere with triple helix folding and are associated with severe clinical consequences. Substitutions on the α1(I) chain have a more severe/Lethal outcome than those in α2(I). The nature of the substituting amino acid, the chain in which it is located, and its position along the chain influence the phenotype. Pathogenic variants in the 3' or 5' splice sites that produce exon skipping do not affect the Gly-Xaa-Yaa triplet pattern but may cause local looping out of chains[1,2]. Pathogenic variants in the C-terminal propeptide, which is cleaved from the mature collagen, impair chain association or delay the incorporation into the collagen trimer[14]. Deletions or duplications of the codons for one or two Gly-Xaa-Yaa triplets shift the chain alignment without interrupting the sequence and produce severe or lethal phenotypes[15]. Due to the direction of the zipper-like folding of the chains, pathogenic variants in the N-terminal region have minimal consequences, whereas those in the C-terminal region cause moderate to lethal outcomes. Substitutions in MLBR3 regions impair extracellular matrix organization and usually have lethal consequences. In the α2(I) chain, severe pathogenic variants are gathered in clusters that are correlated with the proteoglycan binding site on collagen fibrils[16-19] .

IFITM5

Interferon-induced transmembrane protein 5 (IFITM5), also known as bone-restricted IFITM-like, is a short transmembrane protein expressed specifically in osteoblasts and attached to the cell membrane by palmitoylation of cysteines 50 and 5, with a regulatory role in mineralization. IFITM5 plays a crucial role in the regulation of *SERPINF1* expression and the resultant production of the protein pigment epithelium-derived factor (PEDF). Different pathogenic variants in *IFITM5* gene lead to a distinct OI phenotype, named OI V. A heterozygous gain of (new) function variant in the 5' untranslated region (c.-14C>T) is associated with a moderate type of OI with distinctive radiographic findings. This pathogenic variant creates a new start codon, resulting in the elongation of the cytoplasmic N- terminus of IFITM5 protein by five amino acids and inducing increased bone formation[2,20,21]. The characteristic radiographic findings include hyperplastic callus formation, calcification of the interosseous membrane of the forearm, and hyperdense metaphyseal band. Some patients may present radial head dislocation. Histologic examination of bone under polarized light reveals a "*mesh-like pattern*" of irregularly arranged lamellar deposition[22]. Heterozygous missense variants lead to substitution of the serine at position 40 (c.119C>T and c.119C>G), impairment of the palmitoylation process, and are associated with a more severe phenotype. Patients present prenatal fractures or shortening/ bowing of long bones, a severe deforming course, and a fish-scale lamellar pattern at the bone examination under polarized light. Patients do not show radial head dislocation or signs from the radiographic triad. Lim *et al*[23] reported a case of gonadal mosaicism in the unaffected mother[24]. Bisphosphonates (BPs) are more effective in patients with c.119C>T variant than in cases with other variants[25].

Table 1 Genes and proteins in osteogenesis imperfecta[1,2,8,13,17-19]

OI type	OMIM	Gene symbol	Approved gene name	Location	Protein name	Functional group
I	166200	*COL1A1*	Collagen type I alpha 1 chain	17q21.33	Collagen alpha-1(I) chain	A
II	166210	*COL1A1*	Collagen type I alpha 1 chain	17q21.33	Collagen alpha-1(I) chain	A
		COL1A2	Collagen type I alpha 2 chain	7q21.3	Collagen alpha-2(I) chain	
III	259420	*COL1A1*	Collagen type I alpha 1 chain	17q21.33	Collagen alpha-1(I) chain	A
		COL1A2	Collagen type I alpha 2 chain	7q21.3	Collagen alpha-2(I) chain	
IV	166220	*COL1A1*	Collagen type I alpha 1 chain	17q21.33	Collagen alpha-1(I) chain	A
		COL1A2	Collagen type I alpha 2 chain	7q21.3	Collagen alpha-2(I) chain	
V	610967	*IFITM5*	Interferon induced transmembrane protein 5	11p15.5	Interferon-induced transmembrane protein 5	D
VI	613982	*SERPINF1*	Serpin family F member 1	17p13.3	Pigment epithelium-derived factor	D
VII	610682	*CRTAP*	Cartilage associated protein	3p22.3	Cartilage-associated protein	B
VIII	610915	*P3H1*	Prolyl 3-hydroxylase 1	1p34.2	Prolyl 3-hydroxylase 1	B
IX	259440	*PPIB*	Peptidylprolyl isomerase B	15q22.31	Peptidyl-prolyl cis-trans isomerase B	B
X	613848	*SERPINH1*	Serpin family H member 1	11q13.5	Serpin H1	C
XI	610968	*FKBP10*	FKBP prolyl isomerase 10	17q21.2	Peptidyl-prolyl cis-trans isomerase *FKBP10*	C
XII	613849	*SP7*	Sp7 transcription factor	12q13.13	Transcription factor Sp7	E
XIII	614856	*BMP1*	Bone morphogenetic protein 1	8p21.3	Bone morphogenetic protein 1	A
XIV	615066	*TMEM38B*	Transmembrane protein 38B	9q31.2	Trimeric intracellular cation channel type B	B
XV	615220	*WNT1*	Wnt family member 1	12q13.12	Proto-oncogene Wnt-1	E
XVI	616229	*CREB3L1*	cAMP responsive element binding protein 3 like 1	11p11.2	Cyclic AMP-responsive element-binding protein 3-like protein 1	E
XVII	616507	*SPARC*	Secreted protein acidic and cysteine rich	5q33.1	*SPARC*	E
XVIII	617952	*TENT5A*	Terminal nucleotidyltransferase 5A	6q14.1	Terminal nucleotidyltransferase 5A	Unclassified
XIX	301014	*MBTPS2*	Membrane bound transcription factor peptidase, site 2	Xp22.12	Membrane-bound transcription factor site-2 protease	E
XX	618644	*MESD*	Mesoderm development LRP chaperone	15q25.1	LRP chaperone MESD	Unclassified
XXI	619131	*KDELR2*	KDEL ER protein retention receptor 2	7p22.1	ER lumen protein-retaining receptor 2	C
XXII	619795	*CCDC134*	Coiled-coil domain containing 134	22q13.2	Coiled-coil domain-containing protein 134	Unclassified

OI: Osteogenesis imperfecta; OMIM: Online Mendelian Inheritance in Man; ER: Endoplasmic reticulum; LRP: Lipoprotein receptor-related protein.

SERPINF1

PEDF, encoded by *SERPINF1* gene, is a ubiquitously expressed protein, with anti-angiogenic, anti-tumorigenic, and anti-metastatic properties. The binding of PEDF to type I collagen is essential for anti-angiogenic properties. PEDF induces the expression of osteoprotegerin which interacts with the receptor activator of nuclear factor-κβ ligand (RANKL) pathway and regulates the activity of osteoclasts. Kang *et al*[26] suggest that antagonism between PEDF and TGF-β pathways controls osteogenesis and bone vascularization[8,27]. Patients with biallelic pathogenic variants in *SERPINF1* have postnatal fractures, progressive skeletal deformity, vertebral compressions, and a fish-scale pattern at bone examination under polarized light (similar to patients with loss of function mutation in *IFITM5*). These mutations produce OI type VI. The RANKL-antibody is a potential therapeutic agent for this form of OI[1,4,28].

CRTAP, P3H1 and PPIB

Cartilage-associated protein (CRTAP) forms a complex with prolyl-3-hydroxylase 1 (P3H1) and peptidyl-prolyl-cis-transisomerase B (PPIB). This complex is involved in 3-hydroxylation of specific proline residues. Chang *et al*[29] showed that CRTAP and P3H1 are mutually stabilized in the collagen prolyl 3-hydroxylation complex. Biallelic pathogenic variants in *CRTAP* or *P3H1* genes lead to a marked decrease in proline hydroxylation and subsequently to a delay in collagen folding and are associated

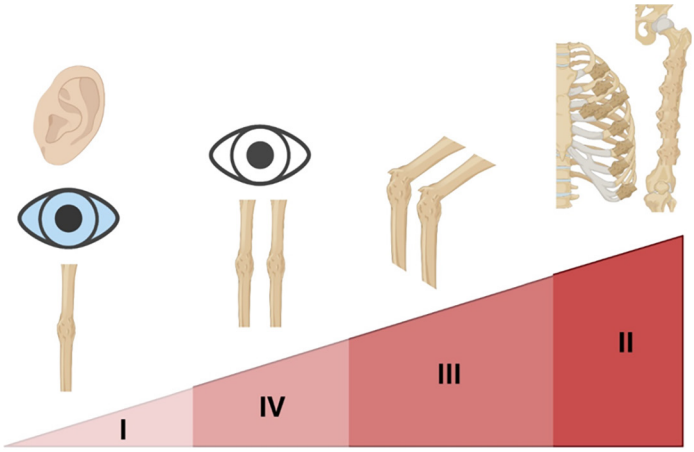

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Figure 1 Clinical osteogenesis imperfecta classification (severity). OI type I – mild form with blue sclerae, hearing loss; OI type IV – mild to moderate form with normal sclerae; OI type III - progressively deforming; OI type II – extremely severe form, lethal perinatal outcome with radiographically broad, crumpled femora and beaded ribs (Created with BioRender.com). OI: Osteogenesis imperfecta.

with a severe/lethal form of OI. Patients have neonatal fractures, rhizomelia, and undertubulation of the long bones[4,13,30-31]. Biallelic pathogenic variants in *PPIB* gene are associated with a low percentage of 3-hydroxylated proline at position 986, but higher than in *CRTAP* or *P3H1* genes mutations. The phenotype overlaps with that caused by *CRTAP* or *P3H1* genes mutation, with the exception of rhizomelia[32,33]. *CRTAP* genes mutations determine OI type VII, *P3H1* genes mutations determine OI type VIII, while *PPIB* genes mutations determine OI type IX.

SERPINH1

Serpin H1 is a collagen-specific chaperone, that localizes in the ER and is encoded by *SERPINH1* gene. Serpin H1 binds to arginine-rich sequences of triple helical collagen and stabilizes it by preventing unfolding and aggregate formation. Also, serpin H1 participates in the shuttling of correctly folded collagen into the Golgi apparatus. Homozygous or compound heterozygous pathogenic variants in *SERPINH1* gene lead to misfolding, intracellular aggregation, and delayed collagen secretion and are associated with a moderate to severe form of OI – OI type X[34-36].

FKBP10

Serpin H1 interacts with peptidyl-prolyl cis-trans isomerase FKBP10, another collagen chaperone, which provides mutual stability and allows for a synergistic effect during collagen folding. FKBP10 is also required for the activity of lysyl hydroxylase 2 (LH2, encoded by *PLOD2* gene). Hydroxylation of the collagen telopeptide lysyl residues is essential in cross-linking. Recessive pathogenic variants in *FKBP10* gene are associated with a wide clinical spectrum which includes a progressive deforming form of OI (OI type XI), Bruck syndrome, and Kuskokwim syndrome. Bruck syndrome is characterized by congenital contractures with pterygia, early onset of fractures, short stature, limb deformity, and progressive scoliosis. Bruck syndrome 2 presents a similar phenotype, but it is generated by a biallelic pathogenic variant in *PLOD2* gene. Kuskokwim syndrome is a congenital contracture disorder with mild skeletal anomalies, occurring in Yup'ik Eskimos in Alaska. Bisphosphonate therapy reduces the fracture rate and pain but has no effect on joint abnormalities[4,37-39].

SP7

SP7 gene encodes transcription factor SP7, a key regulator of osteoblast differentiation and subsequently of osteocyte formation. Recessive pathogenic variants in *SP7* are associated with increased bone porosity, recurrent fractures, skeletal deformities, delayed teeth eruption and hearing loss. This particular phenotype is characteristic to OI type XII. Recently, heterozygous (dominant) missense variants affecting a highly conserved zinc finger domain have been reported in cases with bone fragility, high bone turnover, and patchy sclerosis[40-43].

BMP1

The major function of bone morphogenetic protein 1 (BMP1) involves procollagen I C-terminal propeptide processing, crucial for fibril formation. Other roles are activation of lysyl oxidases (involved in cross-linking), processing of small leucine-rich proteoglycans (*e.g.* decorin - important for collagen fibrillogenesis) and dentin matrix protein 1 involved in bone mineralization, and activation of TGFβ1, a key signaling molecule for bone remodeling. Patients with homozygous or compound heterozygous pathogenic variants in *BMP1* gene present a variable phenotype ranging from mild to severe

progressive deforming OI (OI type XIII). Individuals with *BMP1* pathogenic variants with residual activity of the protein have a milder phenotype than cases with null pathogenic variants. In the majority of cases, increased bone mineral density (BMD) has been noticed. In this context, the indication, dose, and duration of antiresorptive therapy are questionable due to concerns about increasing bone stiffness leading to fracture[2,44-47].

TMEM38B

TMEM38B gene encodes TRimeric Intracellular Cation channel type B (TRIC-B), specific for potassium, also known as transmembrane protein 38 (TMEM 38B). TMEM 38B is involved in the opening of cation channels, after calcium release, and thus the ER membrane potential is maintained. Disruption of intracellular calcium kinetics affects the activity of many proteins required for type I collagen synthesis and folding[48,49]. Webb *et al*[50] revealed characteristics of bone modifications in patients with biallelic *TMEM38B* pathogenic variants: Decreased hydroxylation of collagen helical lysine residues and intracellular retention and degradation of misfolded collagen. The phenotypic spectrum varies considerably ranging from mild scoliosis to severe cases with prenatal bowed femur, early-onset multiple fractures, and growth retardation (OI type XIV). The variability in phenotype severity indicates that other factors may be involved, including genetic modifiers, different genetic backgrounds, and other genes involved in intracellular calcium dynamics. Patients responded well to BPs, but, in some cases, cardiovascular abnormalities and hypotonia were reported (possibly related to abnormal ER calcium kinetics)[51-54].

WNT1

Proto-oncogene Wnt-1 (the wingless-type mouse mammary tumor virus integration site family, member 1) is a glycoprotein with a key role in bone development. WNT1 interacts with the cell surface lipoprotein receptor-related protein 5 (LRP5) and Frizzled receptor leading to the translocation and accumulation of beta-catenin into the cell nucleus and subsequent transcriptional regulation of target genes. WNT/β-catenin signaling is involved in osteoblast progenitor proliferation, osteoblast differentiation, and regulation of osteoclastogenesis in mature osteoblasts and osteocytes through the secretion of osteoprotegerin[55-57]. The WNT/β-catenin pathway is an activator of *BMP2* gene transcription, a member of the TGF-β gene superfamily essential for osteoblast differentiation and osteogenesis[57]. Biallelic pathogenic variants in *WNT1* gene lead to moderate-severe OI, whereas heterozygous *WNT1* gene mutations are reported in patients with 'early-onset osteoporosis' indicating a gene dose effect. Neurologic features such as hypotonia, ptosis, developmental delays, and brain anomalies have been reported in some patients with OI type XV[57-60].

CREB3L1

Cyclic AMP-responsive element-binding protein 3-like protein 1 (CREB3L1), also known as old astrocyte specifically induced substance (OASIS), a leucine zipper transcription factor is encoded by *CREB3L1* gene. In osteoblasts, CREB3L1 is activated by regulated intramembrane proteolysis (RIP) and induces the transcription of *COL1A1* gene by binding to the UPR element-like sequence in its promoter. Also, CREB3L1 plays an important role in the expression of coat protein complex II component SEC24D, involved in procollagen export from ER[45,61,62]. Phenotype severity varies considerably ranging from forms with prenatal fractures, severe demineralization, and early lethal outcome to cases with severe bone deformities and survival to adulthood (OI type XVI). Severe phenotypes are caused by homozygous whole gene deletions or in frame deletions in a highly conserved DNA binding domain (loss of function). Siblings with heterozygous pathogenic variants are mildly affected: fractures with minimal trauma, blue sclerae, and osteopenia[61,63]. Truncating homozygous pathogenic variants (outside the highly conserved DNA binding domain) led to a non-lethal phenotype, while heterozygotes are unaffected[64,65].

SPARC

Secreted protein acidic and rich in cysteine (SPARC), also known as osteonectin or basement membrane protein 40, has a collagen-binding domain and a hydroxyapatite (necessary for mineralization of the collagenous matrix) binding site. During bone development, SPARC is secreted by osteoblasts and has important roles in procollagen processing and assembly in the bone matrix, cross linking, and mineralization[66,67]. Pathogenic variants (substitution, nonsense or splice site) that affect the collagen-binding domain have been reported in patients with OI. Common features of this type of OI (OI type XVII) are multiple postnatal fractures, scoliosis, delayed motor development, neuromuscular weakness (especially of the lower extremities), and brain MRI abnormalities[68-70].

TENT5A

Terminal nucleotidyltransferase 5A (TENT5A) belongs to the nucleotidyltransferase fold superfamily proteins and acts as a noncanonical poly(A) polymerase. TENT5A forms a complex with SMAD proteins and induces transcription of BMP target genes. TENT5A is involved in embryonic development, adult bone formation, and hemin-induced hemoglobinization[2,71,72]. Doyard *et al*[73] reported biallelic

pathogenic variants (nonsense or missense) in *TENT5A* genes in patients with a severe form of OI (OI type XVIII) with multiple fractures, severe bowing of lower limbs, joint hyperlaxity, vertebral collapses, and blue sclerae. Lin *et al*[71] considered TENT5A a molecular modulator and a future therapeutic target.

MBTPS2

An X-linked form of OI (OI type XIX) is caused by a mutation in *MBTPS2*, a gene that encodes the membrane-bound transcription factor protease, site-2 (MBTPS2), also known as site-2 protease, a component of the RIP pathway. ER stress - due to retention of unfolded proteins - leads to translocation of CREB3L1, sterol regulatory element-binding protein, and activating transcription factor 6, from the ER membrane to the Golgi membrane, where they are cleaved by endoproteases MBTPS1 and MBTPS2. The resulting fragments regulate the production of collagen and matrix components in the nucleus[1,2,74]. Substitutions that affect a highly conserved MBTPS2 motif, essential for zinc ion coordinating site, are associated with reduced hydroxylation of lysine 87 in both α collagen chains and altered collagen cross-linking. Patients have a form of moderate-to-severe OI with prenatal fractures, generalized osteopenia, long bone bowing, short stature, pectus deformity, and scoliosis, but no dermatological features[75]. Missense pathogenic variants elsewhere in *MBTPS2* have been associated with dermatological conditions - IFAP (ichthyosis follicularis, atrichia, and photophobia) syndrome with or without BRESHECK (Brain anomalies, severe mental Retardation, Ectodermal dysplasia, Skeletal deformities, Ear/eye and Kidney dysplasia/hypoplasia) syndrome, Olmsted syndrome (mutilating palmoplantar keratoderma with periorificial keratotic plaques), and keratosis follicularis spinulosa decalvans[76-78].

MESD

MESD gene (mesoderm development) encodes an ER chaperone for the WNT signaling receptors LRP5 and LRP6. Moosa *et al*[79] reported patients with biallelic pathogenic variants (frameshift predicted to result in a premature termination codon or substitution that removes a highly conserved domain) in exon 3 of *MESD* gene, with partial loss of function, and a progressively deforming type of OI with oligodontia and developmental delay. BPs were not effective in these patients, but antisclerostin antibodies that affect Wnt signaling could be a valid therapeutic option. Two infant deaths due to respiratory insufficiency were reported. Stürznickel *et al*[80] reported three stillbirths with multiple intrauterine fractures and compound heterozygous frameshift pathogenic variants in exon 2 and exon 3 of *MESD* gene. They blamed the lethal phenotype on a complete loss of function mutation, located within the chaperone domain of MESD (exon 2)[80].

KDELR2

KDELR2 gene encodes ER lumen protein-retaining receptor 2, involved in protein with a KDEL-like peptide traffic from the Golgi to the ER. The protein binds heat shock protein 47 (HSP47), with an essential role in the intracellular processing of procollagen. Biallelic pathogenic variants in *KDELR2* gene are associated with abnormal collagen fibril formation due to the failure of HSP47 to dissociate from collagen type 1. Patients present a progressively deforming type of OI. Efthymiou *et al*[81] reported neurodevelopmental disorders (motor and speech delay) in three cases[82].

CCDC134

CCDC134 gene encodes a secreted coiled-coil domain-containing protein, involved in the regulation of MAPK pathway, especially phosphorylation of the extracellular signal-related kinase (Erk) or c-JUN N-terminal kinase (JUNK). Erk1/2 and JUNK have an important role in bone morphogenesis, by regulating osteoblast extracellular matrix protein deposition in response to stress. Loss of function pathogenic variants in *CCDC134* gene were associated with reduced *COL1A1* and *SPP1* (ostepontin) mRNA expression and mineralization in osteoblasts. Dubail *et al*[83] reported patients with homozygous pathogenic variants in *CCDC134* gene and a severe form of OI with intrauterine growth retardation, multiple pre and postnatal fractures, short stature, low mineral density, and no response to BPs[84,85].

GENETIC COUNSELING AND PROPHYLAXIS

The identification of the inheritance pattern is essential for genetic counseling and management. Up to 90% of OI patients have an AD pathogenic variant in *COL1A1, COL1A2,* or *IFITM5* genes, with a 50% risk to transmit this variant to their offspring[86]. Nearly half of the OI cases are caused by *de novo* pathogenic variants[87]. Although advanced paternal age is associated with a high risk of *de novo* pathogenic variants in monogenic disorders, Mei *et al*[88] reported a significantly younger paternal and maternal age at conception in OI patients with a *de novo* mutation. Pyott *et al*[89] reported a 16% rate of parental mosaicism in couples with a child affected by lethal AD OI. In couples with two or more children with lethal AD OI, the recurrence rate of this mosaicism was 27%[89]. The rate of parental mosaicism is estimated at approximately 5–8% in all OI cases[86]. Persons with mosaicism for AD

pathogenic variants are often asymptomatic or have subtle clinical findings depending on the percentage of cells that carry the pathogenic variant[88].

About 10% of OI patients have pathogenic variants with autosomal recessive (AR) inheritance. The distribution of these AR variants is different across populations due to consanguinity or founder effect. In a genetically isolated Dutch group, the carrier frequency of a *CRTAP* frameshift variant was 4.1% while in the general Dutch population is < 0.2%[90]. Founder pathogenic variants in other genes associated with recessive OI have been reported: *P3H1* in West African, United States African American populations and ethnic Kinhs, *TMEM38B* in Palestinians, and Israeli Arab Bedouins, *FKBP10* in indigenous southern Africans, Palestinians, Bavarians, and Samoan islanders, *SEC24D* in southwestern Germans, *WNT1* in the Finnish Hmong group, and *PPIB* in Chinese people[33,91-95]. A few cases with X-linked pathogenic variants in *MBTPS2* or *PLS3* have also been reported[75,96].

Genetic testing is essential for the identification of pathogenic variants, inheritance pattern, and differential diagnosis. Based on the clinical and radiographic features, and family history either the sequencing of *COL1A1* and *COL1A2* or a comprehensive next-generation sequencing panel (all OI genes and genes associated with skeletal dysplasia) is initially recommended. The interpretation of genetic testing results can sometimes be challenging: Identifying unknown significance variants, or sequence variants in a new gene (not previously reported in OI cases). Genotype-phenotype correlations are sometimes difficult to establish, due to the wide OI phenotypical variability, in association with genetic or epigenetic modifiers[97]. Some OI lethality/ severity prediction algorithms were established with variable accuracy[98].

Preconception carrier screening is recommended in healthy couples in different circumstances: positive OI family history, consanguineous marriage, or members of founder populations. Carrier screening cannot detect parental germline mosaicism or predict the possibility of *de novo* pathogenic variants. A couple with a significant recurrence risk - affected parent(s), carriers of AR pathogenic variants - has many reproductive options: *In vitro* fertilization (IVF) with gamete or embryo donation, IVF with own cells, and preimplantation genetic diagnosis (PGD), adoption, or natural pregnancy with prenatal diagnosis. Gamete donation is usually recommended in couples with infertility or affected women, because repeated superovulation procedures are associated with an increased risk of osteoporosis and cardiovascular problems[99]. PGD has the advantage of also detecting aneuploidies, but the accuracy rate is 95 to 99.5%, so there is a small risk of false negative results. Moreover, the success rate for artificial reproductive techniques is below 30%. Prenatal testing should be recommended after implantation to confirm the PGD result. In this context, a debatable issue is the transfer of AR variants heterozygous embryos. A parental argument not to transfer an AR carrier embryo would be the prevention of difficult reproductive options for the future child[86,100,101].

Prenatal testing

Prenatal genetic testing includes non-invasive prenatal testing (NIPT), and invasive techniques. NIPT has the advantages of early testing (first trimester), less invasive procedure (circulating cell-free fetal DNA extracted from maternal blood), and no associated miscarriage risk. The disadvantages of NIPT are the risk of false-positive, false-negative, or inconclusive results due to confined placental mosaicism (the trophoblastic origin of cell-free fetal DNA is associated with a much higher mutation rate than other fetus cells), or vanishing twin syndrome. NIPT is technically challenging for X-linked and for AR forms when both parents are carriers of the same pathogenic variant due to the presence of the relevant variant from maternal cells in the circulating cell-free DNA. Moreover, NIPT does not cover all the genes involved in OI pathogeny. NIPT results should be confirmed by invasive prenatal testing[102-106].

Invasive prenatal testing uses fetal cells extracted by chorionic villus sampling (CVS), amniocentesis, or cordocentesis, and is associated with an increased risk of pregnancy complications, including fetal loss. CVS has an associated risk of false results due to confined placental mosaicism but allows biochemical type I collagen analysis in extracted cells. Amniocentesis avoids misdiagnosis due to placental mosaicism or twin pregnancy but is performed in the second trimester, after 15 wk of pregnancy, and thus means a long distressful waiting period for the couple. Prenatal diagnosis allows pregnancy management decisions, including the alternative to terminate pregnancy or options for mode of delivery, early OI treatment, before (mesenchymal stem cell transplantation), or after birth[86,107,108].

Ultrasound screening

Severe and lethal forms of OI could be detected by ultrasound screening in the second trimester. Abnormal ultrasound findings suggestive of severe OI include long bone shortening (especially femur length), bowing, and multiple fractures. Moreover, lethal forms have severe demineralization with a thin, easily compressible calvarium, and no posterior acoustic shadowing from long bones[107,109]. Femur length-to-abdominal circumference ratio < 0.16, fetal lung volume below the fifth percentile for gestational age (measured by ultrasound or MRI), and polyhydramnios were associated with lethal outcome. Ultrasound findings do not allow an accurate differential diagnosis with other skeletal dysplasias[107,110,111]. Three-dimensional helical computed tomography provides more accurate data about skeletal anomalies but there are concerns regarding the safety of radiation exposure (even to low

doses)[112].

Mode of delivery

In the past, cesarean delivery was considered safer and more useful for the prevention of fractures at birth than vaginal delivery. Recent studies on babies with types I, III and IV of OI showed that the delivery mode does not influence the rate of fractures at birth. Also, the breech presentation seems to be more frequent in OI type III. Bellur *et al* suggested that cesarean delivery should be performed only for usual maternal or fetal indications, not for fracture prevention in OI. Pregnant women affected by OI require close monitoring to detect possible complications such as cardiorespiratory problems, bone loss, cephalopelvic disproportion, uterine and placenta rupture, and excessive bleeding at delivery[107,113-115].

Therapy

The OI treatment includes physical therapy, medication, and surgical procedures. The major goals are the prevention of fractures, and deformities, maximizing the patient's functional ability, and reducing pain. Fracture healing might be delayed in cases with pathogenic *WNT1* gene variants, or might be altered by hyperplastic callus formation in patients with pathogenic *IFITM5* gene variants. Surgical procedures are used for complex fractures or when correction of deformities is necessary. Intramedullary telescopic rods are used during growth because these have the ability to lengthen. OI patients have anesthetic risks due to abnormal shape or airway, impaired lung function, or the possibility of cervical spine fracture during intubation[4,116]. The rate of fractures decreases in adulthood but the risk of joint osteoarthritis increases[13]. Physiotherapy is essential to improve mobility, due to hypotonia and ligament laxity. Obstructive pulmonary disease (type I collagen is present in lung parenchyma) and scoliosis lead to respiratory complications, a major cause of mortality in OI[117]. Cardiovascular complications include aortic root dilatation left valvular regurgitation, and aortic root dilatation with dissection risk[118]. A multi-disciplinary approach is recommended to address problems related to bone fragility, and also extra-skeletal manifestations.

Antiresorptive bone therapy

BPs are currently the most commonly used pharmacological agents in the treatment of pediatric OI. BPs bind to the hydroxyapatite crystals, promote osteoclasts apoptosis, and decrease bone resorption and remodeling. BPs also interact with osteocytes and interfere with osteoblast recruitment on eroded surfaces[119]. Intravenous infusion is superior to oral administration in improving BMD and decreasing fracture rate. Studies reported that maximum benefits are obtained after 3 years of treatment, but there is no difference in adult fracture rates[120-123]. Long-term treatment is associated with microcrack accumulation and increased potential of progression into fractures, loss of microstructural integrity, and reduced mechanical strength[124]. Another disadvantage of BPs is their long half-life; BPs persist in the bone for years after drug discontinuation. Green *et al*[125] reported decreased birth weight and transient neonatal electrolyte abnormalities (hypocalcemia, hypercalcemia, hyperphosphatemia) associated with maternal use of BPs before or during pregnancy. Whether BPs should be used for a long time at similar or lower doses is debatable. Also, BPs do not have the same efficiency in all types of OI[13,126].

Denosumab is a monoclonal antibody that targets RANKL and inhibits osteoclast activity without binding to the bone. The mechanism of action is similar to BPs, antiresorptive. Denosumab has a shorter half-life (months) and showed promising results in increasing BMD in a few studies. Further studies are necessary to assess the efficiency of fracture prevention[126,127].

Osteo-anabolic agents

Osteo-anabolic therapies stimulate osteoblast activity and bone formation, instead of inhibiting osteoclast function as antiresorptive. Growth hormone (GH) has been used to stimulate long bone growth in GH deficiency, but GH therapy showed only limited benefits in increasing bone mass density compared to BPs (mostly in OI type IV). GH has been less efficient in the more severe forms of OI (type III)[128,129]. Teriparatide, a recombinant parathyroid hormone, leads to a significant increase in BMD in adults with type I OI but seems less effective in patients with types III and IV. Teriparatide has not been used for more than 24 mo and its use in children is contraindicated due to the concern of increased risk of osteosarcoma reported by animal studies[116,129-131]. Lately, the US FDA removed the warning because the risk was only confined to animal studies.

Sclerostin-inhibitory antibodies, romosozumab, and setrusumab, neutralize sclerostin, a negative regulator of Wnt signaling in osteoblasts. Studies revealed good responses of BMD and bone turnover markers to sclerostin-inhibitory antibody treatment in adults with OI[132,133]. Lv *et al*[134] revealed that romosozumab might increase the risk of cardiovascular adverse events in the elderly.

Animal studies have shown that TGF-β signaling is an essential element of pathogenesis, and blocking TGF-β improves bone mass and biomechanical properties, so anti-TGF-antibodies could represent a valuable therapeutic option. Song *et al*[135] reported an increase of BMD in children with type IV OI treated with fresolimumab (an anti-TGF-antibody), but no effect in type III and VIII OI. Losartan, an angiotensin II receptor blocker may also have anti-TGF properties[135]. Losartan increased

bone mass and accelerated chondrocyte hypertrophy in the growth plate in an animal study[136].

Cell therapy and gene editing

Stem cell therapy is a promising pre and postnatal option based on the cells' ability to differentiate into osteoblasts that produce normal collagen. Transplantation of bone marrow from HLA-matched siblings and prenatal and postnatal transplantation of mesenchymal stem cells have been associated with improved growth and reduction of fractures rate. In the first group (bone marrow from HLA-matched siblings), the effect was transient, the growth rate slowed over time and a second transplantation with bone marrow/mesenchymal stem cells has been used. There is limited experience in this area, so further trials are necessary[137,138]. The application of cellular reprogramming to create induced pluripotent stem cells (iPSCs) opens a new therapeutic approach.

Advances in gene editing technology bring the possibility of correcting the pathogenic variant. A recent approach involves the silencing of a dominant (gain of function) pathogenic variant, leading to allele suppression and converting the severe forms into a milder phenotype. Different strategies have been used: Antisense oligonucleotides, short interfering RNA, and hammerhead ribozymes. Another approach, gene addition therapy, involves the correction of the expression of deficient or absent alleles in affected cells. In cases where an abnormal collagen chain is produced and affects triple helix assembly, this method will not influence the phenotype. The efficiency of gene editing is still debatable, there are no data about the duration of the positive effects, and concerns regarding off-target effects, risks of an immune response, and genotoxicity are raised. Clinical trials are needed[126,139].

The combination of the CRISPR–Cas9 gene editing tool with induced pluripotent stem cells may improve therapeutic options. Jung *et al*[140] demonstrated the restoration of type I collagen expression in iPSCs in an OI patient corrected by the CRISPR–Cas9 system.

A new promising therapy is the chemical chaperone 4-phenylbutyrate (4-PBA), involved in protein folding and aggregation in ER. 4-PBA also has histone deacetylase inhibitor activity. Experimental studies reported the reduction of fracture rate and improvement of growth deficiency in animal OI models after 4-BPA treatment[141,142].

CONCLUSION

In recent decades, great progress has been made in identifying genes and molecular mechanisms underlying OI. These advances demonstrate that OI is an extremely heterogeneous collagen-related disease. The classical clinical Sillence classification is now partially revolute, and the involvement of different causative genes and the presence of different inheritance patterns generate challenges for genetic counseling. However, genetic classification allows an accurate identification of the inheritance for family planning, and offers the possibility of the development of genotype-based therapeutic approaches.

FOOTNOTES

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MINIREVIEWS

Emerging role of dual biologic therapy for the treatment of inflammatory bowel disease

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Abstract

Biologic agents have now been used in the management of inflammatory bowel disease (IBD) for many years where experience, expertise and confidence in their use has developed over time. In the United Kingdom, there are well established guidelines and recommendations for both single agent biologic treatments, and with combination therapy of a biologic agent with a small molecule agent in maintenance therapy. In recent times, there has been increasing interest and experience using dual biologic therapy (DBT) in IBD, primarily in difficult to treat and refractory cases with high disease burden. However, published data on use, experience and safety profiles is limited and large-scale studies remain low in number in this developing area. We therefore aim to present a summary and review of the available published data in this area to help us better understand the emerging role of DBT in IBD.

Key Words: Dual biologic therapy; Inflammatory bowel disease; Crohn's disease; Ulcerative colitis; Combination therapy; Biologic safety

Core Tip: For patients with difficult to treat or refractory inflammatory bowel disease (IBD), biologic therapy and combination therapy with small molecule agents has helped improve patient outcomes and maintenance success. There is growing interest in the use of dual biologic therapy in IBD but published data remains limited. Whilst initial data suggests positive effects on reduction in morbidity, more studies are still required in this emerging area with further comparison of different biologic combinations and their safety profiles.

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INTRODUCTION

Inflammatory bowel disease (IBD) comprises Crohn's disease (CD) and ulcerative colitis (UC) and is typically characterised by chronic inflammation of the gastrointestinal tract with a relapsing and remitting disease course that can lead to significant complications and morbidity[1]. Disease burden for many patients remains onerous and although some patients can achieve remission through corticosteroids or aminosalicylates, effective maintenance therapy is key to successful outcomes and reduction in life-long complications such as strictures, fistulas, abscess or surgical resection[2]. Whilst there is well established experience and national guidance for varying maintenance therapies, the use of dual biological maintenance therapy in difficult to treat and refractory disease is still a novel area with little research or published data.

The British Society of Gastroenterology consensus guidelines on the management of IBD in adults (2019)[3] provides guidance on single-agent biologic therapy in CD and UC, sequential therapy in UC following treatment failure, and combined biologic and small molecule therapies in CD. However, combinations of biologics have yet to be included in this emerging area.

In recent years, advancements in the medical management of IBD have been seen and aided by novel small molecule and biologic drugs, but observed clinical response still remains limited and sub-optimal. Treatment strategies for IBD are therefore rapidly changing to help combat ongoing disease burden and morbidity. At present, clinician experience has guided potential novel therapy combinations with most data outlined in case reports and case series in the absence of large-scale studies[4]. Dual biologic therapy (DBT) presents an attractive and potentially safe option for those who have failed previous biologic therapies and have refractory disease. We therefore aim to outline, summarise and review the current available literature on the use of dual biological therapy for IBD, and establish whether such treatment could be beneficial in severe and/or refractory cases.

COMBINATION THERAPY

Biologic agents are commonly used as monotherapy for IBD, however only 40% of patients achieve remission within one year of therapy[5]. Consequently, the use of monoclonal antibodies which target tumour necrosis factor, TNF (infliximab, adalimumab, etanercept, and golimumab) in combination with newer agents which target interleukin (IL)-12 and IL-23 (ustekinumab, UST), a4b7-integrin (vedolizumab, VDZ) or a4-integrin (natalizumab), has become an increasing area of interest in patients with high disease burden. Patients often selected for DBT either present with refractory IBD and/or poorly controlled extra-intestinal symptoms[6].

VDZ, an anti-integrin, is a popular choice of biologic used in combination, often with anti-TNF treatment. It binds to a4b7, where T lymphocytes require a4b7 bound to mucosal addressin cell adhesion molecule 1 (MAdCAM-1) in order to migrate within the gastrointestinal tract. Inhibition therefore reduces inflammation by preventing T cells migrating to the gut mucosa[7,8]. IL-12/23 stimulates production of interferon-γ and TNF. UST has also been used in a number of cases[9-11], which inhibits IL-12 and IL-23 by binding to the p40 subunit (high levels of which are expressed in IBD), therefore preventing them from binding to receptors on T cells and natural killer (NK) cells[12].

Whilst combination therapy with a biologic and immunomodulator has previously been well studied; such as in the 2010 Study of Biologic and Immunomodulator Naive Patients in Crohn's Disease (SONIC) trial[13]; there has been relatively little research in this area for the use of DBT in IBD. It should be noted however, that the first reports indicating safety of DBT emerged as early as 2007[14].

There have been several reports, including the aforementioned 2007 randomised controlled trial by Sands *et al*[14], retrospective studies, case studies (which make up the majority of the reports available), and systematic reviews, which concur that dual therapy may be a safe option for treating severe IBD and extra-intestinal symptoms[4]. These are summarised in Table 1.

RANDOMISED CONTROLLED TRIAL

In 2007, Sands *et al*[14] studied the use of infliximab (IFX) in combination with natalizumab for treatment of CD in a randomised control trial, where efficacy and safety of this combination had not been previously reported. Seventy-nine patients were identified with a CD activity index (CDAI) score

Table 1 Summary of trials, case reports and retrospective studies on dual biological therapy for inflammatory bowel disease

Ref.	Study type	No. of patients	Disease	Treatment used
Sands *et al*[14], 2007	RCT	79	CD	IFX + natalizumab
Anita and Michael [16], 2016	CR	1	CD	VDZ + ADA
Bethge *et al*[17], 2017	CR	1	UC	VDZ + ETN
Liu and Loomes[9], 2017	CR	1	CD	UST + VDZ
Huff-Hardy *et al* [10], 2017	CR	1	CD	UST + VDZ
Roblin *et al*[19], 2018	CR	1	UC	GOL + VDZ
Buer *et al*[20], 2018	CS	10	4 × CD, 6 × UC	Anti-TNF + VDZ
Mao *et al*[21], 2018	CS	4	CD	VDZ + UST/GOL
Olbjørn *et al*[11], 2020	CS	13	9 × CD, 4 × UC	IFX + UST/VDZ
Glassner *et al*[22], 2020	Retrospective	50	CD + UC	UST + ANTI-TNF/VDZ, tofacitinib + VDZ/UST/anti-TNF, Cyclosporin, rituximab, SEC, leflunomide, tacrolimus
Yang *et al*[23], 2020	Retrospective	22	CD	VDZ + UST/anti-TNF, UST + anti-TNF
Privitera *et al*[24], 2020	Retrospective	16	11 × CD, 5 × UC	UST + CZP/IFX/ADA/VDZ, VDZ + ADA/SEC/IFX/CZP/aprelimast
Kwapisz *et al*[26], 2021	Retrospective	15	14 × CD, 1 × UC	VDZ + anti-TNF/UST, UST + anti-TNF/VDZ
Goessens *et al*[27], 2021	Retrospective	98	58 × CD, 40 × UC	ADA + VDZ/UST, VDZ + INF + azathioprine, VDZ + UST + azathioprine, UST + ETN, IFX + VDZ + methotrexate, CZP + VDZ + methotrexate
No author listed [15], 2022	RCT	214	UC	GOL + guselkumab

ADA: Adalimumab; CD: Crohn's disease; CR: Case report; CS: Case series; CZP: Certolizumab; ETN: Etanercept; GOL: Golimumab; IBD: Inflammatory bowel disease; IFX: Infliximab; RCT: Randomised controlled trial; SEC: Secukinumab; TNF: Tumour necrosis factor; UC: Ulcerative colitis; UST: Ustekinumab; VDZ: Vedolizumab.

of 150 or more whilst on IFX; fifty-two of these were treated with both IFX and natalizumab, whilst twenty-seven remained in the control group and received IFX plus a placebo. Those who received combination treatment showed an improvement in disease compared to the control; mean CDAI score was noted to be lower in those who received both IFX and natalizumab, compared to IFX alone.

Overall, combination therapy was deemed to be well tolerated and whilst both groups experienced adverse effects including infection, rates were similar in both groups. Other effects reported were headache, nausea and exacerbation of CD. The data suggested that treating patients with combination therapy had a greater efficacy than IFX monotherapy. Additionally, more patients developed antibodies to IFX compared to natalizumab (4% and 14%, respectively), and 5% developed hypersensitivity reactions to IFX but this was not seen in any patients secondary to natalizumab.

More recently, the VEGA study[15] assessed the use of guselkumab (an IL-23 subunit antagonist) in combination with golimumab for the treatment of moderate to severe UC. Of the 214 patients in the trial, those treated with combination therapy achieved a greater response (36.6% remission) compared to patients on monotherapy of guselkumab or golimumab (21.1% and 22.2% remission, respectively). Adverse events were deemed comparable between the groups, with one case developing severe influenza and sepsis.

CASE REPORTS

In 2016, Anita and Michael[16] reported a case of CD in a 23-year-old woman with enterocolitis, who had disease recurrence following multiple immunomodulators in combination with IFX, the latter of which led to an infusion reaction. The patient was initially switched to adalimumab (ADA) with 6-mercaptopurine (6MP) in 2006 with an initial response, however had relapsed within six years. Certolizumab pegol was ineffective, and moderate colitis was noted on colonoscopy. Subsequently, she was

commenced on VDZ, 6MP and prednisolone. The patient continued to be symptomatic and was unable to reduce the steroid dose, and was therefore started on ADA in combination with VDZ. The patient showed improvement symptomatically, biochemically and endoscopically after 3 mo. Steroids and 6MP were discontinued. VDZ was stopped after 6 mo, and she continued ADA alone, with no further symptoms and normal inflammatory markers noted.

Much like in 2016, anti-TNF has been used in combination with VDZ in additional case reports. A study in Germany reported successful therapy of severe chronic refractory pouchitis, and spondyloarthritis (SpA)[17]. Interestingly, VDZ monotherapy led to intestinal symptoms improving, however SpA worsened. The addition of etanercept (ETN) led to resolution of the SpA symptoms. Whilst arthralgia has been reported as a common side effect of VDZ[18], Bethge *et al*[17] concluded that as there was no statistical significance in the test group *vs* the placebo group and suggest that VDZ may not provide benefits to IBD related arthralgia, rather than causing the symptoms.

Additional reports from France[19], Norway[11,20] and the United States[21] have reported that dual therapy was safe and generally well tolerated, with clinical and endoscopic remission in both CD and UC.

Roblin and colleagues reported a case of severe UC with ankylosing spondylitis (AS) who initially received IFX and methotrexate, then ADA and methotrexate, followed by VDZ for treatment of recurrence. Despite this, the patient developed recurrence of AS symptoms and raised inflammatory markers but after one year of combined treatment with golimumab (GOL) and VDZ, the patient was in remission both clinically and endoscopically[19].

In Norway, ten IBD patients were given DBT; nine received IFX and VDZ and one received ADA and VDZ. Eight patients were able to stop IFX; after follow-up, all were in clinical remission, whilst six were in biochemical remission and five were in endoscopic remission[20]. A later study in Norway, which looked at IBD in children found that combination therapy was well tolerated. Of the eight patients who received IFX and VDZ, four achieved clinical remission, whilst the remaining four required surgery. They noted that VDZ therapy alone led to a flare up of IBD in two of their patients. Additionally, UST alone was useful in treating skin lesions, such as psoriasis, but similarly to VDZ, monotherapy did not alleviate IBD symptoms, highlighting that combination therapy was more beneficial[11].

Mao *et al*[21] reported four cases of CD treated with DBT; one patient remained symptomatic due to CD; he was initially treated with ADA, but later developed antibodies, and was subsequently switched to VDZ with azathioprine. Endoscopically, the patient demonstrated ongoing terminal ileitis, and later developed worsening AS symptoms. He was subsequently commenced on ETN, as his AS had previously responded to anti-TNF. VDZ was switched to UST and joint pain remained controlled. The remaining three cases achieved remission of CD following treatment with VDZ and UST, VDZ, and GOL and VDZ, GOL and 6MP, respectively. All four patients tolerated dual therapy, further supporting the use of VDZ in DBT[21].

UST has also been reported in studies from 2017; Liu and Loomes[9] reported a case of severe CD and iron deficiency anaemia on UST alongside azathioprine, allopurinol, mesalazine (oral and per rectal suppository) and budesonide. Symptoms continued, faecal calprotectin (FCP) remained elevated, and magnetic resonance imaging demonstrated ongoing inflammation. Consequently, VDZ was added, with subsequent mucosal healing, reduced FCP and symptom control[9].

UST was used by a team in the United States, also for refractory CD, associated with strictures (requiring end ileostomy) and vulvo-perianal disease where UST alone was not effective. The addition of VDZ and methotrexate starting post-proctectomy and perianal reconstruction, achieved remission endoscopically, radiologically and biochemically[10].

RETROSPECTIVE STUDIES

In 2020, Glassner *et al*[22] published a retrospective study looking at combination biologic or small molecule therapy in IBD. The study included fifty patients who had failed to respond to biologic monotherapy. Fifty percent were found to be in clinical remission, and 36% in endoscopic remission, and inflammatory markers were also found to have improved[22].

A later retrospective study including twenty-four trials of DBT in twenty-two patients, found endoscopic improvement on 43% of trials and 26% endoscopic remission (assessed *via* Simplified Endoscopic Score). Clinically; 50% had clinical response and 41% were in clinical remission (CD patient-reported outcome 2 score; PRO-2). Additionally, perianal fistulas reduced from 50% to 33%. Various biologics were used, however VDZ plus UST was found to have a higher rate of endoscopic improvement; endoscopic remission and adverse event rates were similar to other combinations of DBT [23].

An Italian study, also from 2020[24], included sixteen patients with IBD, of which, fourteen had IBD with concurrent extra-intestinal manifestations. Seven of these started dual therapy due to intestinal symptoms, whilst nine received treatment for extra-intestinal symptoms, such as psoriasis or arthritis. The patients were treated with VDZ plus anti-TNF or UST. Eight patients were receiving corticosteroids and six of these were able to withdraw them following DBT. One patient had reactivation of pouchitis,

which improved with VDZ. Reactivation was thought to be due to secukinumab induction, which inhibits IL-17; as this has been reported to be associated with developing IBD or relapse and is generally advised to be used with caution in those with IBD[25].

Further data from the United States similarly demonstrates improvement in IBD with DBT; fifteen patients were treated with a combination of biologics (anti-TNF and VDZ, n = 8; anti-TNF and UST, n = 2; UST and VDZ, n = 5). Eleven patients reported improvement in symptoms, ten were able to reduce their use of corticosteroids and four demonstrated endoscopic or radiological improvement. However, three of the fifteen patients needed further surgery[26].

A 2021 European retrospective study identified 104 combinations in 98 patients; combination therapy was used for active IBD in 67% of cases, and 27% of cases were for extra-intestinal manifestations (EIM) or active immune mediated inflammatory disease (IMIM) (AS, psoriasis, rheumatoid arthritis and psoriatic arthritis). In 70% of patients, disease activity clinically improved, whilst EIM/IMIM activity improved in 81%. Worsening of symptoms was seen in 16 combinations (13 for IMID, 3 for EIM)[27].

SYSTEMATIC REVIEWS

A 2019 systematic review with pool analysis aimed to assess the effectiveness and safety of DBT with anti-TNF, VDZ or UST. Seven studies were included, comprising of a total of eighteen patients (fifteen were treated with anti-TNF plus VDZ, whilst the remaining three were treated with VDZ and UST). Overall, all patients were found to have clinical improvement, whilst 93% of patients showed endoscopic improvement, and no serious adverse events were noted[28].

Ahmed *et al*[29] published a later systematic review with meta-analysis which identified 30 studies with 288 trials of dual biologic or small molecule therapy in 279 patients; 48% were treated with anti-TNF plus VDZ, 19% were treated with UST and VDZ and 7% were treated with anti-TNF plus UST. Pooled rate of clinical remission was 59%, whilst endoscopic remission was 34%, with 12% needing surgical intervention. Overall, combination therapy showed better response in patients with extra-intestinal manifestations compared to those with refractory IBD alone.

The most recent available systematic review with meta-analysis (2022) also suggested that DBT and small molecule combined with biologic therapy (SBT) was a safe and effective therapeutic option with the caveat that evidence is still limited[30]. 13 studies were included, comprising a total of 273 patients undergoing 279 trials; seven patients (eight trials) were excluded due to being on biologics/small molecule therapy that was not approved by the FDA. Patients on VDZ and anti-TNF achieved 77.9% clinical response and 55.1% clinical remission. Those on VDZ plus tofacitinib (a Janus kinase, JAK inhibitor) showed clinical response of 59.9% and clinical remission of 47.8%. Patients administered VDZ plus UST had a pooled clinical response of 83.9% and remission 47.0%.

ADVERSE EFFECTS

Wheat *et al*[31] concluded in their meta-analysis that therapies used in the treatment for IBD were not linked to increased risk of serious infection. Furthermore, no specific treatment combination demonstrated a higher risk of serious infection compared to others. However, due to the small number of studies included for specific therapies, confidence intervals were subsequently wide, and therefore a significant increase cannot be excluded. Patients on a combination of biologics and immunomodulators did not show an increased risk compared to those on biologic monotherapy.

A systematic review by Bonovas *et al*[32] found that the use of biologics increased the risk of infection (odds ratio, OR 1.19), and these drugs also posed a significant increase in the risk of opportunistic infections (OR 1.90). Similar to Wheat *et al*[31], risk of serious infection was not found to be higher in patients on biologics (OR 0.89), and in fact showed to reduce this risk. Furthermore, they found that biologics did not increase the risk of malignancy, however data on this area remains insufficient.

In 2019, Borren *et al*[33] also carried out a systematic review with meta-analysis to establish the safety of biologic therapy in older patients. Fourteen studies identified that older patients were at higher risk of malignancy (OR 3.07) compared to younger patients, and infection (OR 3.60) compared to those who did not use biologics. Interestingly, comparison of older patients who used biologics to older patients not on biologics did not show higher odds of malignancy (OR 0.54). It concluded that older age is a recognised risk factor for malignancy, however biologics themselves do not appear to be linked to a higher risk of cancer.

Nevertheless, it is important to note that these analyses were based on studies on patients on either biologic monotherapy, or a combination of biologics with immunomodulators. Data on infection risk and long-term effects in DBT remains limited and therefore it is difficult to ascertain whether these risks apply to patients on DBT.

From review of the literature, whilst adverse events include arthralgia, IBD flare up and skin lesions (including eczema and psoriasis), infections appear to be the most common issue reported, which are summarised in Table 2.

Table 2 Summary of infections reported in randomised controlled trial and case studies of patients on dual biologic therapy for inflammatory bowel disease

Ref.	Infections documented
Sands *et al*[14], 2007	Nasopharyngitis
Buer *et al*[20], 2018	Tonsillitis × 2
	Sinusitis × 1
Olbjørn *et al*[11], 2020	Skin infection
Mao *et al*[21], 2018	Clostridium difficile × 2
	Hand, foot and mouth disease
	Influenza
Yang *et al*[23], 2020	Pneumonia
	Clostridium difficile
	Actinetobacter bacteraemia
Privitera *et al*[24], 2020	Perianal abscess
Kwapisz *et al*[26], 2021	Salmonella
	Clostridium difficile
	4 × patients needing antibiotics
Goessens *et al*[27], 2021	Osteomyelitis
	Enterocutaneous fistula infection
	Perianal abscess
	Viral URTI
	Campylobacter
	Pneumonia
	Herpetic meningoencephalitis
	Oesophageal candidiasis
	Influenza

URTI: Upper respiratory tract infections.

DISCUSSION

Although Sands *et al*[14] established that natalizumab was able to lead to improvement in disease burden in patients with CD, clinicians have subsequently opted for alternative biologics with a safer profile. Natalizumab binds to the a4 subunit of integrin to prevent interaction with MAdCAM-1. Similar to the more specific VDZ, natalizumab prevents migration of lymphocytes into the mucosa, thus reducing T cell mediated inflammation[34]. Whilst this has been approved in the United States for CD, its associated risk with developing progressive leukoencephalopathy due to the John Cunningham virus has led to a lack of widespread use[35].

VDZ was a prevalent choice in many of the cases examined, however it was noted that in some patients, it did not control extra-intestinal manifestations when used alone. For example, patients reported arthralgia[17,20], and in some cases they developed severe and disabling symptoms of concurrent arthropathy, which subsequently improved on administering an anti-TNF agent[19,21]. In a paediatric study, lack of IFX led to a flare of IBD in one patient, another also experienced an IBD flare and rheumatoid arthritis, whilst one developed a perianal fistula[11]. As a result, it has been suggested that the use of DBT may be helpful as a form of bridging therapy until a patient is in remission[24]. Furthermore, the use of VDZ or UST is an attractive possibility due to their favourable safety profile[23] combining biologics with different mechanisms of action may be safer and more effective. Although current data is encouraging in terms of the use of DBT, it is still unclear which combination works best; many favour the use of anti-TNF plus VDZ or UST but anti-TNF is not always an option, especially for patients in which this is contra-indicated or not tolerated[36].

In addition to DBT, other agents such as JAK inhibitors are also increasing in use. JAK inhibitors are a class of small molecule drugs which have proven useful in the treatment of a range of inflammatory conditions such as rheumatoid arthritis, psoriasis, dermatitis, and IBD. Le Berre *et al*[36] published the first case report involving a JAK inhibitor; a 67-year-old woman with UC, associated with HLA B27 positive SpA. The patient developed multiple mononeuropathies secondary to IFX, which then resolved on discontinuation. As a result, further anti-TNF therapy was deemed a contraindication in this patient. She was subsequently treated with VDZ and methotrexate but went on to develop arthralgia and flare up of her IBD. Methotrexate was replaced with tofacitinib, with clinical remission of symptoms within three months.

Tofacitinib has been approved for use in moderate to severe UC, where treatment with anti-TNF has failed. Unlike biologics, which are given intravenously and can have a slow onset of action, JAK inhibitors can be administered orally, with a rapid onset of action, short half-life and does not trigger an immune response[37]. Whilst other studies have found that the use of anti-TNF may help with extra-intestinal manifestations, this study also highlights an alternative option for managing these symptoms.

JAK inhibitors should, however, be used with caution, as they have been associated with an increased risk of developing Herpes zoster infection, thus highlighting the need to consider vaccination in high-risk patients[38]. Additionally, JAK inhibitors are thought to also increase the risk of cardiac event, malignancy, venous thromboembolism and gastrointestinal perforation[37,39]. Although, these events occur in higher numbers in patients who are at higher risk (for example, active UC is deemed a hypercoagulable state), suggesting that there is no significant difference in the risks due to JAK inhibitors compared to biologics[40].

From the data that is currently available, DBT in IBD may be a suitable option for managing severe refractory cases with or without extra-intestinal symptoms. Whilst rates of remission may vary, it is important to note that the population included in these studies are already high risk and difficult to treat. As a result, worsening of symptoms and/or requiring surgical intervention should come as no surprise, particularly in those with strictures or perianal disease. These cases could instead, be deemed as a failure to respond to medical therapy, rather than a true complication of combined biologic therapy [27].

In terms of adverse events, Goessens *et al*[27] reported that 42% of patients experienced 42 significant adverse events in total, particularly infections. Furthermore, Alayo *et al*[30] reported that the most common adverse event from their systematic review and meta-analysis was increased infection, making up approximately 75% of all events. This risk may be reduced by considering discontinuation of immunomodulators prior to starting DBT[22]. Interestingly, the use of biologics has been shown to increase the risk of opportunistic infections but reduce the risk of serious infections in some meta-analyses[31,32]. Although increased infections have been noted in many of the cases reported so far, it is important to consider whether this was somewhat inevitable due to being on a biological agent, or, if these are a direct consequence of being on dual therapy. The former hypothesis is supported by the VEGA study, which found comparable rates on infection in patients on dual therapy and monotherapy with biologics. More importantly, when considering long term effects of these agents, they did not report any cases of malignancy, tuberculosis or deaths[15].

Additionally, a prospective observational study by CLARITY IBD found that patients on infliximab treatment were more prone to breakthrough infection due to SARS-CoV-2 (despite three doses of appropriate vaccination) compared to those on vedolizumab, highlighting the importance of booster doses[41].

At present, one of the main limitations when evaluating the safety and efficacy of the use of DBT is the lack of further randomised controlled trials. Thus, short- and long-term safety profiles of biologic combinations in IBD is yet to be investigated in detail. Randomised controlled trials in other inflammatory conditions highlight some serious adverse effects, particularly in patients being treated with anti-TNF[5]. To combat this, IBD has gut specific options available in the form of VDZ and UST, and the combination of these two agents has shown some encouraging results[9,10].

As DBT does not demonstrate 100% efficacy and potentially increases the risk of some adverse events, it is important to explain both risks and intended benefits of treatment to patients using joint decision-making processes and discuss cases using a multi-disciplinary team approach[42].

CONCLUSION

The increasing use of dual biologics, alongside small molecule therapies, particularly in earlier disease, may help to improve cost effectiveness and reduce morbidity experienced by patients with IBD. However, further dedicated research is still needed in this area particularly looking into efficacy and short- and long-term safety profiles of DBT, but reported data, albeit small in number, remains promising at this stage.

FOOTNOTES

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MINIREVIEWS

Pancreatic cancer and depression

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Abstract

Pancreatic cancer is a highly devastating disease with high mortality rates. Even patients who undergo potential curative surgery have a high risk for recurrence. The incidence of depression and anxiety are higher in patients with cancer than the general population. However, patients with pancreatic cancer are at most of risk of both depression and anxiety and there seems to be a biological link. In some patients, depression seems to be a precursor to pancreatic cancer. In this article we discuss the biological link between depression anxiety and hepato-biliary malignancies and discuss treatment strategies.

Key Words: Pancreatic cancer; Depression; Anxiety; Cytokines; Gastrointestinal malignancies

Core Tip: Pancreatic cancer has one of the highest mortality rates of all malignancies. There is a strong correlation between pancreatic cancer and depression and we discuss the evidence behind this.

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INTRODUCTION

Pancreatic cancer is the third leading cause of cancer death, with very poor 5-year survival rates[1]. The majority of patients present at a late stage with incurable disease.

Initial symptoms can be vague and are often wrongly attributed to more common diagnoses. It is usually only when an individual develops visible changes (*i.e.* jaundice as a result of bile duct blockage) that they receive medical attention, by which time, the cancer tends to be more advanced. The significant morbidity and mortality of the disease could explain why pancreatic cancer has the highest incidence rates of depression compared with other types of gastrointestinal cancers[2]. There is a known correlation between malignancies and depression[3]; however it is unclear as to whether the depression is a result of the challenges of the cancer itself, reactive to the diagnosis or related to physiological changes from the cancer. Some studies have suggested depression before a cancer diagnosis is actually a sign of the malignant process at work; implying that it is individual symptom of the cancer[2]. The link between pancreatic cancer and depression was identified nearly a century ago. Retrospectives from the 1930's; identified as associated with pancreatic cancer and three psychological symptoms: Depression, anxiety; and sense of impending doom[4]. It appeared that these symptoms had preceded the somatic clinical symptoms of pancreatic cancer (*i.e.*, pain; jaundice; weight loss). This article will review the suggested biological link between depression, anxiety and pancreatic cancer, with the aim to identify potential biomarkers, which could be implemented in a more individualized and targeted approach in pancreatic cancer treatments.

RECOGNIZING THE ASSOCIATION OF PANCREATIC CANCER AND PSYCHOLOGICAL SYMPTOMS

Yet rather than a reactive effect of being given a life changing prognosis, research has shown that depression can be the presenting symptom of pancreatic cancer, with the subsequent development of anorexia, weight loss, jaundice, and pain[4]. It is well reported that pancreatic cancer has the highest incidence rate of depression among all other tumours of the digestive system[5]. It is also known that psychological symptoms are quite common in the course of visceral disease, most noticed in advanced stages of gastro-intestinal diseases and other chronic diseases. Previous research studies have reported that abdominal pain is more likely to cause depression, than pain in any other region. One of the first studies by Yaskin *et al*[4], dated back in 1931, focused on four case reports with "nervous symptoms", predominantly anxiety, followed by anorexia, weight loss and weakness. In all four cases, the nervous symptoms significantly preceded any of the definite gastro-intestinal symptoms and signs by several months. Pancreatic adenocarcinoma was later confirmed in three of the four cases, and in the fourth case this was the most probable diagnosis. In 1970s, a retrospective study of patients with known gastric and pancreatic cancer, revealed that depression was already present at the time of the diagnosis of cancer, in 14% of patients with pancreatic cancer, as opposed to 4% of patients with gastric cancer[6]. Further research conducted by Mayo Clinic, attempted to assess patients with abdominal symptoms, following surgical resection, and it was found that 76% of patients with confirmed pancreatic cancer had symptoms of depression and anxiety, compared to 20% of patients with other neoplasms[2]. Interestingly, in half of the patients the psychiatric symptoms started as early as 43 mo before the somatic symptoms. This was an important research mark, as psychiatric symptoms could be used as a key to make an earlier diagnosis of pancreatic cancer[7]. A systematic psychiatric evaluation of 21 patients with intraabdominal malignancy (pancreatic or gastric carcinoma) also revealed that depression was more frequently associated with patients with pancreatic carcinoma, whereby this finding was not observed in patients with gastric cancer[8]. A further study of 107 patients with advanced pancreatic cancer and 111 patients with advanced gastric cancer, were assessed with the' Profile of Mood States' before beginning combination chemotherapy in a national cancer clinical trials group[9]. The pancreatic cancer patients had more severe depression, anxiety, fatigue, and mood disturbances. These data support prior observations that patients with advanced pancreatic cancer experience significantly greater general psychological disturbances compared to patients with other abdominal malignancies in advanced stage[9]. A comprehensive meta-analysis by Massie *et al*[10] revealed that the prevalence of depression in pancreatic cancer ranges from 33% to 50%, based on a small number of studies, and including 229 patients in total[7-10]. A large retrospective study by Zabora *et al*[11], examined 4496 patients with 14 different cancer diagnoses, and found that patients with pancreatic cancer had the highest mean score for depression and anxiety. 36.6% of patients with pancreatic cancer had distress as evaluated by the Brief Symptom Inventory.

One of the largest studies conducted in United States, evaluated the rates of depression before and after a diagnosis of pancreatic cancer, which were the highest in pancreatic cancer compared to other types of cancer, and demonstrating a peak within 6 mo before or after a pancreatic cancer diagnosis[12]. This study demonstrated that 21% of pancreatic cancer patients had depression prior to the cancer diagnosis. This supported the hypothesis that depression is potential antecedent to pancreatic cancer and therefore could be an early sign of pancreatic cancer. Recent prospective observational studies have assessed the prevalence of preoperative fatigue, depression and anxiety among patients undergoing pancreatic surgery for pancreatic cancer, and the possible link with postoperative outcomes. These studies have supported that patients with metastatic disease who experienced depression or anxiety before the pancreatic cancer diagnosis, were associated with a reduced likelihood of receiving

chemotherapy, and decrease in overall survival[13]. This can be considered as a benchmark in future design of prospective clinical trials, which could suggest new treatment strategies, including antidepressant pharmacological agents, by implementing pre-existing depression as a stratification factor. The challenge remains on whether these new treatment strategies could be translated into survival benefit in this group of patients.

BIOLOGICAL LINK

One of the most challenging features of this disease is the paucity of clear biomarkers compared with other solid malignancies. Whilst several have been proposed, there remains no gold standard that has been validated for use. By understanding what biological drivers cause depression as an initial symptom, a biomarker may be used to identify underlying pancreatic malignancy. It is widely known that gastrointestinal malignancies are commonly causes for psychological and mental health conditions. This could be explained by the mechanical pressure of the tumour and interference by its toxic effects and metabolic changes. Chemical changes in the body have a causative relation to abnormal emotional states, with common examples being depression of hyperthyroidism and the anxiety and restlessness of abnormal blood sugars[4]. Several studies have attempted to prove a relationship between depression and cytokine production[14]. Increased levels of cytokines in the hypothalamus play a vital role in the cachexia-anorexia syndrome in cancer. Moreover, the increase of pro-inflammatory cytokines, such as IL-1beta, TNF-alpha, Il-6, IL-18 is noticed in malignancy, and they may have impact on the hypothalamic-pituitary-adrenal axis and the corticotropin-releasing factor[15]. The pro-inflammatory cytokine IL-6 has been found to be significantly increased in pancreatic cancer cells, and is related to proliferation of tumour cells and reduced apoptosis, further suggesting a potential resistance to systemic treatments[16]. A study with 75 patients, conducted by two centres in New York, enrolled patients with pancreatic cancer with or without major depressive episode. Pancreatic cancer patients had significantly higher levels of IL-6 and IL-10 compared to healthy participants. This study demonstrated an association between depression and IL-6, but not with other cytokines. IL-6 had the strongest association with pancreatic cancer[14]. TNF-alpha was not associated with pancreatic cancer or any psychological distress. Another comprehensive study, published in 2008, assessed the clinical significance of -174G/C IL-6 gene polymorphism and IL-6 serum levels, which were significantly raised in patients with pancreatic adenocarcinoma and in patients with chronic pancreatitis, compared to the control group[17]. Hormonal theories support that pancreatic cancer patients might have increased urinary excretion of 5-hydroxyindolaceetic acid (5-HIAA), which is a metabolite of serotonin, and high concentration of 5-hydroxytryptophne (5-HTP) or 5-hydroxytryptamine (5-HT). This hypothesis suggests there is a likely correlation between increased metabolism of serotonin in pancreatic cancer, which leads to central nervous system depletion and therefore depression[18]. Serotonin is produced by normal pancreatic cells and plays a role in the pathogenesis of depression[19]. This theory was further supported by suggested study demonstrating an increase in 5-HIAA is a link to depression and explained by the fact that there was treatment-refractory depression, until the tumour was excised[8]. Thyroid hormone abnormalities, hypercalcaemia, inappropriate antidiuretic hormone secretion and increased levels of adrenocorticotrophic hormone have also been documented in pancreatic cancer[19].

An immunological model was proposed by Brown and Paraskevas, whereby immune regulation of serotonin could be modulated in one of two ways. An antibody could be produced in response to a protein released by cancer cells that would cross-react with CNS serotonin receptors, thereby effectively blocking them. Alternatively, antibodies could stimulate the production of anti-idiotypic antibodies, which would reduce the synaptic availability of serotonin by acting as an alternate receptor. Depression contributes to impairment of immune competence or to development or progression of pancreatic cancer[20]. Furthermore, biochemical mechanisms support that tumours of the gastro-intestinal tract, which are rich in neuropeptides, may lead to production of biogenic amines that alter the psychological state. Some studies support the possibility of a tumour-related paraneoplastic syndrome, which promotes the production of a false neurotransmitter capable of altering mood[9]. These theories, which are summarized in Figure 1, have led to a better understanding of the biological association between pancreatic cancer and depressive symptoms, but further research is needed to validate new pathways of prevention, screening, and treatments.

In recent years, there has been increasing interest in the immune landscape of pancreatic adenocarcinoma, genetic alterations and tumour microenvironment. A number of genetic alterations have been identified in pancreatic cancer, with KRAS mutations found in the majority of pancreatic cancer patients. Other signalling pathways found to be associated with pancreatic cancer, include alterations in tumour suppression genes (TP53, SMAD4, p16) and overexpression of growth factor receptors. The direct targeting of the involved signalling molecules and the immune checkpoint molecules, along with a combination with conventional therapies, have reached the most promising results in pancreatic cancer treatment[21]. Several novel targeted agents have failed to demonstrate an improvement in response rates and overall survival. PAK4, a serine threonine kinase, has been found to be overexpressed in pancreatic adenocarcinoma patients, and is known to mediate cell proliferation. PAK4, has

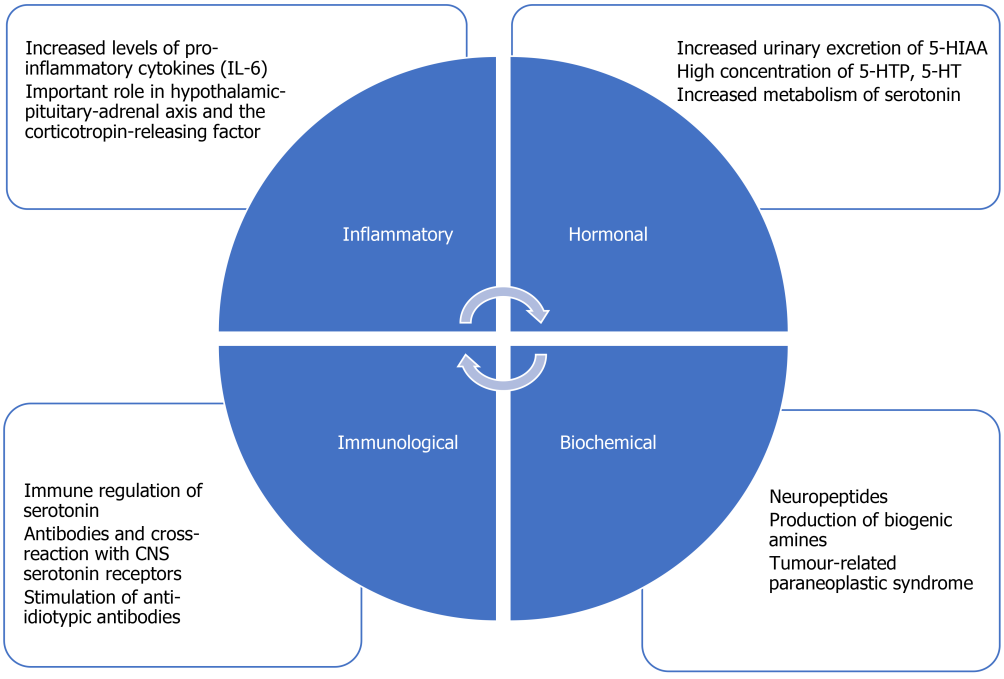

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Figure 1 Biological association between pancreatic cancer and depression and suggested theories.

been identified as a potential target in several tumours and its prominence in pancreatic cancer suggests it could present a therapeutic opportunity[22].

TREATMENT STRATEGIES

Early identification and treatment is essential in the management of patients with pancreatic cancer. Psychiatric symptoms cannot be accurately assessed in the presence of uncontrolled pain; therefore, the first step is to ameliorate the pain, agitation, and insomnia. The pharmacologic therapy includes antidepressant drugs, selective serotonin re-uptake inhibitors, psychostimulants, or benzodiazepines. The choice of the antidepressant agent should be determined according to patient's comorbidities and performance status, main target symptoms, potential interactions with co-administered drugs, and toxicity profile[23]. Tricyclic antidepressants have been reported as the most used drugs for depression in pancreatic cancer patients[24]. These drugs are usually initiated at low doses and then are slowly increased until adequate response is achieved. Amitriptyline has both antidepressant and analgesic action. The psychostimulants are helpful in pancreatic cancer because they stimulate appetite and improve energy[18]. Due to increased serotonin levels in pancreatic cancer, selective serotonin re-uptake inhibitors can be effective and are the preferred first line treatment according to NICE recommendations for depression in adults with a chronic physical health condition[25,26]. Benzodiazepines are more effective to patients with prevalent symptoms of anxiety but may increase psychomotor slowing and fatigue which is a very general complaint of cancer patients. Essential component of the first line treatment of major depression, is supportive psychotherapy. The integration of a mental health professional into the treatment plan of pancreatic cancer significantly decreased all-cause mortality rates compared to patients who were not treated by a mental health professional[12]. This was also supported by Boyd *et al*[27], demonstrating that integrating mental health specialists into patient care once depressive symptoms have been identified could enhance quality of life. However, this therapy is unlikely to significantly improve overall survival. Patients with pancreatic cancer often have unmet psychological support needs, that have a significant impact on their quality of life. Psychological support is crucial from time of cancer diagnosis and highlights the need to assess the psychological impact of fatigue, pain, gastrointestinal symptoms, nutrition, anxiety, and depression[28]. It is also important for patients and their family members to be taught coping strategies. Beyond pharmacological agents and cognitive behavioural therapy, the management of cancer patients as a whole, is essential. Pain control, nutritional support and management of biliary and duodenal obstruction are essential in improving quality of life.

CONCLUSION

Pancreatic cancer remains one of the most challenging malignancies to manage, having very poor prognosis with low 5-year survival rates. It is also the malignancy with the highest incidence rates of major depression[2]. Research has shown that there are clear biological mechanisms linking depression with pancreatic cancer, but further research is urgently needed to unravel this link further and identify potential biomarkers, that could lead to early diagnosis of pancreatic cancer and implement new treatment strategies. The current field lacks biomarker-driven targeted therapy. Furthermore, genomic stratification factors should be implemented in future clinical trials, as selected patients could be chosen based on genetic alterations in order to achieve maximal benefit from treatment and improve survival outcomes[21]. One of the main limitations remains the design of innovating clinical trials and the need of including psychological symptoms and depression as stratification factors. Prospective analyses could demonstrate whether depression and psychological factors have an impact on survival outcomes. It is also fundamental that future research follows a more holistic approach, highlighting the importance of multidisciplinary team support, and early involvement of mental health professionals. Undoubtedly, there are challenges in managing depression and anxiety in the context of malignancy and care must be multi-professional. Whilst depression, although common among patients with pancreatic cancer, does not routinely affect survival, it has significant effects on quality of life and potential adherence to treatment and engagement with care that could negatively impact outcomes[29]. However, early detection of psychological symptoms and involvement of mental health professionals, in combination with appropriate pharmacological agents, can lead to better outcomes and improve quality of life. There is a high unmet need for further improvement in the primary health care services and application of screening tools for early detection of depression and anxiety could be introduced in Rapid Access Diagnostic Clinics, as depression itself could be considered as a precursor to pancreatic cancer.

FOOTNOTES

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MINIREVIEWS

Mediastinal lesions in children

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Abstract

The mediastinum is where thoracic lesions most frequently occur in young patients. The histological spectrum of diseases caused by the presence of several organs in the mediastinum is broad. Congenital lesions, infections, benign and malignant lesions, and vascular diseases are examples of lesions. Care should be taken to make the proper diagnosis at the time of diagnosis in order to initiate therapy promptly. Our task is currently made simpler by radiological imaging techniques.

Key Words: Mediastinum; Thoracic lesions; Vascular pathologies; Trachea and main bronchus pathologies; Esophageal pressure; Imaging in mediastinal lesions

Core Tip: The most common localization of thoracic lesions in children is the mediastinum. Pathologies arising from the presence of different organs in the mediastinum show a wide histopathological spectrum. Lesions may be congenital or include infections, benign and malignant lesions, and vascular pathologies. At the point of diagnosis, care should be taken at the point of starting the treatment quickly and making the correct diagnosis. Radiological imaging methods make our job easier at this point.

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INTRODUCTION

The mediastinum is where thoracic lesions in children most frequently occur. A wide histological spectrum is present in pathologies caused by the presence of many organs in the mediastinum. Infections, benign and malignant lesions, and vascular diseases are examples of lesions, along with congenital lesions. Care should be made at the time of diagnosis to make the appropriate diagnosis and provide treatment as soon as possible. At this stage, our task is made simpler by radiological imaging techniques.

Individuals with mediastinal lesions may not have any symptoms, or they may have symptoms if the lesion has compressed or invaded into an organ nearby. Due to the most frequent injury to the trachea and main bronchi, anterior mediastinal lesions can result in edema of the upper extremities and face from superior vena cava compression and cyanosis in the neck veins, in addition to respiratory symptoms like cough, stridor, and dyspnea. Upper mediastinal lesions may result in Horner's syndrome, posterior mediastinal lesions may result in neurologic symptoms from spinal canal extension, and middle mediastinal lesions may cause dysphagia owing to esophageal compression.

IMAGING MEDIASTINAL LESIONS IN CHILDREN

The most common localization of thoracic lesions in children is the mediastinum. Pathologies arising from the presence of different organs in the mediastinum show a wide histopathological spectrum. Infections, benign and malignant lesions, vascular diseases, and congenital lesions are some examples of lesions[1]. Additionally, because the thymus is seen in young children in a variety of radiological manifestations, it can result in radiological findings that resemble masses.

Patients with mediastinal lesions may not experience any symptoms or may experience symptoms as a result of compression or invasion of the lesion into nearby organs. Because the trachea and major bronchi are most commonly damaged, anterior mediastinal lesions can cause respiratory symptoms such cough, stridor, and dyspnea, as well as edema of the upper extremities and face from superior vena cava compression and cyanosis in the neck veins. Middle mediastinal lesions may cause dysphagia due to esophageal compression, posterior mediastinal lesions may cause neurologic symptoms from spinal canal extension, and upper mediastinal lesions may cause Horner's syndrome[2,3].

Radiological imaging plays an important role in diagnosis, treatment planning and post-treatment follow-up. Direct photography is the first image technique to be employed. There are two ways to approach direct writing. Small lesions may not show up on radiographs, but larger lesions can show abnormal structures as well as an increase in density in the form of soft tissue mass, deterioration in mediastinal contours, and displacement in mediastinal lines[4,5]. The presence of ionizing radiation in direct radiography is its main drawback. However, for mediastinal lesions, its sensitivity in diagnosis is reported as 97%-100% and specificity as 36%[6,7].

The mediastinum is divided into compartments using categories to aid in the diagnosis and assessment of the localisation of various disorders. In the classification based on the lateral radiograph, the mediastinum is divided into three compartments as anterior, middle and posterior mediastinum (Figure 1). Accordingly, the anterior mediastinum is knowledgeable by the sternum anteriorly, the anterior edge of the pericardium posteriorly, the middle mediastinum by the pericardium anteriorly, the line passing 1 cm posterior to the anterior border of the thoracic vertebrae posteriorly, and the posterior mediastinum by the vertebral corpuscles behind this line and the posterior transverse processes[8].

Ultrasonography (US) is a preferred technique because it is simple to use and radiation-free. US is a recommended method since it is simple to use and radiation-free.

Multislice computed tomography (CT) is the most important imaging modality in the evaluation of mediastinal lesions. The most significant benefits include a shorter examination period, improved temporal and spatial resolution, enhanced anatomical clarity, and less respiratory artifacts. Additionally, as the examination time is cut down, so is the amount of time that kids are sedated. By obtaining thin-section images, high resolution multiplanar reformat, maximum intensity projection and volume rendering imaging techniques can be used to obtain images in three planes[9]. These advantages of CT, it plays an important role in evaluating the size, localization, density and contrasting pattern of the lesion, its characteristic features (fat, calcification fluid content) and its relationship with neighboring structures[4,10]. The most important disadvantage of the examination is radiation exposure.

The International Thymic Malignant Interest Group divided the mediastinum into prevascular (anterior), visceral (middle) and paravertebral (posterior) distances based on multislice CT (Figure 2). The paravertebral distance is the space between the vertebral bodies behind this line and the transverse processes posteriorly. The prevascular distance is defined as the space between the sternum anteriorly and the pericardium posteriorly. The visceral distance is defined as the line between the pericardium and 1 cm distal to the anterior border of the thoracic vertebrae. The thymus, adipose tissue, lymph nodes and left brachiocephalic vein are located in the prevascular distance, the heart, vascular structures, trachea, carina, esophagus and lymph nodes are located in the visceral distance, and the

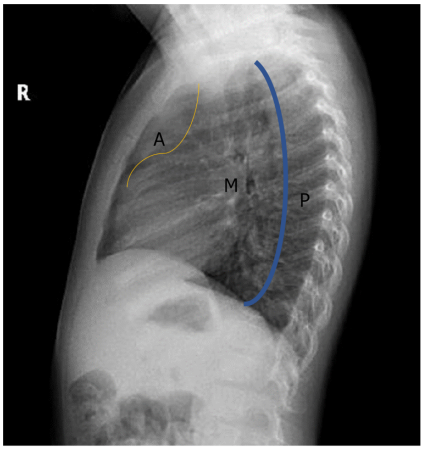

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Figure 1 Mediastinal compartment classification on lateral radiograph. The borders of the mediastineal compartments anterior mediastinum are formed by the sternum anteriorly, the anterior edge of the pericardium posteriorly, the middle mediastinum by the pericardium anteriorly, the line passing 1 cm posterior to the anterior border of the thoracic vertebrae posteriorly, and the posterior mediastinum by the vertebral corpuscles behind this line and the posterior transverse processes. A (yellow line): Anterior; M: Middle; P (blue line): Posterior.

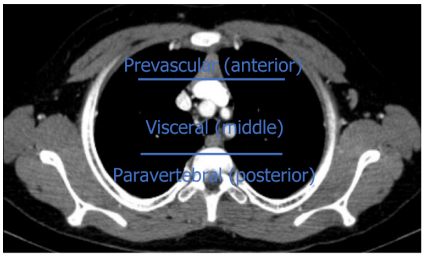

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Figure 2 International Thymic Malignant Interest Group classification. In the axial computed tomography section passing through the superior aortic arch, the area between the sternum and the pericardium is the prevascular distance, the area between the pericardium and the line passing 1 cm distal to the anterior part of the vertebral corpus is the visceral distance, and the area posterior to this line is the paravertebral distance has been defined as.

thoracic vertebrae and paravertebral soft tissue are located in the paravertebral distance[10].

In magnetic resonance imaging (MRI), it gives more detailed information when compared to CT, especially when evaluated in terms of its high soft tissue contrast resolution and the absence of ionizing radiation in the examination. However, the long examination time, pulsation artifacts and the need for sedation in young children are the most important disadvantages. It also has low sensitivity in demonstrating calcifications[9,11,12]. MRI is a crucial imaging technique for mediastinal lesions, particularly for assessing the intraspinal extension of posterior mediastinal lesions, differentiating cystic-solid lesions, figuring out how lesions relate to the heart, pericardium, and great vessels, and demonstrating the cystic-necrotic components of solid lesions[13-15].

The differential diagnosis of mediastinal lesions is given in Tables 1, 2 and 3[16].

PREVASCULAR DISTANCE (ANTERİOR MEDIASTINAL) LESIONS

Thymus is the primary lymphoid organ and is responsible for T lymphocyte maturation. Since the thymus is prominent in infants and young children, it can lead to mass-like appearances on imaging. However, understanding the thymus' radiological characteristics and changes will be useful for making a differential diagnosis. Other anterior mediastinal abnormalities include thymic cyst, thymoma, thymic cancer, thymolipoma, and diseases invading the thymus.

The thymus is particularly prominent in children up to 3 years of age. Size decreases with age. It is located anterior to the superior mediastinum. In infants, it is observed in the form of square, homogeneous soft tissue density and bilobular appearance on direct radiographs. Its edges are convex or straight. Because of the neighborhood, the heart's outlines are removed. The hiluses cannot be chosen on the graph since they are superposed with them (Figure 3). The fact that it doesn't cause pressure is the most crucial characteristic[11,17]. It changes shape with breathing and position. It elongates and contracts in inspiration and shortens and expands in expiration. This finding is important in the differ-

Table 1 Prevascular space lesions

Prevascular space (anterior mediastinum)	Common	Less common
Thymus gland	Normal variations, thymic hyperplasia	Thymoma, thymic carcinomas
Lymphoma	Hodgkin and non-hodgkin lymphoma	
Germ cell tumor	Mature teratoma	Immature teratoma, seminoma, nonseminoma tumors
Thyroid		Intrathoracic goiter
Lymph node enlargement	Benign etiology	Malignant etiology
Cystic masses	Thymic cyst, lymphatic malformation	
Fatty lesions		Thymolipoma and lipoma

Table 2 Visceral space lesions

Visceral space (middle mediastinum)	Common	Less common
Vascular lesions	Vascular ring, pulmonary sling, aneurysm	Pseudoaneurysm
Lymph node enlargement	Benign: Infection	Malignant: Primary or secondary
Foregut duplication cyst	Bronchogenic cyst, esophageal duplication cyst, neuroenteric cyst	

Table 3 Paravertebral space lesions

Paravertebral space (posterior mediastinum)	Common	Less common
Sympathetic ganglia tumor	Neuroblastoma, ganglioneuroma, ganglioneuroblastoma	
Peripheral nerve sheath tumor		Schwannoma, neurofibroma, malignant peripheral nerve sheath tumor
Non neurogenic tumors	Lymph node enlargement, vascular malformation or aneurysm	Extramedullary hematopoiesis, small round blue cell malignancies

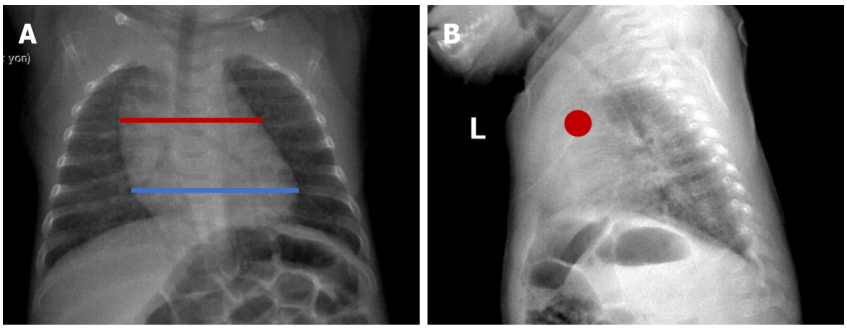

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Figure 3 A 3-year-old boy normal thymus. A: The red line shows the thymus and the blue line shows the heart in the posteroanterior chest radiograph. In infants, the thymus erases the heart contours, and because it is superposed with the hiluses, the hiluses cannot be clearly distinguished. It also does not create a compression effect. B: Anterior location of the thymus is observed with a red dot on the lateral radiograph.

ential diagnosis of solid masses and infiltrative processes, especially in real-time examinations such as US[18].

The thymus can be seen in many different forms on direct radiographs and other radiological images. The wave sign is the appearance of a corrugation on the edge of the thymus at the point where it rests on the ribs (Figure 4). When the right lobe of the thymus is triangular and the minor fissure forms its lower boundary, the sail sign is the result (Figure 5). The cardiothymic notch is the notch that occurs at the junction of the heart and thymus (Figure 6).

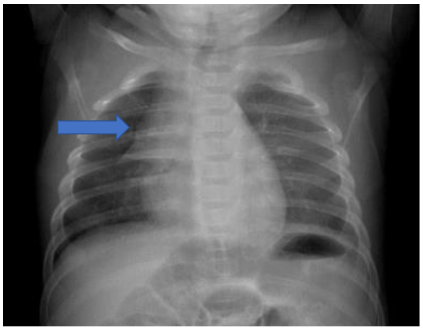

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Figure 4 The wave sign (blue arrow) is the corrugation view of the right lobe of the thymus due to its abutment to the ribs.

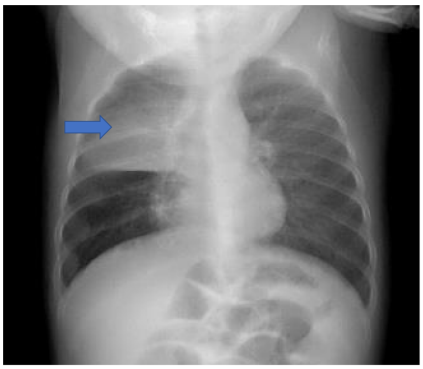

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Figure 5 Sail sign (blue arrow) is the triangular shape of the right lobe of the thymus and the minor fissure forming its lower border.

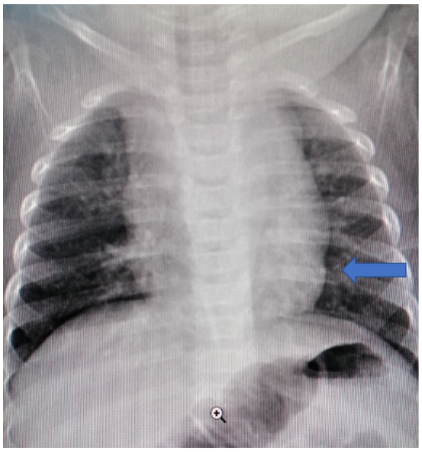

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Figure 6 The contour (blue arrow) formed at the junction of the thymus with the heart is the cardiothymic notch.

In CT, the thymus is observed in the anterior-upper mediastinum, anterior to the main vascular structures and pericardium. In infants and young children, it is in the form of a solid structure with convex edges and homogeneous density, which does not create a compression effect. As the age increases, the edges become flat or concave, while in adolescence, it is observed as a triangular shape with a reduced size[19] (Figures 7-9). In a study on this subject, it was discovered that the thymus, which has a median location and straight lateral contours, is the most prevalent morphological shape in children. The thymus's average transverse and anterior-posterior dimensions were 30 ± 11 mm and 17 ± 5 mm, respectively. The average thymic lobes' width and thickness were roughly 21 ± 5 and 15 ± 7 mm for the right and 26 ± 8 and 15 ± 6 mm for the left, respectively. The anterior-posterior diameter of the thymus was not substantially correlated with age, however the transverse diameter and thymic lobe dimensions of the thymus decreased dramatically with age. Despite the fact that girls' mean thymic attenuation values were higher than boys', this gender difference was not statistically significant[20].

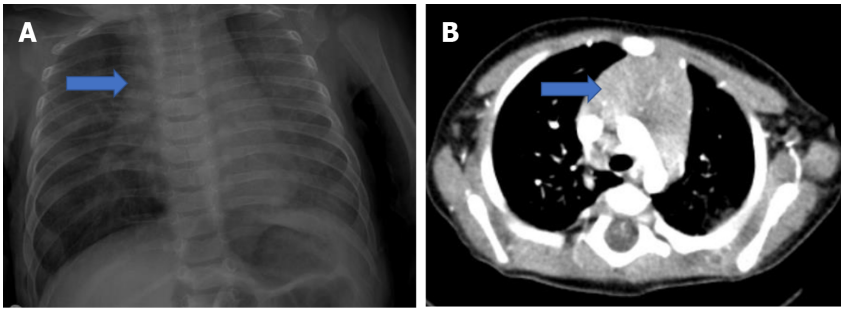

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Figure 7 Normal thymus and axial computed tomography of a 4-mo-old patient. A: Normal thymus on posteroanterior chest radiograph; B: Axial computed tomography (CT) examination of a 4-mo-old patient. In CT, the thymus (blue arrow) arcus is observed in the prevascular distance at the level of the aorta, its edges are convex, with homogeneous density and it does not cause a compression effect.

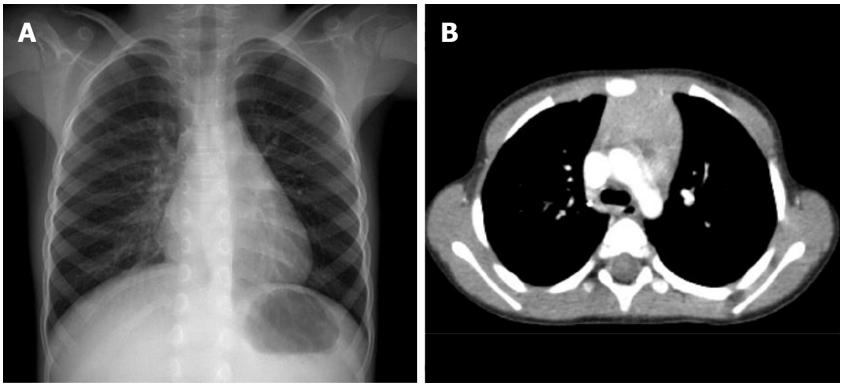

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Figure 8 A 4-year-old patient's posteroanterior chest radiograph. A: It shows a decrease in the dimensions of the thymus; B: Flattened edges in the axial computed tomography examination.

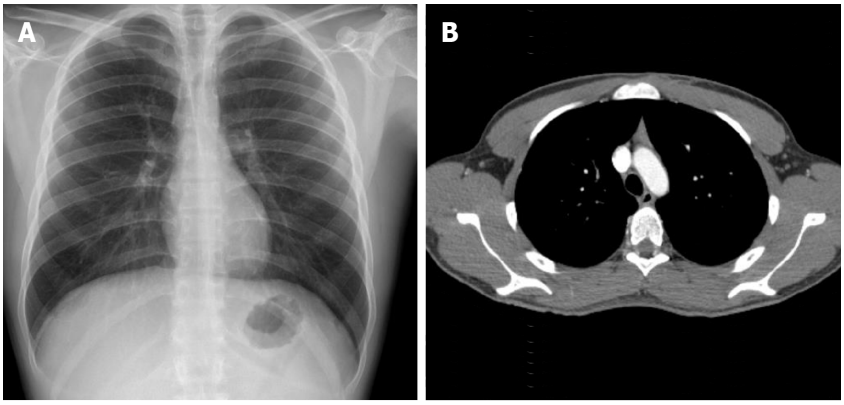

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Figure 9 A 17-year-old patient's examination. A: Thymus is not observed in the posteroanterior chest radiograph of the 17-year-old patient; B: In the axial section, on computed tomography, it is observed as small, triangular in the anterior mediastinum, with concave edges and lower density due to the fat tissue it contains.

One of the rare variations of the thymus that creates a mass appearance on the radiograph is the extension of the thymus to the superior vena cava and posterior to the great arteries[21] (Figure 10).

Thymic hyperplasia, one of the pathologies of the thymus, is seen in two forms as true and lymphoid hyperplasia. The development of atrophy in the thymus as a result of stresses such as systemic infection, burns, chemotherapy, and an increase in thymus size within a period of a few months to two years when the stress is removed is true hyperplasia. It may develop in lymphoid hyperplasia without expanding in size, and a rise in the number of lymphoid follicles is found[22]. It may be associated with autoimmune diseases. In cross-sectional examination, an increase in size is detected in the thymus.

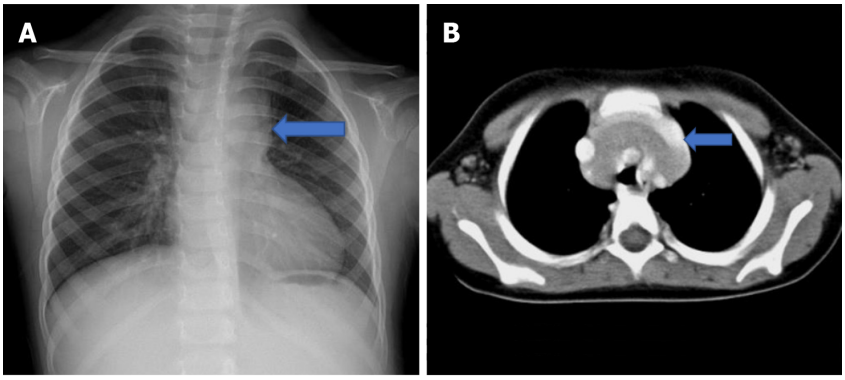

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Figure 10 A 3-year-old patient who presented with the complaint of cough. A: There is mediastinal enlargement on the left in the posteroanterior chest radiograph; B: In the axial computed tomography examination, it is observed that the thymus forms the mediastinal enlargement and the thymus (blue arrow) extends to the posterior of the main vascular structures.

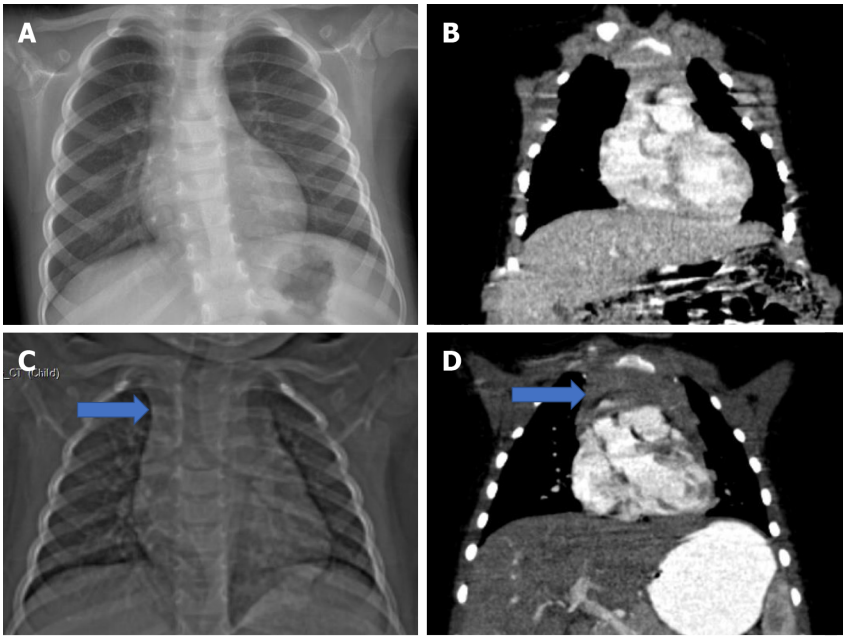

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Figure 11 A 3-year-old patient who was followed up with an operated Wilms tumor during chemotherapy. A: The thymus tissue is observed to be smaller than normal in the posteroanterior chest radiograph; B: Coronal computed tomography examination; C and D: In the second month follow-up of the same patient after the end of chemotherapy. Hyperplasia in the thymus (blue arrow) is observed in the scout (C) and coronal plane computed tomography images (D).

Lobulation can be observed in the contour. However, its density is homogeneous. It does not contain necrosis or calcification (Figure 11). Since the thymus contains adipose tissue histopathologically, measuring the chemical shift ratio in in-phase-out-phase sequences in MRI examination has an important place in distinguishing the thymus from the mass. A chemical shift ratio of less than 0.9 indicates normal thymus tissue[23].

THYMIC PATHOLOGIES

Thymic cyst is one of the rare benign pathologies of the thymus. Radiologically, they are observed with smooth contours, fluid density and homogeneous content. They do not contain solid components. However, an increase in their density may be detected due to hemorrhage or proteinaceous content. It can be unilocular or multilocular. Congenital cysts develop in the anterior mediastinum or neck along the thymopharyngeal canal[22]. It is usually unilocular. Acquired cysts can be seen in patients with Hodgkin lymphoma and autoimmune diseases, trauma, thoracotomy and radiotherapy-chemotherapy [22,23] (Figure 12). Those originating from thymoma or thymic carcinoma from the cyst wall have also been reported in the literature[24,25] (Figure 12). Thymoma is an epithelial tumor and is seen in less

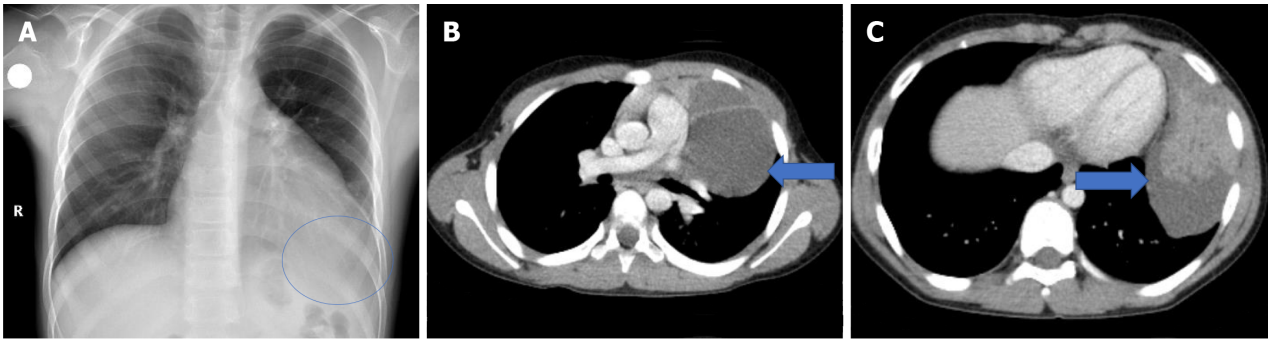

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Figure 12 A 10-year-old patient who is being followed up for asthma. A: Density that erases the heart and diaphragm contours (blue round) on the left is observed on posteroanterior chest radiography; B: Thymic cyst containing septa (blue arrow); C: A solid component of the thymoma (blue arrow) in the inferior of the cyst are observed.

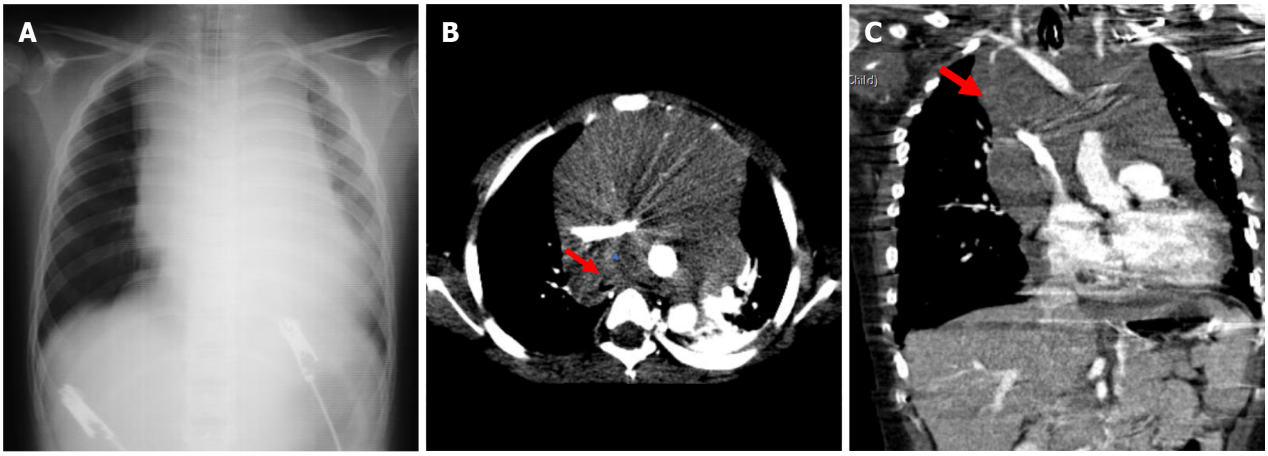

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Figure 13 A 5-year-old patient with T-cell ALL has neck and back pain, shortness of breath, and cough. A: On posteroanterior chest radiograph, significant enlargement of the mediastinum secondary to the mass and increased aeration in the right lung are observed; B: Compression of the right main bronchus secondary to the mass (red arrow) also draws attention; B and C: A mass lesion (red arrow) located in the anterior mediastinum but extending into the middle mediastinum and circulating the main vascular structures is observed.

than 1% of children[26]. It is associated with myasthenia gravis at a rate of 5%-15%[27]. There are two types, non-invasive and invasive. While it is observed as a smooth, homogeneous, solid lesion on CT, irregular contours, calcification and necrosis, heterogeneous enhancement, and pleural invasion should suggest the invasive type[16,19].

Thymic carcinoma is rare in children[18]. Similar radiological findings to invasive thymoma are obtained by CT. It's a tumor that grows quickly.

When illnesses affect the thymus, it manifests as a mediastinal mass. Acute leukemia is the first one of these illnesses. The most common cancer in children is leukemia and constitutes 30% of childhood cancers[27,28]. Acute lymphoblastic leukemia (ALL) constitutes 85% of acute leukemias and can be seen at any age, but is most common between 2-5 years of age. Eighty-five percent of ALL is of B cell origin and 15% is T cell origin[29]. Mediastinal mass due to leukemic infiltration of the thymus, compressive results due to the mass, and pleural effusion are frequently seen in T-cell lymphoblastic leukemia[30] (Figure 13). The same radiological findings occur in T-cell lymphoblastic lymphoma (Figure 14). The differential diagnosis between the two pathologies is made according to bone marrow involvement. In T-cell lymphoblastic lymphoma, less than 20% of blasts are detected in the bone marrow. Both T-cell ALL and T-cell lymphoblastic lymphoma are aggressive and rapidly progressive pathologies. Therefore, the diagnostic phase should be rapid[31].

Another pathology that infiltrates the thymus is Langerhans cell histocytosis. It is frequently seen with multisystemic disease in children under the age of one. It occurs as thymus infiltration and/or mediastinal lymph node involvement and its incidence is reported to be 2.6%[32]. Isolated cases have also been published in the literature. CT findings of thymic infiltration are heterogeneous appearance secondary to enlargement, nodular contour, calcification and cystic changes in the thymus (Figures 15 and 16A and B). The presence of punctate calcifications and the appearance of air cysts should suggest langerhans cell histiocytosis. Differential diagnosis with teratoma should also be made because it

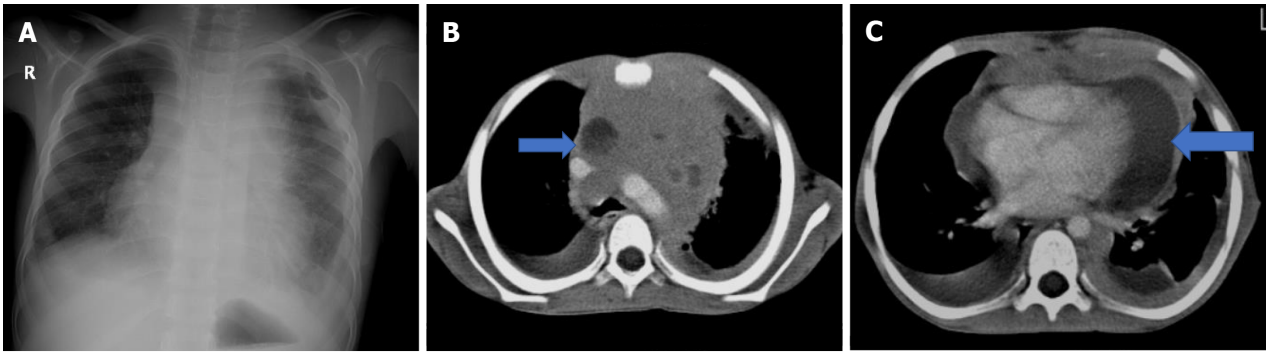

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Figure 14 A 7 years old patient with T-cell lymphoblastic lymphoma. A: There is cough and shortness of breath. Significant enlargement of the mediastinum, pleural effusion in the left hemithorax, and increased aeration in the right lung are observed in the posteroanterior chest radiograph; B and C: In the axial computed tomography examination, a mass lesion with fatty areas is located in the anterior mediastinum. Bilateral pleural and pericardial effusion, and pleural and pericardial fatty solid lesions (blue arrow) are also observed.

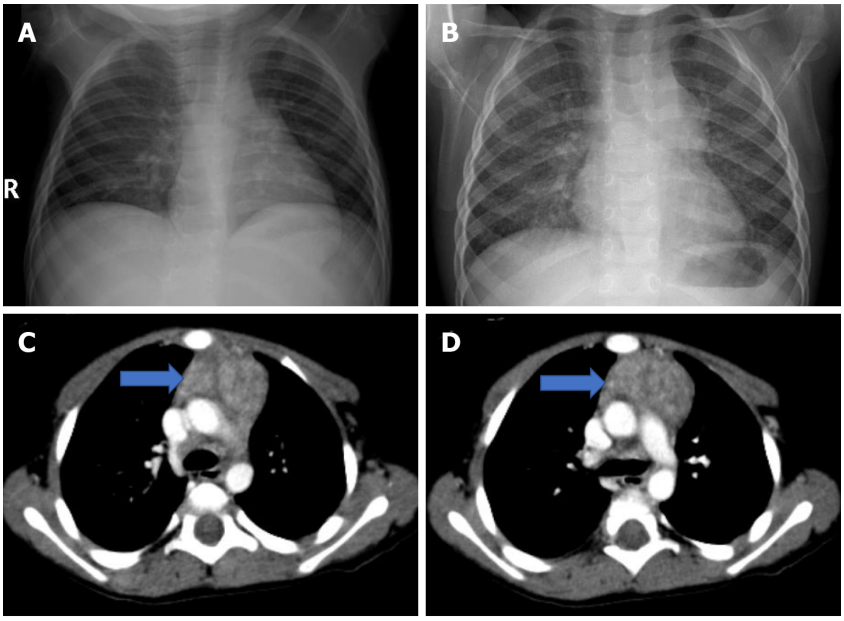

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Figure 15 In the 1 year and 9 mo old patient with langerhans cell histiocytosis. A: The first one; B: The second radiograph taken six months after A, Mediastinal enlargement and lobulation in the left mediastinal contour are observed; C and D: Thymic enlargement (blue arrow), lobulation in the contour and heterogeneous appearance are observed in the axial computed tomography images of the same patient.

contains calcifications[19,33,34].

LYMPHOMA

Lymphoma is the most common tumor of the anterior mediastinum in children. Although non-Hodgkin lymphoma is more common in children, the incidence of anterior mediastinal mass is more common in Hodgkin lymphoma[35]. Mediastinal involvement is seen either as a mass secondary to thymic infiltration or as lymphadenopathies due to lymph node involvement (Figures 16C and D, 17, and 18A and B). In thymic infiltration, mediastinal enlargement and compression findings are detected on chest radiograph. Contrarily, CT might be viewed as a pressure-forming mass with lobulated outlines and necrotic patches. Although calcification is rare, calcification may develop after treatment[16,36]. Pulmonary nodules and pleural effusion may accompany the findings at a rate of 5% in Hodgkin lymphoma[35].

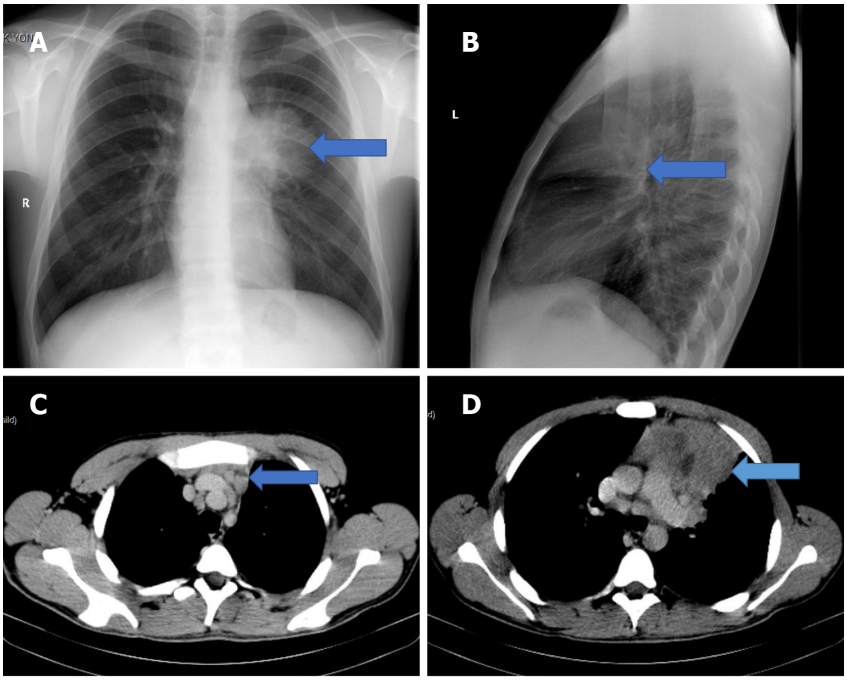

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Figure 16 Hodgkin lymphoma (nodular sclerosing type). A 17-year-old male patient presents with cough and weight loss. A and B: On the 2-way chest radiograph there is a mass density (blue arrow) located in the anterior mediastinum; C: Lymphadenopathies (blue arrow) in the upper mediastinum; D: A mass lesion containing cystic-necrotic areas (blue arrow) in the anterior mediastinum are detected.

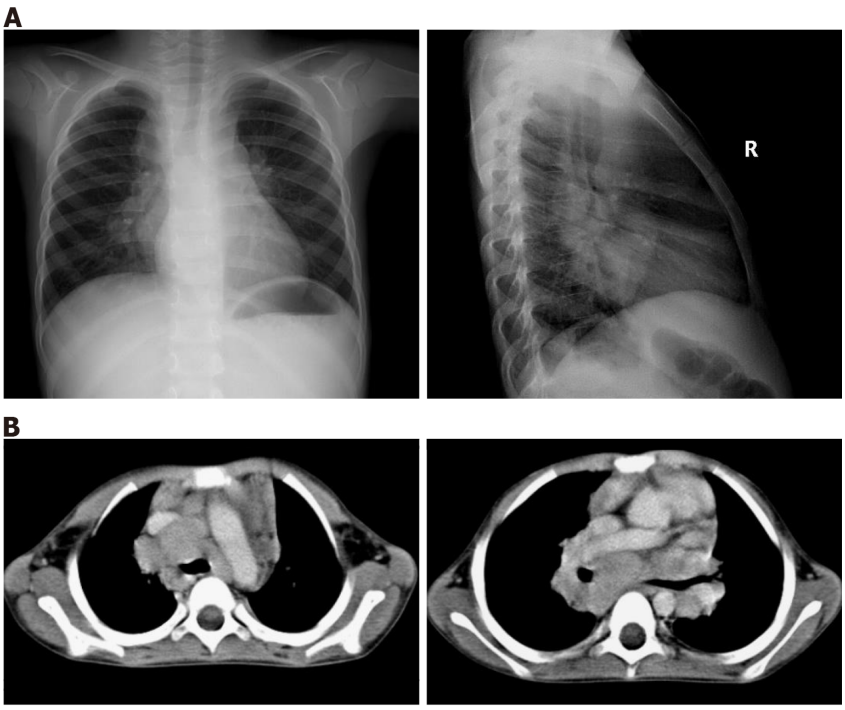

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Figure 17 4-year-old male patient with Hodgkin lymphoma (mixed cellular type). A: Mediastinal enlargement and bilateral hilar lymphadenopathy are observed in the 2-way chest radiograph of the patient with the complaints of fever and anemia; B: Lymphadenopathies forming conglomeration in prevascular, paratracheal, subcarinal, hilar and azygoesophageal recess are observed in the axial computed tomography images of the same patient.

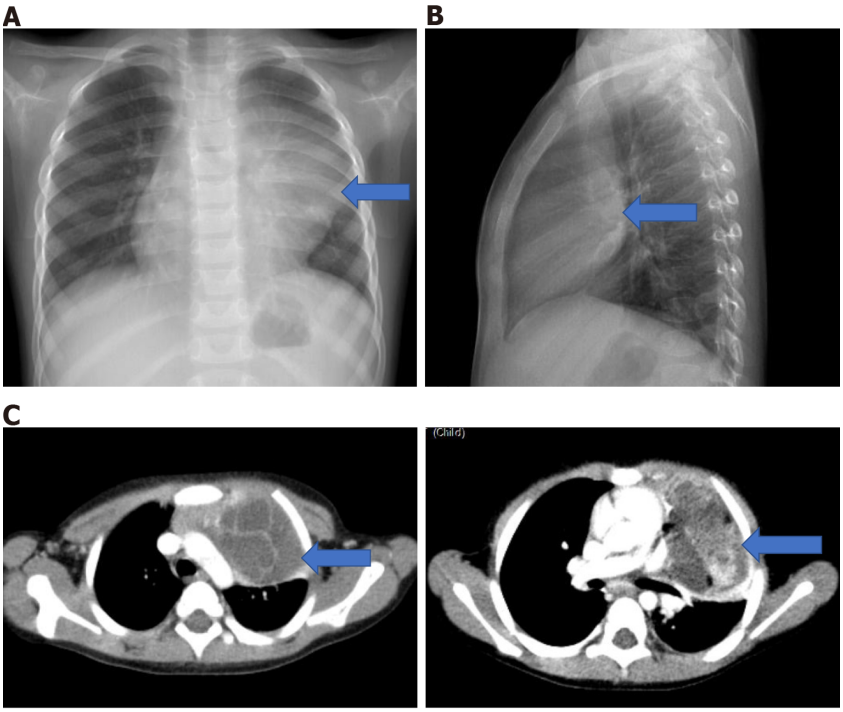

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Figure 18 A 3-year-old girl with mature teratoma. She presents with dyspnea. A: On the posteroanterior chest radiograph the mass (blue arrow) erases the contour of the hilus and heart on the left, slightly compresses the left main bronchus; B: It is located in the anterior mediastinum on the lateral X-ray (blue arrow); C: In the axial computed tomography images of the same patient, a septated mass lesion containing fluid, calcification and fat density (blue arrow) is located in the anterior mediastinum, it compresses the thymus and slightly compresses the left main bronchus. The mass also extends to the left side of the mediastinum.

GERM CELL TUMORS

The most common location of extragonadal germ cell tumors is anterior mediastinum and constitutes 6%-18% of all mediastinal masses[37]. It is located in the thymus or adjacent to the thymus. However, they can also originate from the heart and pericardium, and they may rarely be located in the posterior mediastinum[38]. They peak in the two-year-old period, the first 2 years and the adolescence period [39]. Eighty percent of these tumors are benign and the most common type is teratoma. Teratomas are divided into two groups as mature and immature. Teratomas are observed radiologically as smooth, round or lobulated contours. Fat, calcification and fluid densities are observed in cross-sectional examination. Calcification is observed in 1 or 2 cases out of 5.

These tumors extend to one side of the midline[40] (Figure 18). The lesion should be flagged as an immature teratoma if it is big and diverse, invades nearby tissues, comprises soft tissue components, and is necrotic and hemorrhagic[16,21]. Seminoma and non-seminomatous germ cell tumors (yolk sac tumor, embryonal carcinoma, choriocarcinoma, and mixed type) are less common. They are observed as large masses on direct graphy. However, in cross-sectional examination, seminomas are observed as solid masses of homogeneous density, and they can also metastasize to regional lymph nodes and bone [16]. Although non-seminomatous lesions are observed more heterogeneously due to necrosis and hemorrhage, they may also invade neighboring structures[41]. In addition, non-seminomatous tumors have a more aggressive course and metastases are detected in 85%-95% of them at the time of diagnosis [42]. High levels of B-HCG and AFP are also important laboratory findings in the diagnosis of non-seminomatous tumors. Germ cell tumors may also be associated with Kleinefelter syndrome[43] (Figure 19).

INTRATHORACIC GOITER

It is rarely seen in children. It is located in the anterior mediastinum with a rate of 75%-90% and in the posterior mediastinum with a rate of 10%-25%[44]. It is observed as tracheal deviation or compressive density on direct graphy (Figures 19C and D, and 20). In order to show tracheal compression, cross-sectional examinations are better to direct radiography. They are crucial for preoperative evaluation[14].

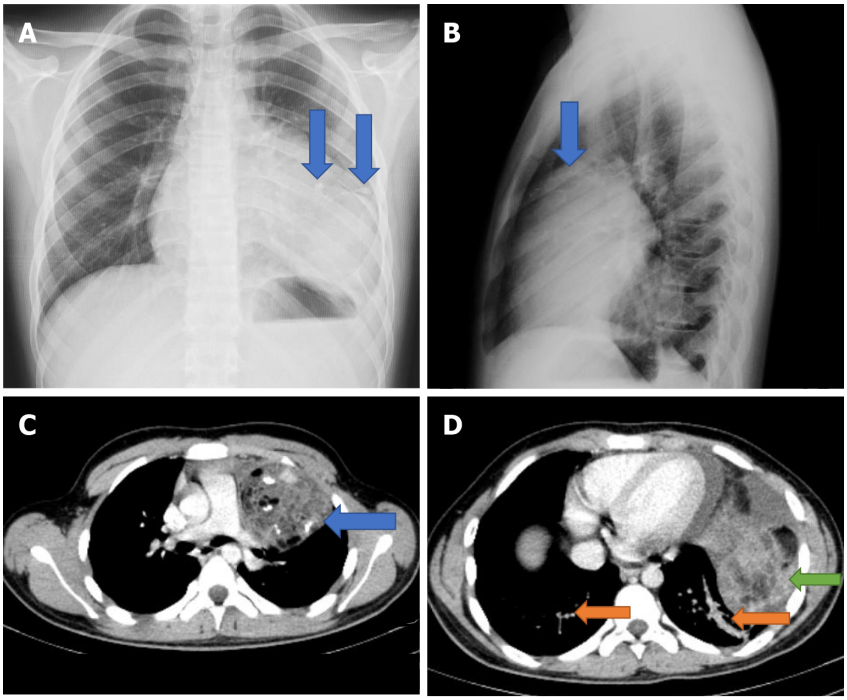

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Figure 19 A 14-year-old male patient with Kleinefelter syndrome. He has been complaining of pain in the left arm and shoulder for 3 d. A: Posteroanterior chest radiograph shows calcifications (double blue arrow) that erases the contour of the heart; B: Diaphragm on the left and the density of a mass located in the anterior mediastinum on the lateral radiograph (blue arrow); C: In the axial computed tomography images of the same patient, a lobulated mass lesion with calcification, fluid and fat densities, located in the left anterior mediastinum, adjacent to the thymus is observed (blue arrow); D: Pericardial and pleural effusion are present in the inferior slices of the same patient (green arrow). In addition, basal linear atelectasia is (double orange arrow).

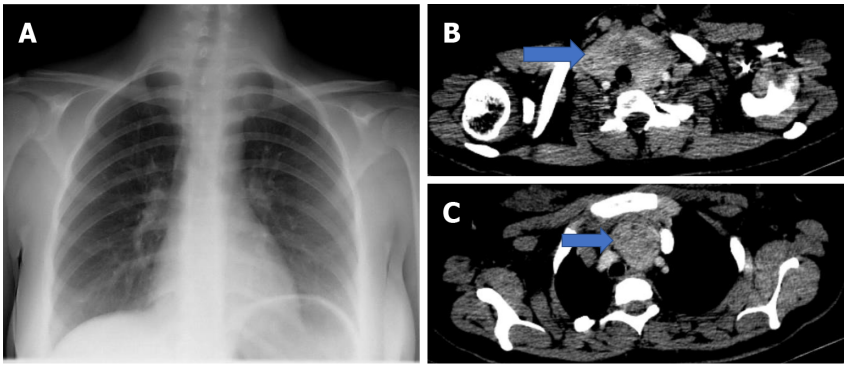

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Figure 20 A 17-year-old girl with intrathoracic goiter. A: In the posteroanterior chest radiograph of the patient followed up for multinodular goiter, enlargement in the upper mediastinum and a density that deviates the trachea to the right are observed. B and C: In axial computed tomography images (blue arrow), the thyroid gland is hyperplastic and contains nodules. In addition its extension is observed in the anterior mediastinum up to the superior aortic arch. Trachea is deviated to the right and no compression is detected.

VISCERAL DISTANCE (MIDDLE MEDIASTINAL) LESIONS

Visceral space lesions are divided into vascular and non-vascular lesions. Childhood vascular lesions lead to congenital abnormalities. Double aortic arch, left aberrant subclavian artery associated with the right aortic arch, right aberrant subclavian artery associated with the left aortic arch, pulmonary artery sling, and double superior vena cava are among these anomalies[16,21] (Figure 21). Thoracic aortic aneurysms are seen in hereditary diseases (Marfan syndrome, Loeys-Dietz syndrome, Aortic tortiosity syndrome, Ehler Danlos syndrome, Cutis laksa syndrome, Noonan syndrome and Alagille syndrome) and congenital heart diseases (aortic coarctation, bicuspid aorta, Fallot tetralogy)[45] (Figures 22 and 23).

Vascular lesions are seen as a mediastinal mass at a rate of 10% on direct X-ray and may present as mediastinal enlargement, increased density, tracheal compression, or thickening of the mediastinal lines. The most effective method in diagnosis is CT Angiography[46].

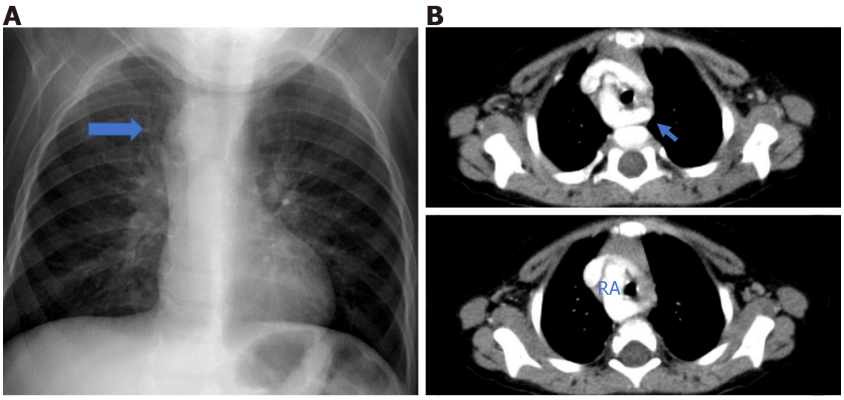

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Figure 21 A 2-year-old male patient with right aortic arch. A: There are complaints of shortness of breath and cough. On posteroanterior chest radiograph, enlargement of the upper mediastinum on the right and compression of the trachea are observed (blue arrow); B: Right aortic arch and left aberrant subclavian artery (blue arrow) are observed in the axial computed tomography angiography images of the same patient. RA: Right aortic arch.

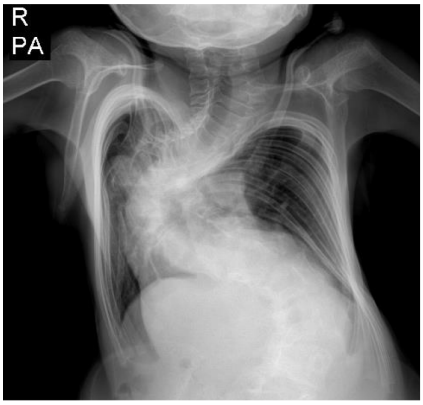

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Figure 22 A 10-year-old male patient with Marfan syndrome. There is mediastinal enlargement and rotoscoliosis in the thoracolumbar region on posteroanterior chest radiograph.

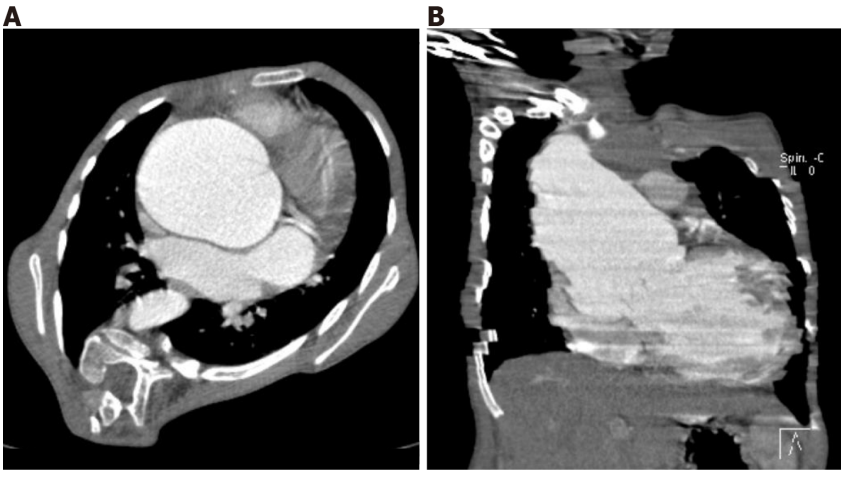

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Figure 23 Aneurysmatic dilatation. A: Aneurysmatic dilatation is observed in the aortic root in the axial; B: Coronal images in the computed tomography Angiography.

LYMPHADENOPATHY

Right paratracheal, peribronchial, aortopulmonary window, hilar, and subcarinal lymph nodes are

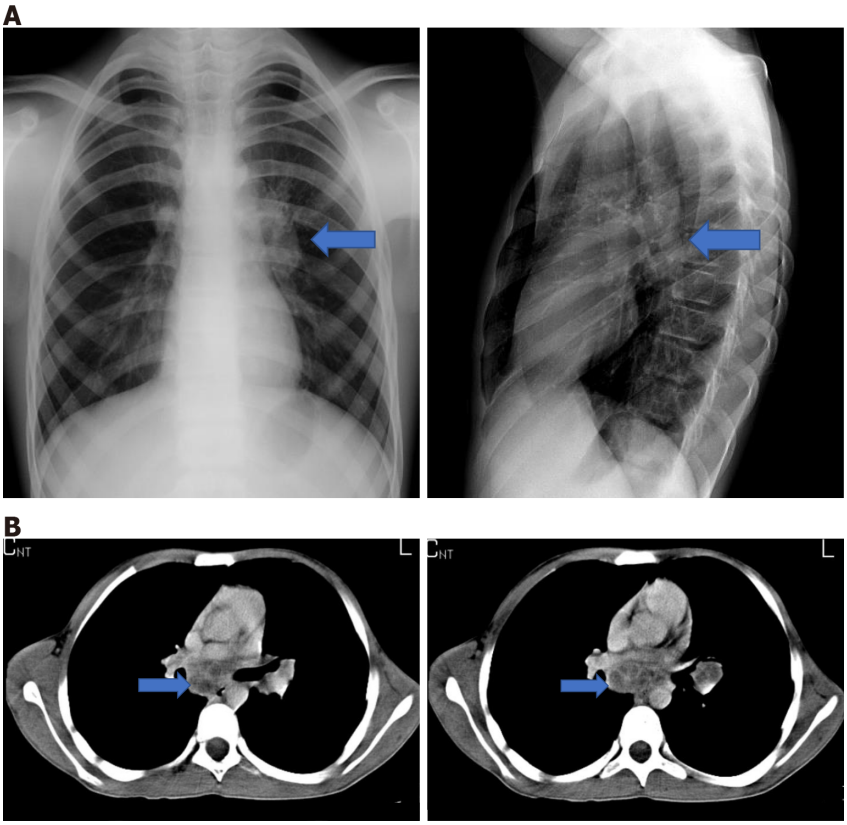

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Figure 24 A 16-year-old male patient with tuberculosis. A: There is fever and weight loss. Left hilar LAP is seen on bidirectional chest radiograph (blue arrow). B: Subcarinal and left hilar necrotic lymphadenopathies (blue arrow) are observed in the axial plane computed tomography examination of the same patient.

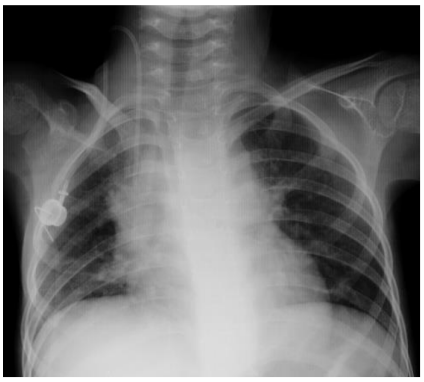

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Figure 25 An 8-year-old female patient followed up with neuroblastoma. Mediastinal enlargement and tracheal deviation are observed in posteroanterior chest radiograph.

situated in the visceral area. The most important causes of lymphadenopathy in children are infections and malignancies. While direct radiography can show symptoms of increased density, mediastinal expansion, compression, or deviation depending on its size, it is also apparent in soft tissue density as an expanded solitary or conglomerating homogenous or heterogeneous solid mass. Lymph node involvement in cancers can be a primary or distant metastasis[21]. Wilms tumor, Ewing sarcoma and osteosarcoma are the most common causes of metastatic lymphadenopathy in children[14]. Lymph nodes may be cystic or calcific. Cystic content indicates necrosis and is often seen in tuberculosis, fungal infections and malignancies such as seminoma, rhabdomyosarcoma[47] (Figures 24-26). Calcified lymph nodes can be seen in granulomatous infections or osteosarcoma, mucinous ovarian carcinoma, and papillary carcinoma of the thyroid[48]. In Hodgkin lymphoma, lymph node calcification may develop after treatment[21].

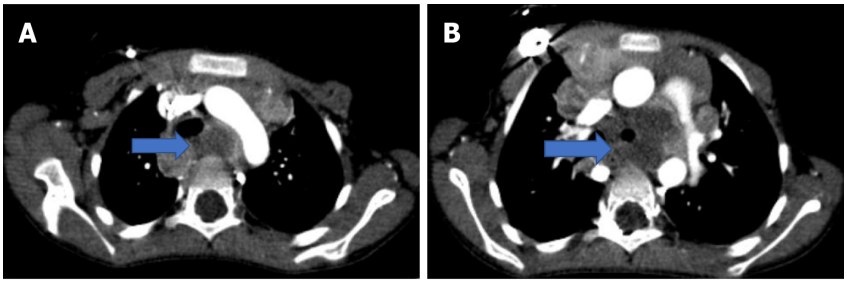

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Figure 26 The axial computed tomography images. A and B: In the axial computed tomography images, necrotic lymphadenopathies (blue arrow) are present in paratracheal, precarinal and subcarinal areas; B: They deviate the trachea anteriorly and invade the left bronchus.

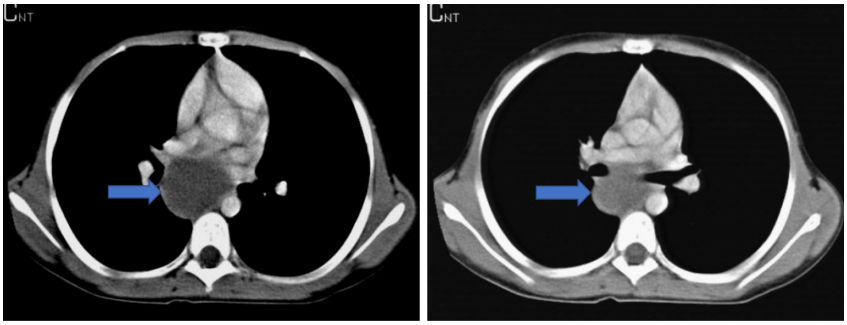

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Figure 27 A 15-year-old female patient with bronchogenic cyst (blue arrow). A 15-year-old female has a complaint of intermittent cough. Axial computed tomography images of the patient at different levels show a cyst located posterior to the right hilum (blue arrow).

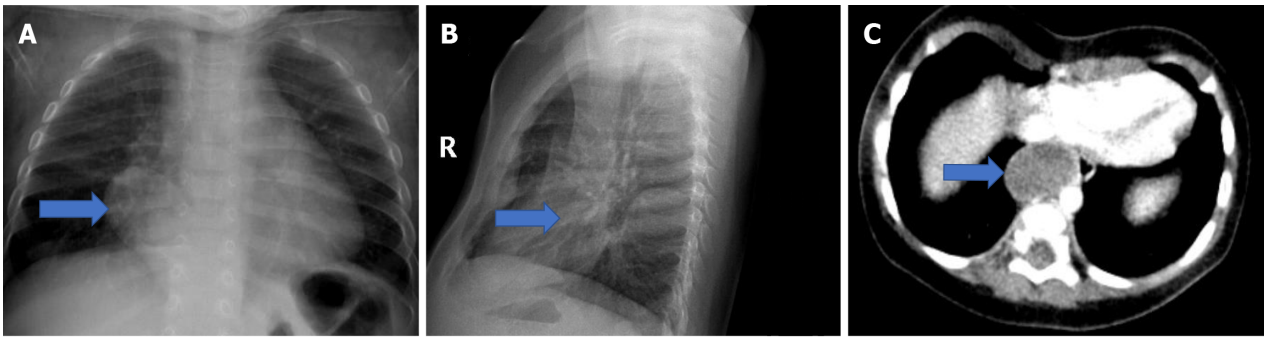

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Figure 28 A 6 mo old male patient. A: On posteroanterior chest radiograph right paravertebral; B: Lateral radiograph posteriorly located smooth-contoured density (blue arrow) is observed; C: Esophageal duplication cyst (blue arrow). In the axial computed tomography images of the same patient, a lobulated contoured cyst is observed in the middle mediastinum, adjacent to the esophagus, and it extends into the posterior mediastinum.

FOREGUT DUPLICATION CYST

Foregut duplication cysts are developmental malformations that occur during embryogenesis of the tracheobronchial tree, esophagus, and vertebral column. Esophageal duplication cyst and neuroenteric cyst are two subtypes of bronchiogenic cyst.

Bronchogenic cyst is the most common cyst of the mediastinum. It is seen in approximately 42% of children and the most common location is the middle mediastinum[49]. It frequently appears in the paratracheal, subcarinal, and hilus of the middle mediastinum, with intrapulmonary localisation occurring less frequently (Figures 27 and 28A).

The incidence of esophageal duplication cyst (Figures 28 and 29) is reported as one in 8200 Live births [50]. It is most commonly seen in the lower 1/3 of the esophagus, and the cysts do not show any relation with the esophageal lumen at a rate of 90%[51]. It is localized in the esophageal wall or in its immediate vicinity.

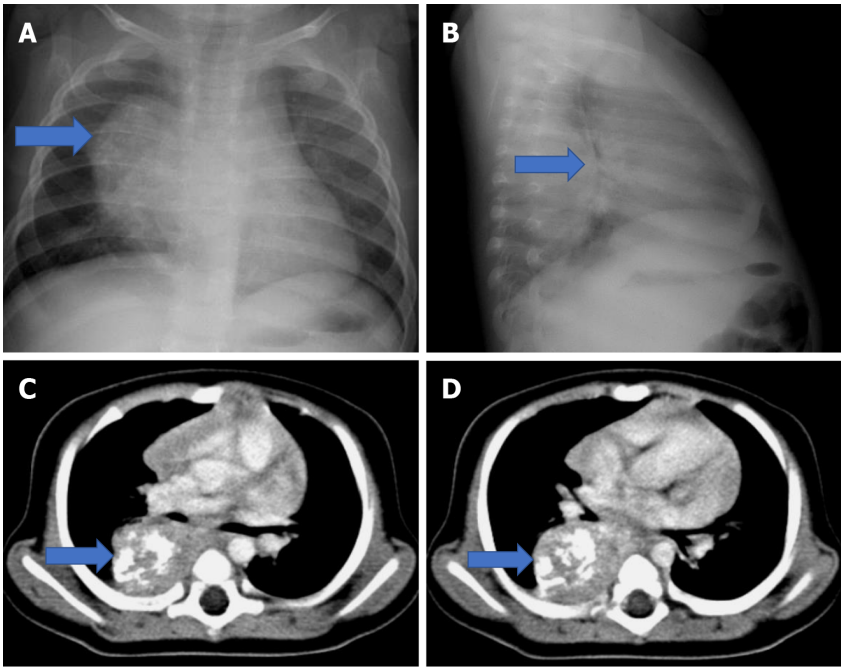

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Figure 29 A 7 mo old girl with Neuroblastoma. He is admitted to the hospital because of cough and wheezing. A: On posteroanterior chest radiograph (blue arrow) the mass is seen on the right paravertebral area; B: On the lateral radiograph a posteriorly located mass with a smooth outer contour and calcifications (blue arrow) is seen; C and D: In the axial computed tomography images of the same patient, a homogeneous mass with smooth contours and punctate-coarse calcifications (blue arrow) is observed in the paravertebral distance. The mass extends to the midline and mild compression is detected on the right main bronchus.

Neuroenteric cyst is the rarest type. It is located in the posterior mediastinum 90% and mostly localized at the superior carina level. It may be associated with vertebral anomalies such as hemivertebrae, butterfly vertebra, and scoliosis[4,52].

Foregut duplication cysts are asymptomatic when they are small in size. However, by compressing nearby structures, big lesions may exhibit symptoms as chest discomfort, dysphagia, and dyspnea[53]. Although they are seen as a smooth-contoured density on the direct graphy, they may cause compression-related findings depending on the size of the lesion. On the other hand, CT is observed as a single lesion with oval or round, smooth contours, thin walls, and fluid density. Typically, wall contrast does not appear. Hemorrhage or the presence of protein cause the fluid density to increase[21,53].

PARAVERTEBRAL DISTANCE (POSTERIOR MEDIASTINAL) LESIONS

Approximately 30%-40% of mediastinal masses are located in the posterior mediastinum[36] and 85%-90% of the lesions are of neurogenic origin[52,54]. Neurogenic tumors consist of sympathetic ganglion tumors, peripheral nerve sheath tumors and paragangliomas. However, neuroblastoma, ganglioneuroblastoma and ganglioneuroma constitute the majority of these tumors from sympathetic ganglion tumors. Neuroblastoma and ganglioneuroblastoma are malignant, while ganglioneuroma is benign. Imaging findings are similar in these tumors, but demographic features may be helpful in the differential diagnosis[16]. Age of onset for neuroblastoma is three years, for ganglioneuroblastoma it is before ten years, and for ganglineuroma it is beyond ten years[22]. Neurogenic tumors are observed as paravertebral vertical elongated density on direct radiography. Its outer contour is smooth and convex. In addition, erosion in the vertebral body, rib, enlargement-erosion in the neural foramen and an increase in the intercostal distance may also be detected[22,35]. Calcification is observed at a rate of 30%[21,36]. On CT, calcification is seen in 80%-90% of neuroblastoma and 42%-60% in ganglioneuroma[55,56]. On CT, these tumors can be seen as a well-contoured mass containing calcifications in the paravertebral area (Figures 29 and 30). They can be homogeneous or heterogeneous due to necrosis and hemorrhage. Depending on the size of the mass, compression findings, rib erosion, neural foramen invasion and extension into the spinal canal are also displayed on CT (Figure 31). However, MRI is superior to CT in showing the extension into the spinal canal[14] (Figure 32).

As a result, a wide variety of pathologies occur due to different tissues and organs located in the mediastinum. Imaging methods play an important role in the classification and evaluation of these pathologies. It should be remembered that it will result in congenital vascular diseases in children as well as mass-like imaging abnormalities in normal organs like the thymus.

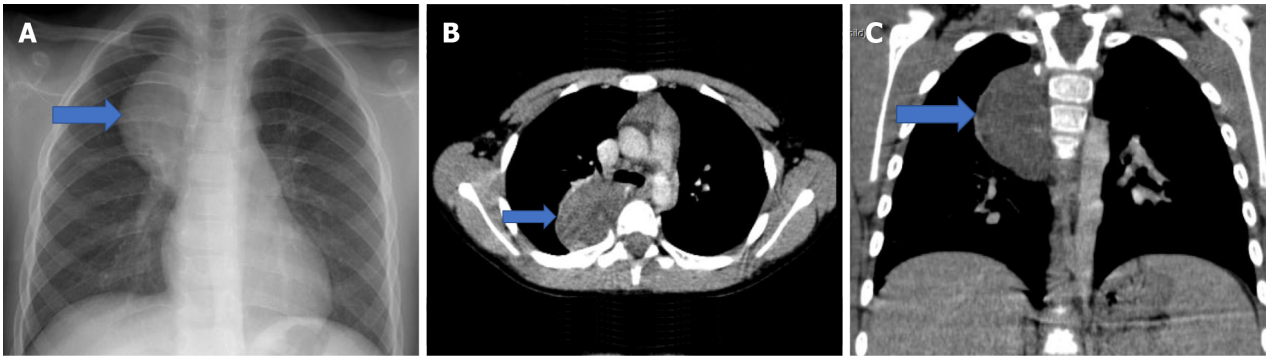

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Figure 30 A 6-year-old female patient with Ganglioneuroma. There is a cough complaint that has been going on for 3 mo. Posteroanterior chest radiograph shows a density (blue arrow) of paravertebral, well-contoured mass causing enlargement of the mediastinum on the right; B and C: In the axial and coronal computed tomography images of the same patient, a well-contoured, homogeneous mass (blue arrow) is observed in the paravetebral distance on the right.

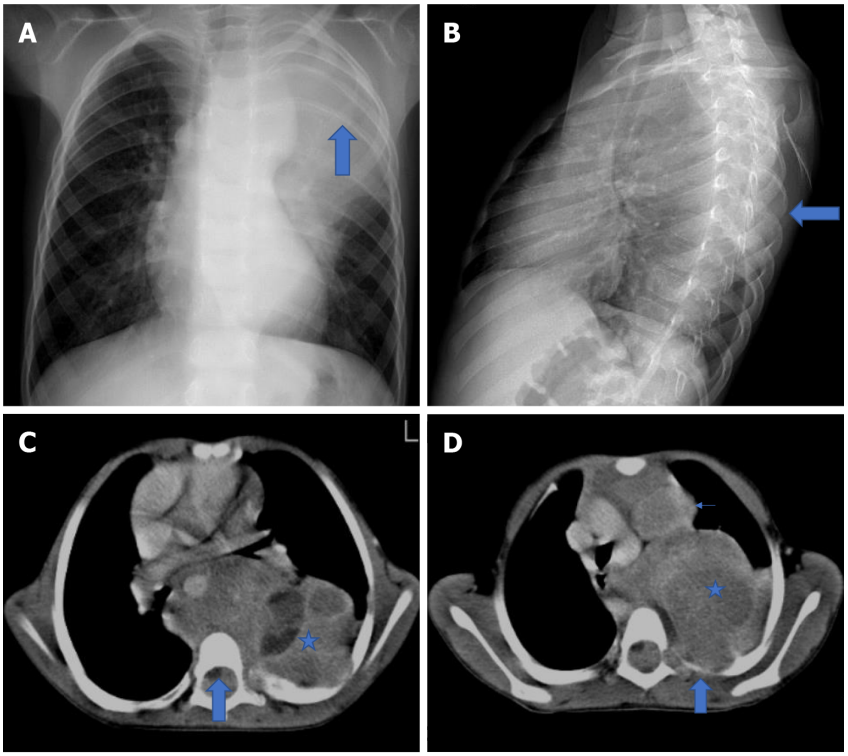

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Figure 31 A 5-year-old girl with Ganglioneuroblastoma. There are complaints of cough and left flank pain. A: A lobulated contoured mass lesion is observed in the Posteroanterior chest radiograph (blue arrow) that causes mediastinal enlargement on the left, deviates the trachea to the right; B: It is seen posteriorly on the lateral radiograph and causes erosion in the ribs (blue arrow); C and D: In the axial computed tomography images of the same patient, a heterogeneous mass lesion is seen (blue star).

CONCLUSION

The aim of the study is to ensure that physicians who are at the diagnostic level are more careful in terms of differential diagnoses and to support them with imaging methods.

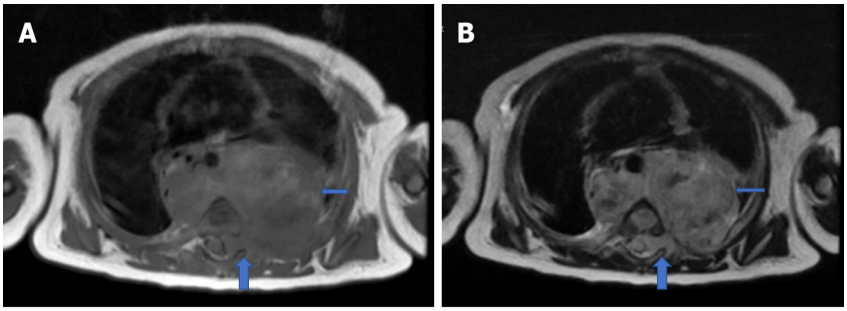

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Figure 32 A 4-mo-old male patient diagnosed with neuroblastoma. A: A heterogeneous mass is observed on both sides in the paravertebral area in T1W-weighted; B: T2W-weighted sections in the axial plane. The descending aorta is surrounded by the mass (thin blue arrow) and pushed anteriorly. It is also noteworthy that the mass invades the left neural foramen, extending into the spinal canal and compressing the spinal cord (A and B, thick blue arrow).

FOOTNOTES

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MINIREVIEWS

Exit strategies in inflammatory bowel disease: Looking beyond anti-tumor necrosis factors

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Abstract

The long-term management of patients with inflammatory bowel disease (IBD) is still a matter of debate, and no clear guidelines have been issued. In clinical practice, gastroenterologists often have to deal with patients in prolonged remission after immunomodulatory or immunosuppressive therapies. When planning an exit strategy for drug withdrawal, the risk of disease relapse must be balanced against the risk of drug-related adverse events and healthcare costs. Furthermore, there is still a dearth of data on the withdrawal of novel biologics, such as the anti-α4β7 integrin antibody (vedolizumab) and anti-IL12/23 antibody (ustekinumab), as well as the small molecule tofacitinib. Models for estimating the risk of disease relapse and the efficacy of retreatment should be evaluated according to the patient's age and IBD phenotype. These models should guide clinicians in programming a temporary drug withdrawal after discussing realistic outcomes with the patient. This would shift the paradigm from an exit strategy to a holiday strategy.

Key Words: Exit strategy; Biologic withdrawal; Drug holiday; Vedolizumab; Ustekinumab; Tofacitinib

Core Tip: Clinicians are still uncertain about whether and when to consider stopping conventional therapies in inflammatory bowel disease (IBD) for fear of disease relapse. Our review aims to shed light on the optimal discontinuation strategies for biologics and the small molecule tofacitinib in IBD.

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INTRODUCTION

Early initiation of immunosuppressive treatment and rapid escalation of therapy in the course of inflammatory bowel disease (IBD) appear to improve disease outcomes by tightly controlling inflammation[1-3]. However, once remission has been achieved, both clinicians and patients are faced with the thorny issue of the feasibility and timing of discontinuing therapy.

Undoubtedly, there has been a tendency in recent years to continue immunosuppressive treatment indefinitely in IBD patients in remission, fearing the detrimental effects of loss of disease control, impairment of previous drug efficacy, and adverse events after retreatment[4-5]. However, the risk of disease relapse must be balanced against the risk of immunosuppressive-related adverse events, particularly opportunistic infections[6-8] and malignancies[9,10].

In addition to safety issues, the cost of biological therapy must also be considered. The cost of medications represents an increasing proportion of the total cost of IBD treatment and has gradually surpassed the costs of surgery and hospitalization[11]. Thus, as expected, a de-escalation strategy for IBD patients in remission has resulted in significant cost savings, even with the advent of biosimilar drugs[12,13]. Consequently, there are both individual and societal reasons to re-examine the indefinite use of immunosuppressive drugs in IBD patients[14,15]. This is especially true as the number of available therapies has doubled in the last decade with the introduction of novel biologics, such as anti-α4β7 integrin and anti-IL12/23 antibodies, and the approval of small molecules. As a result of this vast treatment landscape, the evaluation of less expensive and safer withdrawal strategies is paramount to providing personalized and appropriate IBD treatment.

SELECTING THE IDEAL CANDIDATE FOR THERAPY WITHDRAWAL

Patient selection must take into account patient demographics and clinical characteristics, as these are crucial when considering discontinuation of IBD therapy. The most predictive factors of relapse after treatment withdrawal are the presence of poor prognostic features, challenging disease control prior to discontinuation, or biochemical disease activity[5,14-17] (Table 1). To date, CRP and fecal calprotectin have been recognized as the best biomarkers for assessing the risk of short-term (< 6 mo) relapse after stopping biologics[18-20]. Using mass spectrometry-based proteomics on the basal serum of Crohn's disease (CD) patients from the STORI trial[5] at the time of infliximab (IFX) discontinuation, Pierre *et al* [21] recently identified two protein panels (15 and 17 proteins) associated with short-term and mid- to long-term relapse (> 6 mo), respectively, reflecting two distinct pathophysiological processes. Notably, the discriminatory probability of these novel biomarkers to predict relapse in CD patients following the discontinuation of anti-tumor necrosis factors (TNF) therapy was superior to that of C-reactive protein (CRP) and fecal calprotectin[22,23].

Furthermore, evidence of mucosal healing at either imaging or endoscopy is a key element associated with a reduced risk of relapse after discontinuation of biologic therapy: Several studies in CD and ulcerative colitis (UC) have shown that relapse rates are higher when anti-TNF is discontinued based solely on clinical remission, without taking into account endoscopic remission[14,15] (Table 1).

Some studies have also shown that CD patients who achieved transmural healing, as assessed by either bowel ultrasound or magnetic resonance imaging, had a lower risk of relapse after drug discontinuation and better 1-year clinical outcomes than those with endoscopic mucosal healing[24,25] (Table 1). This finding is not surprising, as it is consistent with evidence suggesting that transmural healing is associated with improved clinical outcomes and reduced long-term disease complications compared to mucosal healing, with some suggesting that it should be considered a deeper therapeutic target in the treatment of CD[26].

There is also a growing body of evidence demonstrating the link between histologic healing and a lower risk of clinical relapse in UC patients[27-29], although not all research points in this direction[30].

Table 1 Predictive factors for disease recurrence after therapy withdrawal

Poor disease prognostic features	CD/UC: Young age at diagnosis and male sex
	CD: Ileal, colonic or perianal disease; stricturing/penetrating disease
	UC: Pancolitis
Challenging disease control before withdrawal	Many relapses requiring add-on steroids
	Anti-TNF escalation while already on
	Need for surgery or anti-TNF post-operative prophylaxis
Biochemical disease activity	High CRP levels
	Elevated fecal calprotectin
	Elevated white cells or neutrophil count
	Low hemoglobin levels
Endoscopic disease activity	No mucosal healing
Radiological CD activity	No transmural healing
IFX trough levels	High IFX trough levels in monotherapy
	Low IFX trough levels in combination therapy with an imunomodulator

CD: Crohn's disease; UC: Ulcerative colitis; TNF: Tumor necrosis factor; CRP: C-reactive protein; IFX: Infliximab.

Infliximab (IFX) trough levels have also been shown to be inversely associated with the risk of relapse, depending on whether IFX monotherapy or immunomodulator combination therapy is discontinued. Low IFX trough concentrations predict a lower risk of relapse when the drug is discontinued[5, 31], suggesting that patients in whom anti-TNF was the main contributor to remission are at a higher risk of relapse after discontinuation. Conversely, in patients receiving combined IFX and immunomodulator therapy, a higher IFX trough concentration predicts a lower relapse rate when the immunomodulator is withdrawn[32] (Table 1).

Several pharmacogenetic studies have shown an association between certain genetic polymorphisms, particularly those in the anti-TNF pathway, and response to biologic therapy[33]. It is therefore reasonable to assume that there is also a correlation with the outcomes of exit strategies, giving the genetic biomarkers a role in the selection of the most suitable IBD patient for therapy withdrawal.

To date, there are no recommendations for gene searches as part of therapy optimization or discontinuation. However, they seem very promising for a future tailored approach.

Although the predictors of the risk of relapse after discontinuation of therapy are well known, they may not be sufficiently weighted at the individual patient level. The landmark STORI trial, conducted on CD patients on combination therapy who discontinued anti-TNF, identified a predictive model (corticosteroid use 6–12 mo prior to anti-TNF withdrawal, no previous surgery, male sex, hemoglobin < 145 g/L, leukocyte count > 6 × 10^9/L, Crohn's Disease Endoscopic Index of Severity score > 0, CRP ≥ 5 mg/L, IFX trough level ≥ 2 mg/L, and fecal calprotectin ≥ 300 μg/g), in which patients with fewer than 3 risk factors had a significantly lower risk of relapse within 1 year than patients with 4, 5-6, or more than 6 factors[5]. However, when validated in an individual participant data meta-analysis of 1317 CD patients in remission, it showed poor discriminative ability (C-statistic, 0.51). The model performance for the risk of relapse after anti-TNF withdrawal improved (C-statistic, 0.59) when other risk factors were considered (clinical symptoms at withdrawal, no concomitant immunosuppressants, adalimumab, second-line anti-TNF, younger age at diagnosis, smoking, upper gastrointestinal tract involvement, younger age at withdrawal, longer disease duration, and C-reactive protein), and when fecal calprotectin was added to them (C-statistic, 0.63)[34]. It would be interesting to investigate whether this clinical score would be superior or complementary to the aforementioned proteomic biomarkers from the study by Pierre *et al*[21]. Moreover, it is worth noting that none of these scores have ever accounted for radiological activity in CD or histologic activity in UC.

In conclusion, stable deep remission (clinical, biochemical, and endoscopic remission) is the key requirement when considering discontinuation of therapy. It is expected that radiological and histological remission, along with novel biochemical and genetic biomarkers, will soon contribute to better patient profiling for a tailored approach.

DISCUSS EXIT STRATEGIES WITH THE PATIENT

The decision to discontinue treatment should be shared with the patient, who should be advised of the pros and cons. A given risk of relapse over time may be acceptable for one patient but not for another; therefore, individual patient preference is critical in formulating a treatment exit strategy.

An interesting survey found that about one-third of patients would not accept any de-escalation if it increased the risk of disease flare-up, and nearly half of them were more concerned about CD activity than the risk of treatment-related malignancy[14,35].

Evidence-based estimates of the risk of relapse after withdrawal and the efficacy of retreatment are discussed separately for each drug in the next section and are summarized in Table 2.

WITHDRAWAL, DE-ESCALATION AND RE-TREATMENT

Research results on immunosuppressive drug withdrawal, de-escalation, and retreatment are presented and discussed in the following subsections. Discontinuation of 5-aminosalicylate in UC patients is beyond the scope of this review and will not be discussed.

Immunomodulator monotherapy

Several randomized controlled trials (RCTs) and observational studies have shown that the withdrawal of immunomodulator monotherapy (thiopurine in CD/UC or methotrexate in CD) is associated with a substantial risk of relapse (30% at 2 years and 50%-75% at 5 years)[15]. A multicenter, double-blind, non-inferiority withdrawal study on CD patients showed that such high relapse rates occur even after long periods (> 3-5 years) of steroid-free clinical remission[36,37]. More importantly, similar recurrence rates (CD 30.8% and UC 58.1% within a median of 15 mo) were observed in a recent prospective study of IBD patients who discontinued azathioprine (AZA) after at least 5 years of treatment, despite being in deep extended remission (normal clinical, endoscopic, fecal calprotectin, CPR, and histologic indexes)[38]. However, the increased risk of potential drug-related lymphoma after long-term immunosuppressive therapy must be considered (incidence rate 0.90 per 1000 patient-years)[9]. Therefore, many authors suggest that the risks and benefits of continued immunomodulatory therapy should be discussed with the patient at least after 3-5 years of stable remission, along with the suggestion that a period off therapy would significantly reduce the risk of lymphoproliferative disorders[14,15].

There is a paucity of evidence on the efficacy of retreatment for relapse after immunosuppression withdrawal, and no study has ever evaluated AZA metabolite concentrations, which may be important in predicting relapse after discontinuation or de-escalation of immunosuppressive monotherapy. Recapture data were reported by Treton *et al*[42] in a small study in which 23 of 32 CD patients who relapsed after AZA withdrawal were retreated with AZA, and all but one achieved clinical remission at a median follow-up of 28 mo[34]. Similarly, high AZA recapture rates were demonstrated in a subsequent multicenter retrospective cohort study in which 74% of CD and 92% of UC patients who resumed AZA at the time of relapse regained and maintained clinical remission, although mostly in combination with systemic steroid re-induction[39]. It should be noted that in both studies, besides the need for corticosteroids, a non-negligible percentage of patients who discontinued AZA required biologic therapy, hospitalization, and/or resectional surgery.

As regards immunosuppressive de-escalation, there are no data on the efficacy and safety of low-dose immunomodulators as monotherapy in IBD. A dose-dependent relationship between AZA and non-Hodgkin's lymphoma and 6-thioguanine nucleotide (6-TGN) concentrations and skin cancer in transplant patients has been shown[40,41].

Anti-TNF monotherapy

Withdrawal of anti-TNF monotherapy (IFX or adalimumab) is associated with a high risk of relapse (between 30%-40% at 6 mo/1 year and > 50% beyond 2 years)[14,15], which is quite significant given that the clinical benefits of discontinuing anti-TNF, such as reduced risk of infection or malignancy, are hypothetical as no controlled study has ever been conducted. The aforementioned STORI trial, which was designed to assess the prevalence of clinical relapse after discontinuation of anti-TNF in quiescent CD while on immunosuppressants, revealed that 44% and 52.2% of patients relapsed one year and two years after discontinuation, respectively[5]. A subsequent meta-analysis by Gisbert *et al*[47] showed that the overall risk of relapse after discontinuation of anti-TNF was 44% for CD and 38% for UC[42].

The more recent STOP-IT RCT showed significantly lower relapse-free survival rates at 48 wk in CD patients who discontinued IFX compared to those who continued IFX (51% *vs* 100%), regardless of deep remission at baseline[43]. In UC patients, the HAYABUSA RCT also showed a significant difference in clinical remission rates (80% *vs* 54%) between the IFX continuation group and the IFX discontinuation group at 48 wk after randomization, even after adjustment for the Mayo endoscopic subscore[44]. The studies that also focused on treatment reported favorable recapture rates (up to 80%-90%) with an acceptable rate of infusion-related reactions[5,40,42]. In terms of efficacy and safety, such findings contrast with the proven increased risk of anti-drug antibody (ADA) development after retreatment[45,

Table 2 Summary of the available evidence for withdrawal of immunosoppressive drugs in inflammatory bowel disease

Drug	Minimum therapy duration before withdrawal, yr	Estimated risk of disease relapse after withdrawal	Therapeutic drug monitoring before withdrawal	Estimated efficacy of re-treatment	De-escalation
Immunomodulators (thiopurine in CD/UC or methotrexate in CD)	3-5	30% by 2, 50%–75% by 5 yr	No data available	75%-90% (often in combination with steroids)	Possible in combination therapy
Anti-TNF	1-2	30%–40% at 6 mo/1 year and > 50% by 2 yr	Possible	80%-90%	Possible (TDM suggested)
Vedolizumab	No data available	65% by 1.5 yr	No data available	50%-65%	No IBD data available beyond 8 wk
Ustekinumab	No data available	59.5% by 1 yr in registrative studies	No data available	39.2%-64% in registrative studies	No IBD data available beyond 12 wk
Tofacitinib	No data available	65 % by 6 mo, 80 % by 1 yr in registrative studies	No data available	75% after 2 months and 50 % after 3 yr in registrative studies	No IBD data available for dosage < 5 mg bid

CD: Crohn's disease; UC: Ulcerative colitis; TDM: Therapeutic drug monitoring.

46], which is associated with infusion-related reactions and long-term loss of response due to faster clearance and lower drug concentrations[47]. Nevertheless, the effect of concomitant immunomodulators, which have been widely used in most studies during drug holidays and retreatment, cannot but be considered since several studies have shown that they are associated with reduced immunogenicity effects[48-49]. The recent REGAIN study showed that early detection of ADAs (week 0 and week 4) after IFX reintroduction can predict subsequent failure and infusion reactions, regardless of the reason for prior discontinuation[50].

Both decreasing the dose of anti-TNF and lengthening the interval between doses have been proposed to de-escalate the drug prior to withdrawal. Whether de-escalation should be guided by clinical/biochemical assessment or by therapeutic drug monitoring (TDM) is still a matter of debate because of the controversial nature of the available results. In the TAXIT study, dose reduction in clinically stable patients with supra-optimal IFX levels (> 7 mg/L) did not lead to flare-ups or elevated inflammatory markers compared to patients whose dosing was based on clinical symptoms; this resulted in significant cost savings[12]. Furthermore, in a subsequent study, trough levels before or after anti-TNF interval prolongation were not significantly associated with the success of the spaced schedule [51], but in a French study, de-escalation based on trough levels was associated with a lower risk of relapse[52]. In any case, it remains unclear whether lower anti-TNF doses lead to fewer anti-TNF-related adverse events in both the IBD and rheumatological fields[53-56].

Combined immunomodulatory and anti-TNF therapy

Withdrawal of immunomodulators in CD patients treated with combination therapy for more than 6 months does not increase the relapse rate compared to continued combination therapy[14,15], as recently confirmed by the SPARE trial[57]. On the other hand, the risk of relapse over 1 to 2 years is between 40% and 50% when the biologic is stopped[5,40].

A topical review by the European Crohn's and Colitis Organization (ECCO) suggests that the decision to discontinue the immunomodulator should also be guided by the anti-TNF TDM[14].

A single small randomized study has found that AZA dose reduction, but not withdrawal, resulted in similar IFX trough levels and relapse rates in patients receiving combination therapy, also supporting a dose de-escalation strategy[58].

Anti-α4β7 integrin antibody: Vedolizumab

Only one observational study has evaluated the risk of relapse after vedolizumab withdrawal, showing a relapse rate of 64% at 18 mo after therapy discontinuation[59]. Although there is no evidence that a longer duration of biologic therapy promotes a lower risk of relapse, it should be noted that most anti-TNF withdrawal studies included patients treated with IFX or adalimumab for at least 2 years, whereas the median duration of vedolizumab therapy in this study was only 14.5 mo. This finding is even more significant when considering vedolizumab's slow onset of action during the induction phase. In addition, most of the patients in this study were previously treated with immunomodulators and anti-TNF, which was not the case in patients who discontinued anti-TNF. Following the reintroduction of vedolizumab, 24 of 61 patients who experienced a clinical relapse were retreated with vedolizumab, and as many as two-thirds of them achieved steroid-free clinical remission at week 14 and during the 11-

month follow-up period. However, it should be noted that patients who were not retreated with vedolizumab (60.7%) underwent surgery or started other biologics, mostly ustekinumab.

In the GEMINI long-term safety study, CD patients on drug holidays for up to one year were retreated with VDZ every 4 wk and experienced clinical benefits: Patients with early withdrawal from GEMINI 2 had an improved remission rate (from 9% to 48% at week 24), while patients who completed the GEMINI 2 maintenance phase on a placebo improved from 53% to 63% at week 52[60]. In this cohort, the percentage of patients who developed ADAs was consistent regardless of the duration of the drug holiday. A subsequent study evaluating the immunogenicity of vedolizumab showed that treatment interruption resulted in a significant increase in the rate of ADAs compared to continuous therapy (19.4% *vs* 2.4%), which was lower when concomitant immunomodulators were used (0.8% *vs* 10.8%)[61]. However, no association between immunogenicity and infusion□related reactions was observed, consistent with previous reports[62,63]. Given that ADAs also do not appear to play a major role in the efficacy of vedolizumab[64], even in patients who discontinue and later restart treatment[65, 66], the addition of an immunosuppressant upon resumption of vedolizumab seems to be unnecessary.

Regarding vedolizumab de-escalation, Vermeire *et al*[67] recently reported that changing the dosing interval from 4 to 8 wk maintained clinical efficacy with high persistence rates after 2 years of follow-up. These results are consistent with those from registrational clinical trials[68,69] and a previously published vedolizumab dose-lengthening study in a subset of patients from the GEMINI study[70], especially when accounting for the unproven exposure-efficacy relationship for vedolizumab in the maintenance phase[71].

Further data are needed to identify de-escalation strategies for vedolizumab, including extending the dosing interval beyond 8 wk, given that current evidence is limited.

Anti-IL12/23 antibody: Ustekinumab

There is a paucity of data on ustekinumab withdrawal and retreatment in IBD, given that it was originally used as second- and third-line therapy in refractory and usually complex patients. In the UNIFI trial, 42 UC patients, among those who responded to ustekinumab induction and were randomized to placebo at maintenance, were retreated with subcutaneous ustekinumab every 8 wk during the long-term extension study[72]. Of these, 16 of the 25 patients (64.0%) who had clinical symptoms successfully regained clinical remission after 16 wk of dose adjustment. Although the incidence of ADAs was higher in the placebo dose adjustment group (13.2%), the safety profile was consistent with that observed in patients randomized to ustekinumab maintenance[73]. Good recapture rates (39.2%) were also observed in the IM-UNITI study, in which 51 CD patients randomized to placebo after responding to induction were retreated with subcutaneous ustekinumab every 8 wk after meeting loss-of-response criteria[74]. This finding is consistent with other studies that have also evaluated the efficacy of intravenous reinduction of ustekinumab in CD patients who lost response to ustekinumab maintenance therapy alone[75].

To gain a sense of the relapse and recapture rates following ustekinumab withdrawal and retreatment, it is also worth looking at the larger data set of patients with moderate to severe plaque psoriasis. In the phase 3 PHOENIX 1 trial, the median time to loss of 75% of the Psoriasis Area and Severity Index (PASI 75) was 15 wk after ustekinumab withdrawal. Twelve weeks after retreatment, most patients achieved a PASI 75 response[76]. Similar findings were observed in the ACCEPT study, where the median time to clinical relapse was 14.4-18.1 wk and recapture rates were 80-90% at 12 wk after the initial retreatment dose[77]. An eight-year observational multicenter study also showed very low cumulative probabilities of being psoriasis relapse-free, with a median time to loss of PASI 50 after treatment withdrawal of 24 wk[78], in line with another previous observational study[79].

As for treatment de-escalation, there are no criteria to decide whether IBD patients should receive ustekinumab every 8 wk or every 12 wk (Q12W)[80,81]. For instance, in the SUSTAIN study, a history of perianal surgery was the only reason CD patients received ustekinumab every 8 wk. In this study, 6.2% of patients with stable remission had their ustekinumab dosage reduced from every 8 wk to every 12 wk, and 65.2% of these patients maintained remission over time[82]. A recent prospective study investigated the clinical response rates in psoriatic patients with extended ustekinumab maintenance dosing intervals (up to every 16-24 wk) and found that a subset of patients with early, high-level responses while on Q12W therapy were more likely to extend the dosing interval and maintain response without experiencing an increase in ADA development[83].

JAK inhibitors: Tofacitinib

The OCTAVE Sustain study demonstrated that clinical response and remission were maintained in nearly one-third and one-fifth of placebo-treated UC patients after interruption of tofacitinib 10 mg twice daily (b.d.) at 24 and 52 wk, respectively. The median time to treatment failure after tofacitinib withdrawal was 169 and 123 days for induction remitters and induction responders, respectively[84]. Following tofacitinib retreatment, clinical response and remission rates were 74.0% and 39% after 2 mo and 37.4% and 48.5% after 36 mo, respectively. The predictors of recapture efficacy following retreatment were less severe disease at the time of retreatment, increased age, no prior use of immunosuppressants, and no use of corticosteroids at induction study baseline, regardless of prior anti-TNF status[72].

The OCTAVE clinical trials also evaluated the effect of dose reduction on the efficacy of tofacitinib. Among patients who received a high dose of tofacitinib (15 mg b.d. or 10 mg b.d.) in OCTAVE Induction 1 and 2 and re-randomization to receive tofacitinib 5 mg b.d. in OCTAVE Sustain, 32.4% of patients were in remission at week 52[85]. An additional post-hoc analysis evaluated the effect of dose reduction in patients in remission treated with tofacitinib 10 mg b.d. for 52 wk, followed by 5 mg b.d. in OCTAVE Open. After tofacitinib dose reduction, clinical response was maintained in 92.4% and 84.1% of patients at months 2 and 12, respectively[86].

The RIVETING trial also showed that most patients in stable remission on tofacitinib maintenance therapy at 10 mg b.d. maintained remission following dose de-escalation to 5 mg twice daily[87]. These data are consistent with previous observational and long-term extension studies of tofacitinib discontinuation and dose reduction in rheumatoid arthritis[88,89].

OPTIMAL MONITORING AFTER THERAPY WITHDRAWAL

Although no specific study has evaluated the optimal strategy for monitoring disease activity after treatment withdrawal, noninvasive markers (ESR, CRP, and fecal calprotectin) may be a more reliable tool than clinical activity[90]. The efficacy of biomarker-driven monitoring in IBD was also demonstrated in the CALM trial, in which patients on tight control had superior clinical and endoscopic outcomes than those managed with a symptom-driven strategy[19].

In particular, fecal calprotectin demonstrated better performance compared to CRP[92], and its elevation (with different cut-offs depending on the study) seems to precede the short-term clinical and endoscopic relapse in patients who discontinued anti-TNF therapy[18-20]. Buisson *et al*[91] also found that calprotectin levels were higher in patients who relapsed after therapeutic de-escalation (which included both a reduction in the drug dose and an increase in the interval between infusions).

Intestinal ultrasound has gained ground in the management of IBD patients due to its reproducibility, lack of risk, and general patient acceptance[92]. Theoretically, these features make ultrasound very appealing for monitoring patients with IBD; however, to date, no study has been undertaken to investigate its role in this specific setting.

The optimal timing for disease monitoring after therapy withdrawal remains to be determined.

As in the HAYABUSA study, the difference between patients who discontinued anti-TNF and those who did not was significant as early as 16 wk after withdrawal, and relapse seems to be more likely to occur in the first months after treatment discontinuation[44].

Based on this scarce evidence, patients discontinuing biologic or immunosuppressive therapy should be closely monitored for disease activity, especially during the first 6-12 mo after therapy withdrawal. Monitoring should include a thorough clinical assessment and repeated measurements of noninvasive biomarkers[14]. Current clinical practice suggests that in the event of biomarker elevation and/or symptom recurrence, a repeat endoscopic or radiological assessment should be performed promptly to rapidly diagnose recurrence and re-establish disease control. No ad hoc studies have examined the role of specific therapeutic interventions (*i.e.*, concomitant drug optimization or new drug introduction) as maintenance therapy after biologic withdrawal.

CONCLUSION

The management of IBD patients in remission remains an important research gap, as stated in the ECCO guidelines[93]. First, as remission is an evolving concept, it should be noted that early studies only included patients in steroid-free clinical remission, without considering biochemical and/or endoscopic remission. Second, the duration of remission itself before therapy discontinuation remains controversial. Little is also known regarding the optimal therapy duration prior to withdrawal: It is interesting to note that, despite the fact that longer durations of immunosuppressive therapy have not been shown to reduce the risk of relapse, the majority of studies included patients treated with biologics for just 1-2 years. Furthermore, although there is a large body of evidence on anti-TNF, there is still very limited real-world data on the withdrawal of novel biologics, such as the anti- α4β7 integrin antibody (vedolizumab) and anti-IL12/23 antibody (ustekinumab), and the small molecule tofacitinib.

Future studies should focus on resolving these issues and identifying predictive factors for relapse after therapy withdrawal in the perspective of a personalized approach for IBD patients.

To date, immunomodulators, anti-TNF, and vedolizumab have demonstrated good recapture rates after retreatment. In light of this evidence, the concept of a holiday strategy/therapy cycling (*i.e.*, planned therapy interruption, close monitoring, and prompt resumption of therapy before the onset of clinical symptoms), rather than a definitive exit strategy, appears to be more realistic when discussing long-term management with patients.

FOOTNOTES

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MINIREVIEWS

Medicinal cannabis products for the treatment of acute pain

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Abstract

For thousands of years, medicinal cannabis has been used for pain treatment, but its use for pain management is still controversial. Meta-analysis of the literature has shown contrasting results on the addition of cannabinoids to opioids compared with placebo/other active agents to reduce pain. Clinical studies are mainly focused on medicinal cannabis use in chronic pain management, for which the analgesic effect has been proven in many studies. This review focuses on the potential use of medical cannabis for acute pain management in preclinical studies, studies on healthy subjects and the few pioneering studies in the clinical setting.

Key Words: Cannabis; Cannabinoids; Endocannabinoid system; 2-arachidonoylglycerol; Anandamide; Analgesia; Acute pain

Core Tip: Medicinal cannabis use for pain management is still controversial. Meta-analysis of the literature has shown contrasting results on the addition of cannabinoids to opioids to in reducing pain. Clinical studies are mainly focused on medicinal cannabis use in chronic pain management, for which the analgesic effect has been proven in many studies. This present review focuses on the potential application of medical cannabis for acute pain, exploring the physiopathology of the endocannabinoid system, preclinical studies, studies on healthy subjects and the few pioneering studies in the clinical setting.

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INTRODUCTION

The definition "medicinal cannabis" identifies the prescription-based cannabis and cannabinoids recognized to treat, modulate or even extinguish signs and symptoms of disease[1].

At the moment its prescription is limited to certain rare clusters of patients such as forms of drug-resistant adult or pediatric epilepsy, third-line antiemetic agents in chemotherapy-treated patients, and spasms in the context of multiple sclerosis (MS). There is some evidence medical cannabis can help certain types of pain, though this evidence is not yet strong enough to recommend it for pain relief[2]. Pain is "an unpleasant sensory and emotional experience associated with, or resembling that associated with actual or potential tissue damage", the International Association for the Study of Pain in the last revision of the pain definition pointed out the concept of the protective role of acute pain in contrast with the maladaptive nature of chronic pain[3]. Acute pain serves as a warning sign of disease or threat to the body; It happens suddenly, starts sharp or intense, is caused by injury, surgery, illness, trauma, or painful medical procedures and generally lasts from a few minutes to less than six months. Acute pain usually disappears whenever the underlying cause is treated or healed[4].

The burden of acute pain worldwide is remarkable and covers 4 out of 10 patients admitted yearly to the Emergency Department (ED)[5]. Their improper/inefficient therapeutic management is capable to cause several hospital new admission and even consolidate a life-long chronic pain status[6]. Their evolution toward pain chronicity is also testified by the opioid use/misuse of these patients in the previous three 3 months, quantified in a recent report regarding 1 out of 5 patients[7].

Remarkably, patients with chronic pain treated with opioids have a higher risk of opioid overdose[8], in particular, the United States population with opioid use disorder was quantified in 1.6 million last year[9]. Even more dramatic are the 30 years of survey data that found 564 thousand patients perished from opioid (medical and illicit) fatal overdoses[10]. In this respect, a multimodal approach to acute pain management with the use of non-opioids medication should be mandatory. This review aims to evaluate medicinal cannabis products for the treatment of acute pain from the physio-pathological rationale to the more recent clinical practice.

THE PHYSIOPATHOLOGICAL RATIONALE FOR THE USE OF CANNABINOIDS IN ACUTE PAIN

The endocannabinoid system (ECS) plays a vital role in managing pain by adjusting the activity of various neurotransmitters and receptors that are involved in the sensation of pain. The ECS is composed of endocannabinoids (such as anandamide and 2-arachidonoylglycerol), their receptors (CB1 and CB2), and numerous enzymes that are responsible for both the synthesis and the degradation of endocannabinoids.

The ECS can modulate multiple pathways involved in the perception of pain. Two primary endocannabinoid receptors, CB1 and CB2, have been identified as being involved in the pathophysiology of acute pain.

The CB1 receptor, which belongs to the family of receptors that are coupled to G-proteins, transmits signals through the release of Gβγ proteins and the decrease of cAMP orchestrated by Gαi in the regulation of neurotransmission, neurodevelopment, and synaptic plasticity[11].

Once activated and dissociated these proteins are modulated by a kinase through a series of interactions mediated by β-arrestins[12].

CB1 receptors are expressed in higher concentration in the central nervous system (CNS), and modulate the release of neurotransmitters, acting as gatekeepers at the pre-synaptic terminals of GABAergic and glutamatergic neurons[13].

Furthermore, these receptors are dispersed throughout the cell, including areas such as lipid rafts, endosomes, and mitochondria. They can also be found in cells such as astrocytes and oligodendrocytes, as well as in various non-neural tissues such as the heart, lungs, and bones. These peripheral receptors are involved in the control and modulation of nociceptive sensitivity, peristalsis, reproduction, energy and muscle metabolism[14].

CB1 receptors have a vital function in controlling the experience of pain by managing the conversion of harmful peripherical stimuli into pain signals at the spinal cord level. They are capable of both diminishing or intensifying the transmission of pain signals to the CNS.

CB1 receptors located in higher brain regions (periaqueductal gray matter and rostral ventromedial medulla) are linked to the perception of pain, initiating the descending inhibition of pain signals or hindering the descending facilitation to the nociceptive circuit of the spinal cord[15].

Furthermore, CB1 is highly expressed in the brain regions related to the emotional and affective aspects of pain in humans, like the frontal-limbic circuits. It's mainly located on the presynaptic terminals of neurons and concentrated in the perisynaptic zone where it can regulate the neurotransmitter release. This mechanism aligns with CB1's role in retrograde neurotransmission, and it's becoming an increasingly important area of research in pain management[16].

CB1 receptors are coupled negatively, by Gi/o proteins, to the enzyme adenylate cyclase.

When activated, the CB1 receptors inhibit the calcium channels and activate the potassium channels, which decreases neurotransmitter release[17].

However, this is a synthetic description of the role of CB1 receptors. *In vivo*, the overall effect of CB1 receptors activation differs within the neural network according to the areas of the brain and the type of presynaptic cell involved in the pain pathway.

CB1 receptors have been found even in B immunity cells and the CNS's glial cells. In the CNS astroglial CB1 receptors play a crucial role in regulating behaviour and plasticity[18].

The CB2 receptor is mostly linked to Gi/o proteins and is involved in signalling pathways that regulate intracellular calcium concentration. Unlike CB1 receptors, the CB2 receptor is not commonly found in the CNS, but it is highly expressed in immune system cells both peripheral (macrophages, lymphocytes, and mast cells).

The activation of CB2 receptors reduces especially inflammatory pain states by anti-inflammatory effect and the reduction of hyperalgesia[17].

There is an ongoing debate about the presence of active CB2 receptors in the CNS, especially in astrocytes and microglia, but the evidence remains inconclusive. Figure 1 offers a synthesis of the distribution of the ECS receptors in the CNS, in the spinal cord and the peripheral nervous system. The receptors expressed in the CNS (mostly CB1) are involved in the modulation of the descending control of nociception and in the emotive perception of pain.

The receptors located in the dorsal horns of the spinal cord have a role in pain ascendent sensitive nociception pathways. The receptors expressed in the peripheral nervous system contribute to the excitability of nervous termination and modulate the immunity system through the immunity cells sensible to endocannabinoids.

THE USE OF CANNABINOIDS FOR ACUTE PAIN IN PRECLINICAL STUDIES

For half a century cannabinoids have been evaluated for their analgesic effect in animal models[19]. In 1973 Sofia *et al*[19] evaluated the analgesic properties of tetrahydrocannabinol (THC) in mice and rats using four different models of experimentally induced pain (Acetic acid-induced abdominal constriction, Haffner's tail pinch, Hot plane test, Randall-Selitto test); THC, in all the models studied, showed greater analgesic activity than aspirin. In 2002 Conti *et al*[20] evaluated the anti-inflammatory action of the synthetic cannabinoid nabilone in a model of acute inflammation (AI) in male Wistar rats: The anti-inflammatory activity and thermal hyperalgesia were explored respectively by measuring oedema and paw withdrawal latencies, using the radiant heat method, after the injection of 0.1 mL carrageenan into the right paw. Paw oedema and thermal hyperalgesia were modulated by nabilone in a dose-dependent manner. Likewise, the CB2 antagonist (SR 144528) pre-administered neutralized the nabilone effect. The authors concluded the effect of nabilone is mediated by an uncharacterized CB_2-like cannabinoid receptor[20]. More recently, Rock *et al*[21] evaluated the effect of cannabidiolic acid (CBDA) and Δ 9-THC in a similar rodent model of carrageenan-induced AI in the rat hind paw. Contrary to the previous study the authors used a CB_1 cannabinoid receptor antagonist (SR141716) to block the anti-hyperalgesia effects of THC while CBDA's effects were blocked by a competitive and selective vanilloid receptor 1 (AMG9810). Consistent with previous literature (Conti *et al*[20]), Rock *et al*[21] demonstrated that THC produced dose-dependent anti-hyperalgesia and anti-inflammatory effects and they are further synergic use of CBDA. CBDA contrasts hyperalgesia *via* vanilloid receptor 1, as testified by its selective inhibition with AMG9810, conversely THC acts on central and peripheral CB1 receptors, as testified by its selective inhibitor SR141716[21].

Cannabinoids improve pain in pre-clinical models of traumatic spinal cord injury (SCI)[22]. SCI causes Neuropathic pain (NP) with different mechanisms, one of which involves oxidative stress. Baron-Flores *et al*[23] established the biomechanism by which CBD may exert a powerful analgesic effect in acute NP: In fact, CBD empowers the natural anti-oxidative cellular defence such as glutathione concentration in a dose-dependent manner. Thus, cells experienced decreased lipid peroxidation (Table 1).

Table 1 Synthesis of a selection of the preclinical studies published on acute pain treatment in preclinical studies

Ref.	Animal	Cannabinoid	Model	Outcome(s)	Assessment
Conti *et al*[20], 2002	Wistar rats	Nabilone	Cg-Induced AI	PWL	1, 2, 3, 10 h
Rock *et al*[21], 2018	Sprague-Dawley rats	CBDA, THC	Cg-Induced AI	PWL	0.5, 1, 3, 6 h
Baron-Flores *et al*[23], 2022	Wistar rats	CBD	Traumatic SCI	LP & GSH	15 d

Cg: Carrageenan; AI: Acute inflammation; PWL: Paw withdrawal latency; CBD: Cannabidiol; CBDA: Cannabidiolic acid; THC: Δ 9-tetrahydrocannabinol; SCI: Spinal cord injury; LP: Lipid peroxidation; GSH: Glutathione concentration.

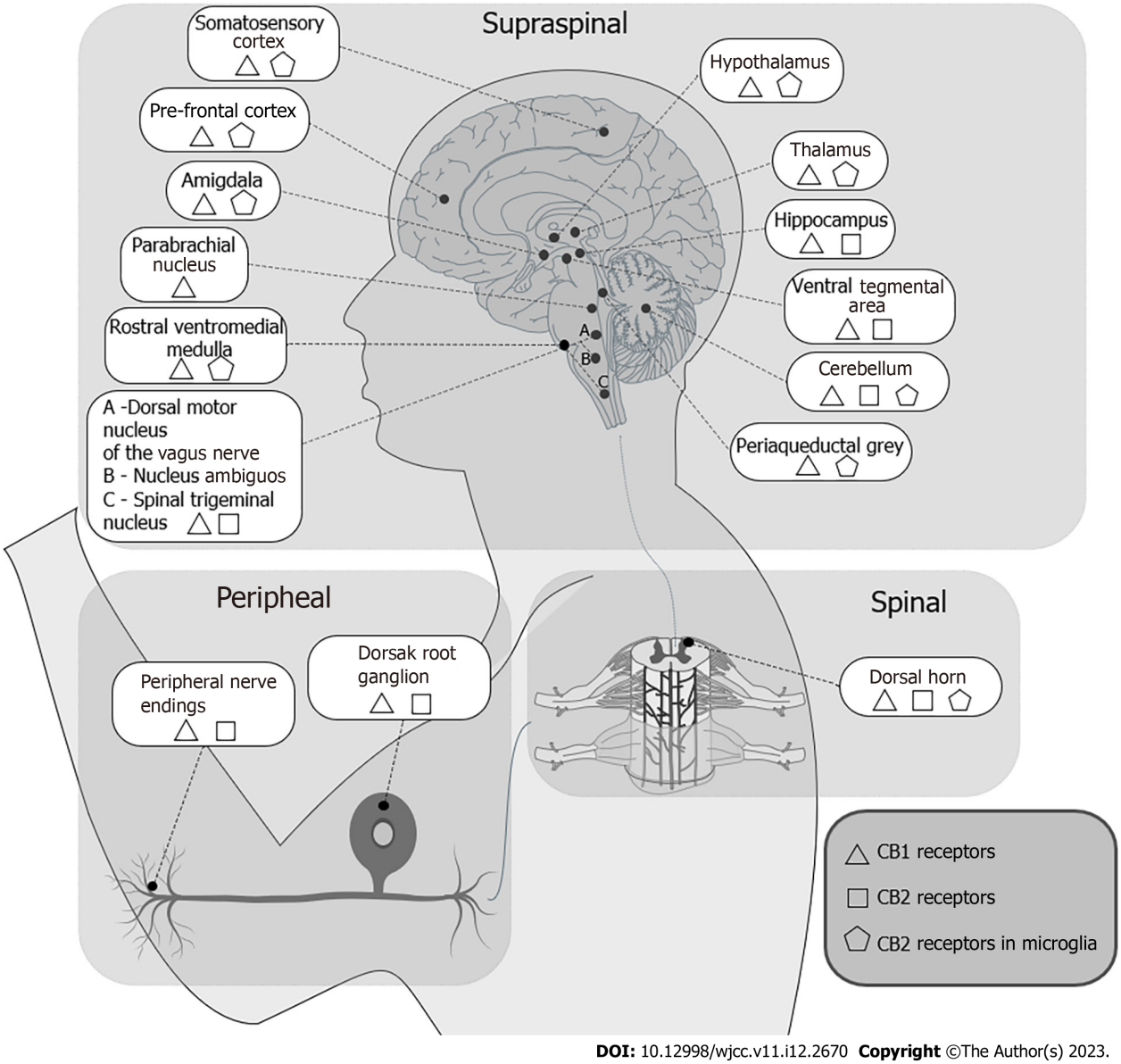

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Figure 1 Distribution of the endocannabinoid system receptors in the CNS. CB: Cannabinoid; CNS: Central nervous system.

THE USE OF CANNABINOIDS FOR ACUTE PAIN IN HEALTHY SUBJECTS

Unlike preclinical studies that showed the efficacy of cannabinoids in acute pain, the results on healthy volunteers (HVs) do not appear to confirm the potential analgesic effect of medicinal cannabis products for the treatment of acute pain. Kraft *et al*[24] demonstrated that THC has no analgesic and antihyperalgesic effects in two human models of physically-induce and chemically induced pain.

Table 2 Synthesis of a selection of studies published on acute pain treatment in healthy subjects

Ref.	Number	Cannabinoid (dose)	Model(s)	Outcome(s)	Assessment
Kraft *et al*[24], 2008	18	THC 20 (mg PO)	Sunburn; Capsaicin ID	Heat and electrical thresholds	1, 2, 2.5, 3, 4, 5, 6, 7, 8 h
Schindler *et al*[25], 2020	11	THC (0.01 mg/Kg or 0.03 mg/Kg IV)	Capsaicin ID	VAS; HA; Heat and electrical thresholds	0.3; 2 h
Schneider *et al*[26], 2022	20	CBD (800-mg PO)	IES	NRS; vFF; DCS	0, 1, 2.1 h
Dieterle *et al*[27], 2022	24	CBD (1600-mg PO)	IES	NRS; HA; AA	1 h

THC: Δ 9-tetrahydrocannabinol; PO: *Per os*; ID: Intradermally; IV: intravenous; VAS: Visual analogue scale; HA: Hyperalgesia Area (cmq); CBD: Cannabidiol; IES: Intradermal electrical stimulation; NRS: Numeric rating scale; vFF: von Frey filament; DCS: Dry cotton swab; AA: Allodynia area (cmq).

Table 3 Synthesis of a selection of studies published on acute pain treatment

Ref.	Patient number	Cannabinoid (dose)	Participants	Conclusion
Beaulieu[28], 2006	41	Nabilone (1 or 2 mg PO)	Major surgery	Pain higher in 2 mg group
Ostenfeld *et al*[29], 2011	123	GW842166 100 and 800 mg	Extractive surgery	Not superiority to placebo
Bebee *et al*[30], 2021	100	CBD (400 mg)	LBP	Not superiority to placebo

PO: *Per os*; CBD: Cannabidiol; LBP: Low back pain.

In line with the previous study, also Schindler *et* colleagues that did not find any THC analgesic and antihyperalgesic effect of THC administered intravenously[25].

In a randomized, placebo-controlled, double-blinded, crossover study (CANAB I), Schneider *et al*[26] colleagues did not find any effect of oral CBD on hyperalgesia and allodynia electrically induced, results conformed in the CANAB II trial doubling CBD dose used in CANAB I trial[27] (Table 2).

THE USE OF CANNABINOIDS IN CLINICAL STUDIES

Beaulieu *et al*[28] colleagues performed a double-blind, randomized, placebo-controlled, parallel-group pilot trial enrolling forty-one patients undergoing major surgery, mainly gynecologic (46%) or orthopaedic (44%). Patients were randomly assigned to four distinct groups (nabilone 1 mg/die *Vs* nabilone 2 mg/die *Vs* ketoprofen 50 mg/die Vs placebo). Despite no differences were detected in terms of 24-h morphine request, interestingly the pain control was statistically significant only in the nabilone 2 mg/die.

Conversely, Ostenfeld *et al*[29] did not find a statistically significant analgesic effect of a single dose of GW842166 (non-cannabinoid CB2 agonist) in patients that underwent dental surgery (third molar surgery). Furthermore, this randomized controlled trial (RCT) only re-affirm the high effectivity of ibuprofen Versus placebo[29]. Furthermore, Bebee *et al*[30] colleagues in their RCT focused on low back pain in patients admitted to ED and evaluated the potential efficacy of 400 mg oral CBD as a combination therapy with the department's standard of care. Pain assessment was performed with a verbal scale rating from 0 to 10 their residual pain after two hours from the therapies. This RCT failed to find a clinically relevant decrease in pain comparing patients that underwent CBD+pain killer *vs* pain killer alone (Table 3).

CONCLUSION

This is the first review of the literature exploring cannabis products use from preclinical to clinical studies. Mice models have highlighted the analgesic properties of cannabinoids[20,21,23] capable to interrupt pain through partially unknown mechanisms targeting the ECS.

In light of the fact that all studies conducted on HVs failed to show the significant efficacy of medicinal cannabis products for acute pain management[24-27], it seems paradoxical that studies have been conducted on patients[28-30]. To date, the use of cannabis products in the treatment of acute pain is clearly disadvantageous compared to available therapeutic alternatives.

Methodologically phase II clinical trials should follow phase I studies when these latest show efficacies. In the case of studies published on the use of medicinal cannabis products for acute pain induced in HVs, no one showed superiority to a placebo so there is no support to conduct phase II clinical trials. Acute pain management in this Era of the "Opioid Crisis" should not deprive itself of a potential therapeutic option[31]. The knowledge of this review should be taken into consideration by researchers before proceeding further with phase II clinical trials, the researchers should take a "step back" to identify effective models for the treatment of acute pain in phase I studies.

FOOTNOTES

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MINIREVIEWS

Role of in vitamin D in irritable bowel syndrome

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Abstract

Irritable bowel syndrome (IBS) is a common chronic functional gastrointestinal disorder affecting 10%-22% of adults. Its development is closely related to the gut microbiota, and the inflammatory and immune responses triggered by the gut microbiota can lead to IBS. Vitamin D (VD) effectively treats IBS with fewer side effects by improving gut microbiota, immune regulation, and anti-inflammatory effects. In the future, it is necessary to carry out epidemiological studies on the relationship between VD and IBS, clinical studies on the efficacy of supplementing VD to improve IBS, and animal studies on the mechanism of VD improving IBS. Therefore, this paper discussed the relationship between VD and IBS.

Key Words: Irritable bowel syndrome; Vitamin D; Gut microbiota; Immune response; Mental status

Core Tip: Irritable bowel syndrome (IBS) is a common chronic functional gastrointestinal disorder affecting 10%-22% of adults. Its development is related to the gut microbiota, and the inflammatory and immune responses triggered by the gut microbiota can lead to IBS. Vitamin D (VD) is effective in treating IBS by improving gut microbiota, immune regulation, and anti-inflammatory effects. It is necessary to carry out epidemiological studies on the relationship between VD and IBS, clinical studies on the efficacy of supplementing VD to improve IBS, and animal studies on the mechanism of VD improving IBS. This paper discussed the relationship between VD and IBS.

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INTRODUCTION

Irritable bowel syndrome (IBS) is a common chronic functional gastrointestinal disorder characterized by abdominal pain, bloating, urinary urgency, voiding incontinence, and altered bowel habits associated with structural and biochemical abnormalities[1] and affects 10%-22% of the adult population[2]. According to Rome IV criteria, IBS is divided into four types: IBS with constipation, IBS with diarrhea, IBS with mixed constipation and diarrhea, and IBS unclassified[3].

In the census statistics of Albanian adult samples, the prevalence of IBS in the study population was 8.6%. There was no sex difference, age differences, and regional differences. IBS with constipation is a common type[4]. However, in Western countries, the ratio of males to females with IBS is 2:1[5]. The disease is mild for most people but can be severe and even life-threatening in 1 in 20[6]. Although the etiology of IBS is unknown, current research suggests that it is related to host and environmental factors. Host factors include the gut-brain axis, serotonin pathway, and gut microbiota, and environmental factors include psychological stress, infection, antibiotic use, diet, and eating habits[7].

Vitamin D (VD) is a fat-soluble steroid that is a key regulator of calcium and phosphorus metabolism [8]. Two forms of VD play a major role in humans, D2 and D3, which are ergocalciferol and cholecalciferol, respectively, and they are similar in function. However, studies in recent years have shown that biochemical indicators show that VD2 seems to be cleared from the tissue faster than VD3. At the same dose, the efficacy of D2 is one-third to one-half of D3. When supplementing VD, we generally tend to choose VD3[9]. Studies have found a strong correlation between VD and type 1 diabetes mellitus[10,11] and obesity[12]. The main source of VD is sunlight, and very little is obtained from food. 7-dehydrocholesterol is converted in the skin to VD3 precursor upon exposure to ultraviolet B (280-310 nm). It isomerizes to VD3, which binds to vitamin D-binding protein. In the liver, VD3 attaches to vitamin D-binding protein and is hydroxylated by 25-hydroxylase to 25-hydroxyvitamin D3 [25(OH)D3], the main circulating form of VD. Later 25(OH)D is hydroxylated in the kidney and eventually converted to 1,25-dihydroxy VD3 [1,25-(OH)2D3][13,14]. Therefore, the main cause of VD deficiency is insufficient sun exposure[15], such as excessive indoor activity time and sun protection habits[16]. The Institute of Medicine defines VD deficiency as 25(OH)D below 20 ng/mL and VD deficiency as 25(OH)D below 21-29 ng/mL[17]. The literature shows that VD can regulate calcium and phosphorus metabolism[18], inhibit inflammation[19], regulate immune response[13], affect the intestinal barrier[20], and play an important role in the pathogenesis of diabetes[11], obesity, and IBS. This article provided an overview of research progress on the link between VD supplementation and the pathogenesis of IBS (Figure 1).

PATHOGENIC RELATIONSHIP BETWEEN VD LEVELS AND IBS

VD deficiency is closely related to IBS occurrence, development, and complications. Experiments by Nwosu *et al*[21], Cho *et al*[22], and Khayyat and Attar[23] showed that children and adults with IBS had insufficient or inadequate VD levels. Observational studies have also demonstrated that the prevalence of VD deficiency in IBS patients is as high as 82%[24]. Between April 2015 and April 2017, a prospective randomized controlled trial evaluated 112 VD-deficient adolescents aged 14 years to 18 years with IBS. Compared with the placebo, the clinical status of adolescents with IBS who took VD was significantly improved. This study suggests that VD supplementation effectively treats adolescent IBS[25].

Furthermore, a systematic review and meta-analysis assessed the efficacy of VD supplementation in improving IBS. Four randomized controlled trials found that VD supplementation improved symptoms and quality of life in people with IBS[26]. Nevertheless, Williams *et al*[27] conducted a randomized, double-blind, placebo-controlled study that demonstrated that there were no improvements in the IBS symptom severity and quality of life between the trial (VD supplementation) and placebo groups. However, the current research has not confirmed the clear pathogenesis of IBS. Many experimental results only prove a link between VD and IBS, but there is no definite explanation. Most of the guesses shown in the literature tend to be intestinal flora adjustment, inflammation inhibition, and mental relief in IBS patients.

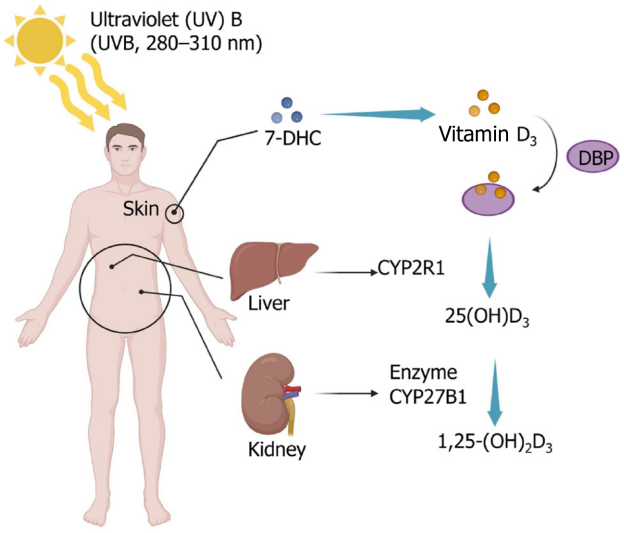

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Figure 1 Vitamin D synthesis through sunlight. 1,25-(OH)2D3: 1,25-hydroxyvitamin D3; 25(OH)D3: 25-hydroxyvitamin D3; 7-DHC: 7-dehydrocholesterol; DBP: Vitamin D-binding protein.

VD IMPROVES IBS BY MODULATING GUT MICROBES

Gut microbial diversity maintains intestinal homeostasis, among which Firmicutes, Bacteroidetes, Proteobacteria, and Actinobacteria are the most important phyla. Disturbances in this microbial balance can lead to many diseases, including IBS[28]. However, VD supplementation may treat IBS by improving the type and abundance of gut microbes. A comprehensive systematic review of the gut microbiota and IBS revealed the presence of Enterobacteriaceae (phylum Proteobacteria), family Lactobacillaceae, and genus *Bacteroides* (phylum Bacteroidetes) in patients with IBS compared with normal individuals. In addition, IBS patients had potentially harmful microbiota, such as the family Lactobacillaceae and genus *Bacteroides*, which caused bloating and diarrhea[29]. VD is an essential hormone to maintain gut barrier function, along with many other roles in the gut[30]. Intervention studies in IBD have shown that VD alters the gut by increasing the relative abundance of beneficial bacteria (*e.g.*, *Ruminococcus*, *Akkermansia*, *Faecalibacterium*, *Lactococcus*, *Coprococcus*, *Bifidobacteria*) and decreasing the Firmicutes microbial composition[28].

IMMUNOMODULATORY EFFECT OF VD IN IBS

VD may play an immunomodulatory role by improving the gut microbiota. The intestinal epithelial barrier (IEB) is the primary interface between the *in vitro* and the *in vivo* environments[31]. In addition to absorbing water and nutrients, it is also responsible for defending against harmful substances. The IEB secures mucus, and substances are exchanged through intercellular and paracellular pathways. Meanwhile, in addition to secreting short-chain aliphatic hydrocarbons, such as acetate, propionate, and butyrate, specific gut microbes can also regulate the permeability of IEB[32]. Dysbiosis of gut microbes leads to a decrease in the abundance of short-chain aliphatic hydrocarbon-producing *Akkermansia*, *Phaecococcus*, and *Coprococcus* and an increase in the quantity of lipopolysaccharide-producing Enterobacteriaceae so that proinflammatory responses outweigh anti-inflammatory responses and cause intestinal inflammation[33]. Furthermore, *Faecalibacterium prausnitzii* increases butyrate production, which stimulates regulatory T (Treg) cell maturation, and better balances intestinal inflammation[33].

As an immunomodulator, VD can improve the gut microbiota[34], increase the production of antimicrobial peptides, improve the intestinal barrier, regulate the integrity of intestinal epithelial cells, inhibit helper T (Th) 1/Th17 cells, relieve Treg cells, and benefit the adaptive immune system[35]. The VD receptor (VDR) is a ligand-dependent transcription factor that could recognize 1,25-(OH)2D3[36]. VD requires the mediation of VDR to exert its biological actions[37]. The VD/VDR signaling pathway plays an inhibitory role in infection by activating the transcription of genes related to innate immunity[38], such as inducing and regulating autophagy[39]. Therefore, the VD/VDR axis may be an important inhibitor of inflammatory response. Under the influence of VD, macrophages can increase the secretion of interleukin (IL)-10 while reducing the secretion of tumor necrosis factor-α[40]. At the same time, studies have shown that the expansion of ILC3 requires VD, and the IL-22 secreted by ILC3 regulates epithelial tight junction proteins to enhance gut epithelial integrity and regulates the intestinal microbiota[41] (Figure 2).

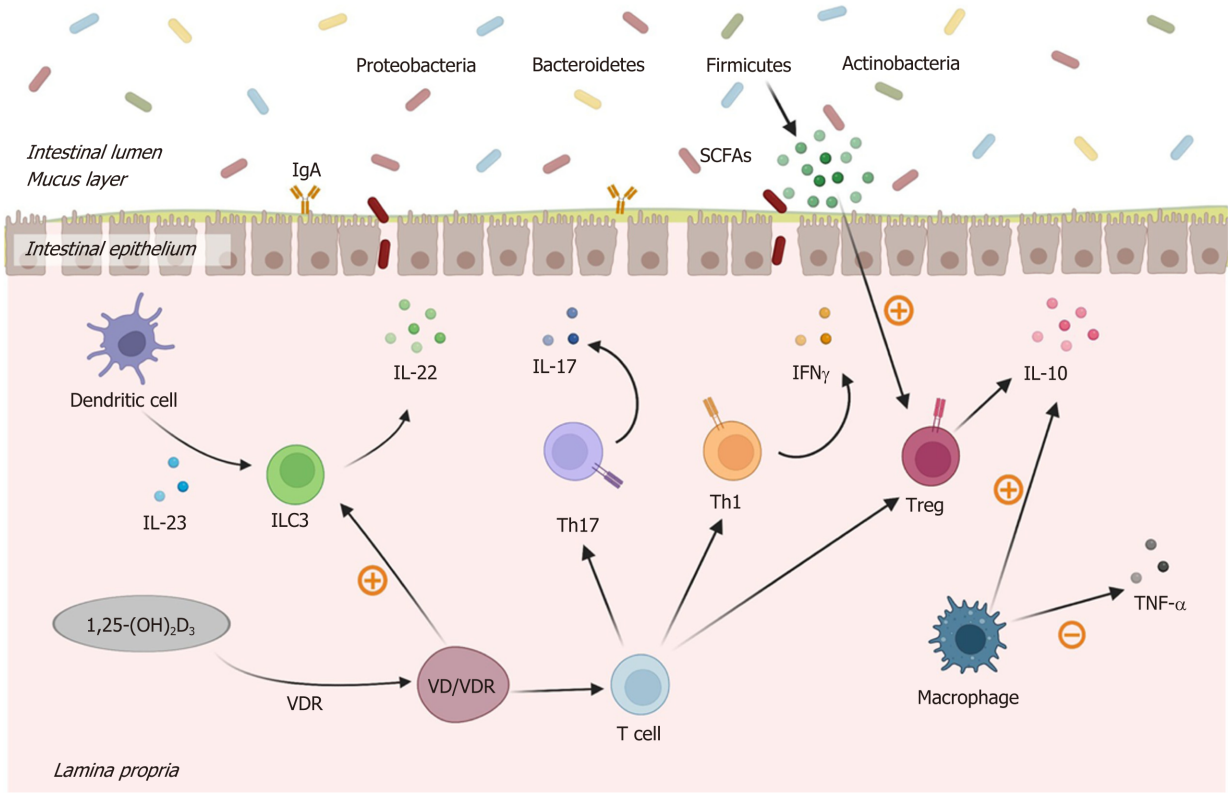

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Figure 2 Anti-inflammatory effects of 1,25-dihydroxyvitamin D3 in the gut of irritable bowel syndrome. 1,25-(OH)2D3: 1,25-dihydroxyvitamin D3; IFN-γ: Interferon-gamma; IgA: Immunoglobulin A; IL: Interleukin; SCFA: Short-chain fatty acid; Th: T helper cell; TNF-α: Tumor necrosis factor-alpha; Treg: Regulatory T cell; VDR: Vitamin D receptor; VD: Vitamin D.

VD IMPROVES MENTAL STATUS IN IBS PATIENTS

Growing evidence suggests that the underlying pathophysiological mechanism of IBS is a disruption of brain-gut interactions. Up to 94% of IBS patients have also been diagnosed with psychiatric disorders [42], of which anxiety and depression are the most common[43]. Psychological stress alters gut motility and permeability, visceral sensitivity, immune response, and gut microbiota composition, leading to IBS [44]. Although research on VD and psychiatric disorders has not been well defined, there is evidence that adequate levels of VD are required for normal brain neuropsychiatric function and that VD regulated through brain cell differentiation, axonal growth, and calcium signaling, as well as neurotrophic factors, affect the brain[45]. In addition, VD can induce the expression of the tryptophan synthesis gene tryptophan hydroxylase 2 while inhibiting the expression of tryptophan hydroxylase 1, thereby preventing depression by maintaining normal serotonin levels[46]. Therefore, VD positively affects anxiety and depression in IBS patients.

FUTURE OUTLOOK FOR VD SUPPLEMENTATION

Compared with the side effects of eating disorders and other drugs, VD supplements are significantly more effective, with only mild side effects. Long-term excessive VD intake is relatively rare. If the amount of VD supplementation is well-controlled, side effects can be effectively avoided[24]. It is also more convenient and efficient to get VD outdoors in sunlight. More research is needed to determine whether oral VD intake increases indoor exposure to ultraviolet B (280–310 nm) in people who work indoors for long periods.

CONCLUSION

IBS is a chronic gastrointestinal functional disorder whose etiology may be primarily relevant to gut microbiota and immune regulation. At the same time, VD can increase the number of beneficial bacteria in the gut, inhibit the inflammatory response, inhibit Th1/Th17 cells, stimulate Treg cells, and relieve the mental state of patients. However, the experiment of VD on IBS in the community population is

more complicated, which increases the difficulty of the investigation and reduces the accuracy of the results. Hence, the treatment of VD on IBS is still controversial. In the future, it is necessary to carry out epidemiological studies on the relationship between VD and IBS, clinical studies on the efficacy of supplementing VD to improve IBS, and animal studies on the mechanism of VD improving IBS.

FOOTNOTES

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Analysis of oxidative stress and antioxidative potential in premature ovarian insufficiency

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Abstract

BACKGROUND

Premature ovarian insufficiency (POI) is characterized by an early decline in ovarian function, inducing secondary amenorrhea. While the cause of POI has not yet been identified, the function of mitochondria in the ovaries and the cytotoxicity associated with reactive oxygen species (ROS) have been implicated in follicle pool depletion and a decline in follicle quality. Recently developed tests have enabled easy measurement of diacron-reactive oxygen metabolites (d-ROMs) and biological antioxidant potential (BAP). The combination of these two tests is used to comprehensively assess oxidative stress in the blood.

AIM

To comprehensively assess the oxidative stress of d-ROMs and BAP in POI.

METHODS

Participants were classified into two groups: A POI group of 11 women aged < 40 years examined between January 2021 and June 2022 with a history of secondary amenorrhea for at least 4 mo in our hospital and an FSH value of ≥ 40 mIU/mL; and a control group of healthy women of the same age with normal ovarian function in our hospital. Plasma d-ROMs and BAP were measured in both these groups underwent. Differences between groups were assessed using the *t*-test.

RESULTS

The mean age and mean body mass index (BMI) were 35.8 ± 3.0 years and 20.1 ± 1.9 kg/m^2 in the control group and 35.8 ± 2.7 years and 19.4 ± 2.5 kg/m^2 in the POI group, respectively. The mean gravidity and parity in control and POI groups were 0.6 ± 0.7 and 0.4 ± 0.5 and 0.6 ± 0.9 and 0.3 ± 0.5, respectively. The two groups did not differ significantly in terms of mean age, BMI, gravidity, or parity. The d-ROMs level was significantly higher in the POI group than in the control group (478.2 ± 58.7 *vs* 341.1 ± 35.1 U.CARR; $P < 0.001$); however, the BAP level did not significantly differ between the two groups (2078.5 ± 157.4 *vs* 2029.0 ± 186.4

μmol/L). The oxidase stress index (d-ROMs/BAP × 100) was significantly higher in the POI group than in the control group (23.7 ± 3.3 *vs* 16.5 ± 2.1; $P < 0.001$).

CONCLUSION

Oxidative stress was significantly greater in the POI group than in the control group, suggesting oxidative stress as a factor that can serve as a POI biomarker.

Key Words: Premature ovarian insufficiency; Reactive oxygen species; Oxidative stress; Ovary; Antioxidant

Core Tip: We hypothesized that oxidative stress, suggested to be a factor in premature ovarian insufficiency (POI) and a potential POI biomarker, is likely a useful target for the treatment and early intervention for various conditions, including early POI diagnosis and infertility treatment. In this retrospective study, we discovered that oxidative stress was significantly higher in patients with POI than in healthy controls, suggesting the use of this measurement as a biomarker of POI.

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INTRODUCTION

Premature ovarian insufficiency (POI) is a syndrome in which women aged < 40 years experience amenorrhea involving persistent hypergonadotropic hypoestrogenemia for at least 4 mo[1,2]. Primary ovarian insufficiency naturally develops in 1 in 100 women[3], with an incidence of approximately 1% at ages 30-39 years, 0.1% at ages 20-29 years, and 0.01% at < 20 years[3,4]. However, with many women now marrying and conceiving later in life, those who had previously achieved pregnancy prior to POI onset may now require fertility treatment, although other recent studies have indicated that the incidence of POI itself may be on the rise[5-8].

Early ovarian depletion is thought to be caused by various factors, such as chromosomal abnormalities, genetic mutations, polyendocrine syndrome (adrenal insufficiency, hypothyroidism), autoimmune abnormalities (chiefly rheumatoid arthritis and systemic lupus erythematosus), metabolic disease, and iatrogenic factors associated with pelvic surgery, anticancer agents, and pelvic radiotherapy; nonetheless, many factors influencing POI have not yet been sufficiently determined[9-17].

Regardless of the cause of POI, early follicular depletion and impaired follicular development cause a decrease in the number or complete disappearance of residual oocytes and follicles[11,12]. Generally, when the number of residual follicles in the ovaries falls below 1000, the primordial follicles cease to activate, thereby stopping the recruitment of developing follicles and preventing the remaining follicles from achieving ovulation. Consequently, granulosa cells, the primary source of estrogen production, disappear almost completely owing to the absence of developing follicles, thereby reducing estrogen levels in the blood. Consequently, the endometrium does not thicken, the absence of the corpus luteum following ovulation halts the secretion of progesterone, and withdrawal bleeding associated with regression of the corpus luteum does not occur, resulting in amenorrhea.

In summary, in POI, the loss of ovarian function leads to low estradiol levels, which can trigger the development of some mental disorders, such as climacteric symptoms, depression, anxiety, and cognitive disorders. Therefore, appropriate POI management is essential to improve the quality of life and prevent fractures caused by bone and circulatory diseases and decreased bone density[1,18-22].

A major problem associated with POI is extremely severe infertility. In POI, amenorrhea and anovulation associated with follicular pool depletion may result in major infertility[23]. Although only approximately 25% of patients with POI demonstrate decreased ovulation, the lifetime pregnancy rate among these patients with their own ova is only 5%-10%[11,12,23,24], causing intractable infertility in patients with POI. Currently, no reliable treatment is available for infertility caused by POI. The European Society of Human Reproduction and Embryology (ESHRE) Guidelines on POI state that other than oocyte donation, there are currently no medical interventions worth recommending[25,26]. This situation demands the determination of the cause of POI and early diagnosis and intervention.

Oxidative stress, which is defined as a breakdown in the balance between the generation of reactive oxygen species (ROS) in the body and the antioxidant mechanisms that counteract these ROS[27-29], has

been implicated in the pathogenesis of many diseases. ROS and free radicals are byproducts of oxygen-consuming energy metabolism reactions. These metabolites are unstable and highly reactive, and their excessive production results in the oxidation of proteins, lipids, nucleic acids, and other biopolymers, thereby increasing the risk of dysfunction. The body is equipped with a defense system (antioxidant potential) that uses antioxidant enzymes and antioxidants to remove and neutralize free radicals and ROS to avoid this type of damage. Oxidative stress occurs when the production of ROS and free radicals (degree of oxidation) surpasses the antioxidant potential and reportedly triggers senescence, cardiovascular disease, neurodegenerative disease, cancer, and other refractory diseases[30-33]. The function of mitochondria in the ovaries and cytotoxicity associated with ROS production by this mitochondrial function have been indicated as factors in follicular pool depletion and the decline in oocyte quality observed with age[34-36].

Active oxygen is a state in which oxygen has become chemically active and is generally very unstable, complicating its measurement method. Recently developed tests have enabled the easy measurement of diacron-reactive oxygen metabolites (d-ROMs) and biological antioxidant potential (BAP), and the combination of these two tests is now used to comprehensively assess oxidative stress in the blood[37-41]. The d-ROM test uses a color reaction to measure the levels of blood compounds, such as hydroperoxide, which is generated by ROS and free radicals[42]. In contrast, the BAP test assesses antioxidant potential by measuring the reducing ability of antioxidants, which involves donating electrons to ROS and free radicals, to terminate oxidation reactions[42].

In this study, we aimed to comprehensively assess oxidative stress in POI in terms of oxidative stress (d-ROMs) and antioxidant potential (BAP) in the blood to determine the cause of POI and investigate the potential of d-ROMs and BAP as biomarkers of POI.

MATERIALS AND METHODS

This study was approved by the Institutional Review Board of the International Health and Welfare Hospital (approval no. 21-Im-075, approved on 3/22/2022). The participants were patients aged < 40 years who were examined at the International Health and Welfare Hospital between January 2021 and June 2022. All participants received oral and written explanations of the study and provided verbal and written informed consent to participate. The following patients were excluded due to the consideration of the potential effects of different conditions on oxidative stress and antioxidant capacity: patients with obstetric and gynecological diseases, patients with severe menstruation-associated symptoms requiring analgesics, patients using other pharmaceuticals or supplements, and smokers.

Participants were divided into two groups: The POI group, comprising women aged < 40 years who had experienced secondary amenorrhea for at least 4 mo and demonstrated a follicle-stimulating hormone (FSH) level of ≥ 40 mIU/mL; and a control group, comprising healthy women aged < 40 years with normal ovarian function.

Blood was collected during the follicular phase (within 5 d of the initiation of the menstrual cycle). Ovarian function was measured in terms of FSH, anti-Müllerian hormone (AMH), and antral follicle count (AFC), measured using a diagnostic ultrasound device (Voluson S10 Expert; GE Healthcare Japan, Tokyo, Japan). Oxidative stress was assessed using a test for d-ROMs, a marker of oxidative stress, and a test for BAP, a marker of antioxidant potential. To comprehensively assess the oxidative stress defense system, the latent antioxidant potential was calculated using the oxidase stress index (OSI) (BAP/d-ROMs × 100).

Assessment of ovarian function

FSH levels were measured using a chemiluminescent immunoassay (CLIA) (CL AIA-PACK®FSH TEST; Tosoh Corporation, Tokyo, Japan), and AMH levels were measured using a chemiluminescent enzyme immunoassay (CLEIA) (Access AMH®; Beckman Coulter, Tokyo, Japan).

Measurement of oxidative stress and antioxidant potential

Oxidative stress in the blood during the follicular phase (d-ROM) and antioxidant potential (BAP) was measured using a free radical analysis device (FREE Carrio Duo; Diacron International, Grosetto, Italy). Measurements using this device have been reported to be valid and reproducible in previous studies[43-45].

d-ROMs were measured as follows: After blood samples were centrifuged, 20 μL of serum was collected and mixed into a pH 4.8 acidic buffer solution. A colorless aromatic amine solution (color reaction chromogen) was added, and the mixture was placed in a photometer in the free radical analysis device. After 5 min, the reduction in absorbance at 505 nm was measured, and the rate of change was used to calculate the concentration of hydroperoxide in the serum. D-ROMs are measured using color reactions to measure the blood levels of hydroperoxide (functional group: ROOH), which is generated from ROS and free radicals in the body, serving as a comprehensive assessment of the degree of oxidative stress in the body[37,46-48]. The unit of d-ROM is U.CARR, with 1 U.CARR equivalent to 0.08 mg/dL hydrogen peroxide. The reference values were as follows: normal, 200-300 U.CARR; borderline,

301-320 U.CARR; mild oxidative stress, 321-340 U.CARR; moderate oxidative stress, 341-400 U.CARR; severe oxidative stress, 401-500 U.CARR; and highly severe oxidative stress, ≥ 501 U.CARR[37,46-48].

BAP was measured as follows: A reagent containing a tricyanic acid derivative was mixed with a reagent containing iron ions, which was placed in the photometer in the free radical analysis device, and the absorbance at 505 nm was measured. Next, 10 μL of serum was added to this mixture, which was incubated at 37 °C for 5 min, after which absorbance was measured again. The concentration of oxidized iron ions was calculated based on the change in absorption over 5 min. The BAP represents the capacity of the serum solution to reduce iron from ferric (Fe^{3+}) to ferrous (Fe^{2+}) form (reduction reaction). The unit of BAP is μmol/L, with reference values as follows: Optimal value, > 2200 μmol/L; borderline, 2000-2200 μmol/L; slight reduction, 1800-2200 μmol/L; moderate reduction, 1600-1800 μmol/L; strong reduction, 1400-1600 μmol/L; very strong reduction, < 1400 μmol/L[49-51].

Statistical analysis

Differences between groups were assessed using the *t*-test. All results are shown as the mean ± SD, with $P < 0.05$ considered to indicate statistical significance. Statistical analyses were performed using JMP® version 14.2 (SAS Institute Japan Co. Ltd, Tokyo, Japan), and IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY, United States) was used for statistical processing.

RESULTS

Of the 23 participants, 1 was excluded for being a smoker. Finally, the POI group included 11 participants with secondary amenorrhea persisting for ≥ 4 mo and an FSH level ≥ 40 mIU/mL, whereas the control group comprised 11 participants with normal ovarian function (Figure 1).

Table 1 presents the participants' basic characteristics. The control group had a mean age of 35.8 ± 3.0 years and a mean body mass index (BMI) of 20.1 ± 1.9 kg/m^2, whereas the POI group had a mean age of 35.8 ± 2.7 years and a mean BMI of 19.4 ± 2.5 kg/m^2. The mean gravidity and parity in the control and POI groups were 0.6 ± 0.7 and 0.4 ± 0.5, respectively, *vs* 0.6 ± 0.9 and 0.3 ± 0.5, respectively. The two groups did not differ significantly in terms of mean age, BMI, gravidity, or parity (Table 1).

The mean AMH levels in the control and POI groups were 2.8 ± 1.4 ng/mL and 0.4 ± 0.3 ng/mL, respectively; the mean AMH level was significantly lower in the POI group than in the control group ($P < 0.001$) (Figure 2A). The mean AFC in the control and POI groups were 9.5 ± 2.4 and 0.7 ± 0.9, respectively, indicating that the mean AFC was significantly lower in the POI group ($P < 0.001$) than in the control group (Figure 2B).

The mean d-ROM values in the control and POI groups were 341.1 ± 35.1 U.CARR and 478.2 ± 58.7 U.CARR, respectively. The mean d-ROM value was significantly higher in the POI group than in the control group ($P < 0.001$) (Figure 2C). Conversely, the mean BAP values were 2078.5 ± 157.4 μmol/L and 2029.0 ± 186.4 μmol/L, respectively, in the control and POI groups, and there were no significant differences between the two groups ($P = 0.28$) (Figure 2D). The mean OSI (d-ROMs/BAP× 100) in the control and POI groups was 16.5 ± 2.1 and 23.7 ± 3.3, respectively, indicating a significantly higher OSI in the POI group than in the control group ($P < 0.001$) (Figure 2E).

DISCUSSION

POI is diagnosed as ovarian amenorrhea in women aged < 40 years. In patients with POI, normal ovarian function is lost, and a decline in ovarian function leads to a hyperestradiolic state, which is likely to result in infertility, menopausal symptoms, reduced bone density and associated fractures, cardiovascular disease, and mental disorders (depression, anxiety, and cognitive impairment); thus, proper management of this condition is essential to maintain quality of life. Although genetic factors, iatrogenesis, autoimmunity, metabolism, infection, and environmental factors have been proposed as causes of POI, most cases are idiopathic, and a clear cause has not yet been identified[11,12].

The ovaries are believed to decline in function earlier than other organs. As women age, the follicular pool and quality of oocytes decline, resulting in infertility[52,53]. These processes are thought to involve the activation of apoptotic pathways[54,55], which is believed to be triggered by the dysfunction of mitochondria in oocytes and the resulting ROS cytotoxicity[34-36].

Oxidative stress is defined as the difference between the oxidative damage potential of ROS generated in the body and the antioxidant potential of the antioxidant systems in the body[27-29]. Most ROS are produced in the mitochondria; these reactive molecules damage the mitochondria themselves, along with lipids, proteins, and DNA, which is considered to result in senescence at the cellular level, further triggering arteriosclerosis, diabetes, malignant disease, and various other diseases[30-33].

The membrane potential of mitochondria in oocytes harvested from older women, which demonstrates follicular pool depletion and diminished oocyte quality, has been found to be significantly lower than the mitochondrial membrane potential of oocytes in younger women[56]. Mitochondria

Table 1 Characteristics of the study participants

	Control group (*n* = 11)	POI group (*n* = 11)	*P* value
Age (yr)	35.8 ± 3.0	35.8 ± 2.7	0.50
BMI (kg/m^2)	20.1 ± 1.9	19.4 ± 2.5	0.24
Gravidity (times)	0.6 ± 0.7	0.6 ± 0.9	0.50
Parity (times)	0.4 ± 0.5	0.3 ± 0.5	0.36

Values are expressed as means, with the error bar representing the standard deviation. There were no significant differences between the two groups. POI: Premature ovarian insufficiency; BMI: Body mass index.

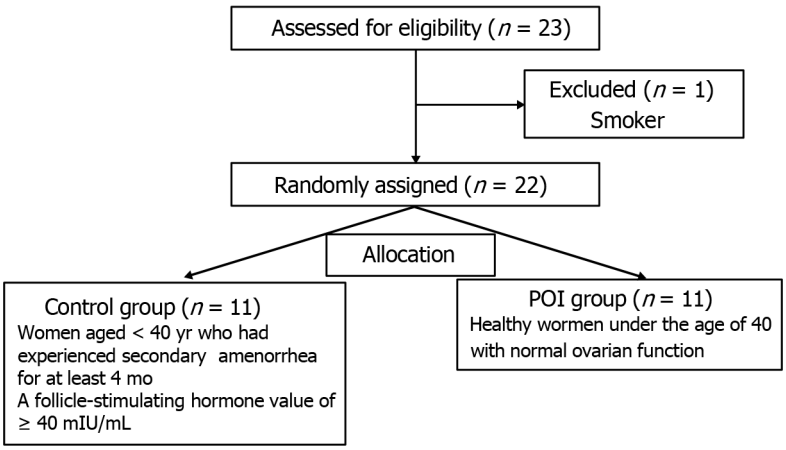

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Figure 1 Participant distribution in this study. POI: Premature ovarian insufficiency.

contain mtDNA, double-stranded circular DNA comprising a unique genome; oocytes retrieved from older women reportedly have greater percentages of mtDNA deletion and point mutations than oocytes from younger women[57,58]. In a study in which microarrays were used to examine differences in gene expression in oocytes collected from aged and younger mice, the oocytes of old mice demonstrated reduced expression of genes involved in mitochondrial function, inhibition of oxidative stress, and stabilization of DNA and chromosomes[59]. A similar study conducted on human oocytes also demonstrated reduced expression of genes in the same categories[60]. These studies have all suggested the importance of mitochondrial dysfunction in ovary degradation. Mitochondria are cellular organelles that metabolize energy and supply intracellular ATP *via* oxidative phosphorylation. Mitochondrial dysfunction is known to cause various diseases[61,62]; although ROS are generated during oxidative phosphorylation, they are quickly eliminated and regulated to prevent exposure to excessive oxidative stress. However, the molecules and enzymes associated with the ROS elimination system decline in number and function as oocytes age[58,59,63].

In this study, we comprehensively assessed the levels of oxidative stress in the blood of patients with POI to determine the cause of POI and examine whether oxidative stress in the blood can serve as a biomarker of POI. The d-ROM levels, which indicate oxidative stress, were significantly higher in the POI group than in the control group. In contrast, BAP, which reflects antioxidant potential, did not differ significantly between the two groups, indicating that antioxidant capacity did not decline. However, OSI, similar to d-ROMs, was significantly higher in the POI group than in the control group, indicating that the POI group presented a state of oxidative stress. Factors suggested to be involved in age-related decline in the quantity and quality of oocytes include the function of mitochondria and attendant ROS cytotoxicity[34-36]. Although patients with POI do not demonstrate a diminished antioxidant potential, excessive oxidative stress is suggested to be involved in early depletion of follicular and inhibition of follicle development.

Additionally, continuity is observed in the attenuation of ovarian function in the pathogenesis of POI. Knauff *et al*[64] previously described the process of POI as the following steps: (1) Menstruation is normal at first but subsequently shifts to incipient ovarian failure (IOF), in which FSH is slightly elevated (> 10.2 IU/L); (2) transitional ovarian failure, which presents with elevated FSH and irregular menstruation; (3) amenorrhea, in which FSH is ≥ 40 IU/L for at least 4 mo; and (4) follicle depletion and/or a halt in follicular development[64]. Extremely severe infertility is a major problem associated with POI. Although only approximately 25% of patients with POI demonstrate decreased ovulation, the

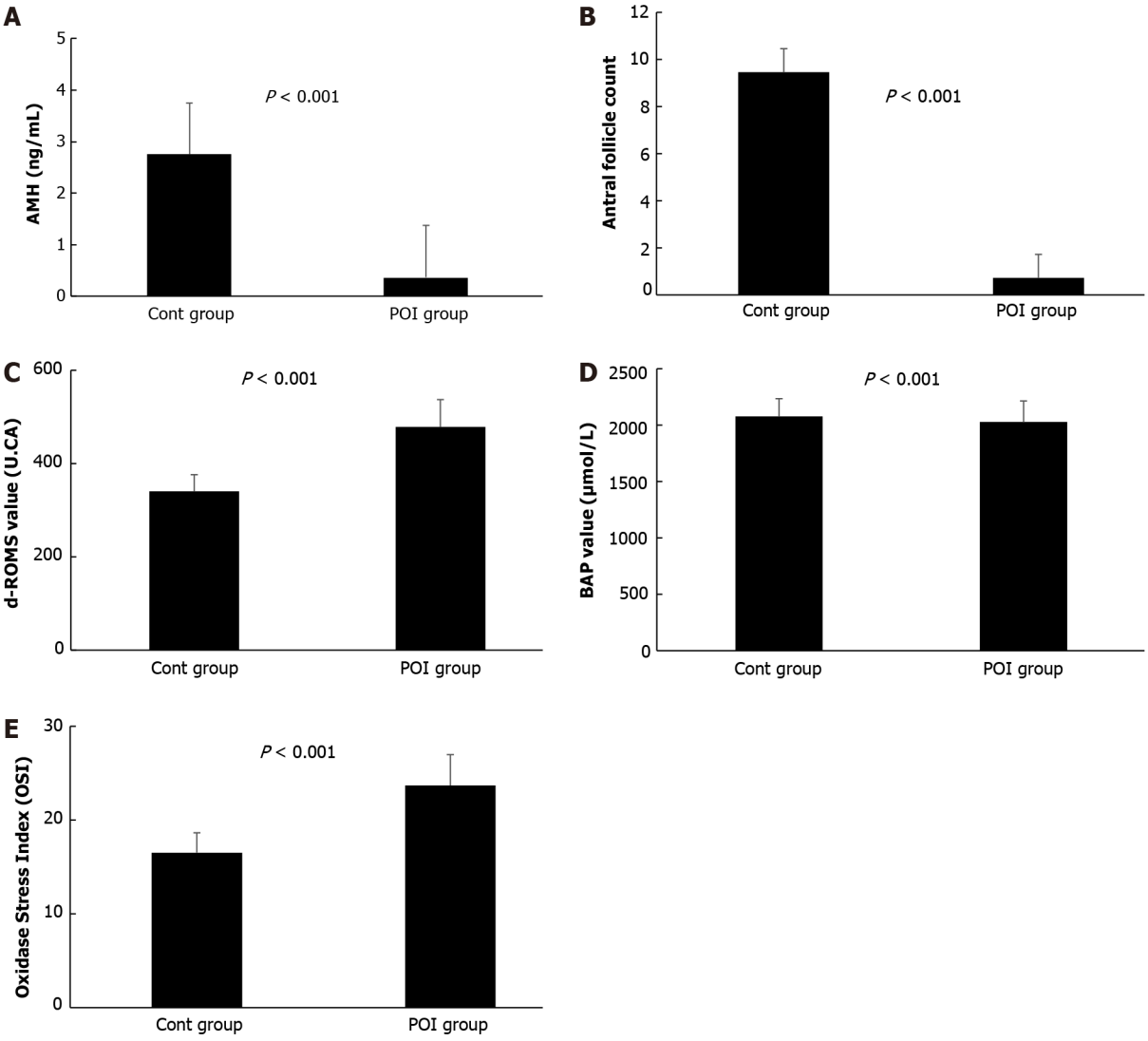

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Figure 2 Comparison of anti-Müllerian hormone, antral follicle count, mean plasma levels of diacron-reactive oxygen metabolites, mean plasma levels of biological antioxidant potential, and the mean oxidase stress index between the control and premature ovarian insufficiency groups. A: Anti-Müllerian hormone; B: Antral follicle count; C: Mean plasma levels of diacron-reactive oxygen metabolites; D: Mean plasma levels of biological antioxidant potential; E: Mean oxidase stress index. Values are expressed as means, with the error bar representing the standard deviation. Significant difference between the control and premature ovarian insufficiency groups, $P < 0.001$. POI: Premature ovarian insufficiency; Cont: Control; AMH: Anti-Müllerian hormone; d-ROMs: Diacron-reactive oxygen metabolites; BAP: Biological antioxidant potential; OSI: Oxidase stress index.

lifetime pregnancy rate with their own ova among these patients is only 5%-10%[11,12,23,24], suggesting intractable infertility in patients with POI. To date, no reliable treatment option is available to maintain reproductive capacity in POI, and the ESHRE guidelines hold that there is no medical intervention worth recommending other than oocyte donation[25,26]. Progressive ovarian insufficiency is a persistent condition, and women with POI who wish to conceive require treatment before their remaining follicles are depleted. This situation requires early diagnosis before the patient's condition progresses to POI. In this study, we comprehensively assessed POI in terms of oxidative stress in the blood (d-ROMs) and antioxidant potential (BAP), which have been suggested as potential biomarkers of POI; however, ROS and free radicals are unstable, complicated, and hinder their measurements. The d-ROM test does not directly measure ROS or free radicals but instead measures the level of blood hydroperoxide generated by ROS and free radicals, thereby conceivably reflecting oxidative stress in the blood more sensitively. In the future, we intend to examine whether the comprehensive assessment of d-ROMs and BAP in the blood in IOF and transitional ovarian failure (the stages before POI) can be used as a biomarker to facilitate the early diagnosis of POI and investigate the potential for early diagnosis and therapeutic intervention for POI.

This study was limited by the small sample size. However, as the number of target cases at this time was small, we will continue to accumulate data and examine a larger sample size in the future and investigate how the state of oxidative stress in the blood and local factors, such as a decrease in the number of remaining follicles associated with ovarian dysfunction and an increase in egg quality, affects

POI pathogenesis. Moreover, in future studies, we intend to examine in detail how the cytotoxicity of ROS, which is thought to be the cause of this decrease, is reflected.

CONCLUSION

Oxidative stress (d-ROM, OSI) was significantly greater in the POI group than in the control group, suggesting that oxidative stress status is a factor in POI and could serve as a biomarker of POI. This result suggests that the oxidative stress status is likely useful for fertility treatment and other forms of early therapeutic intervention. In the future, we plan to investigate the detailed mechanism underlying how the state of oxidative stress in the blood affects the pathology of POI.

ARTICLE HIGHLIGHTS

Research background

Premature ovarian insufficiency (POI) is characterized by the premature decline of ovarian function, inducing secondary amenorrhea and leading to severe infertility. Excessive production of reactive oxygen species (ROS) induces DNA damage, lipid peroxidation, and protein denaturation, while oxidative stress causes or exacerbates various diseases. The function of mitochondria in the ovaries and the cytotoxicity associated with ROS have been implicated in follicle pool depletion and follicle quality decline. Diacron-reactive oxygen metabolites (d-ROMs) and biological antioxidant potential (BAP) can be easily measured, and tests have been developed for the comprehensive evaluation of blood oxidative stress by combining the d-ROMs and BAP tests.

Research motivation

Most cases of POI are idiopathic, and no definitive cause has yet been identified. Investigation of the cause of POI, early diagnosis, and early intervention are warranted.

Research objectives

This study sought to comprehensively assess the oxidative stress status with d-ROMs and BAP tests in POI and to investigate whether these can be biomarkers for POI.

Research methods

To comprehensively assess oxidative stress status, we measured plasma d-ROM and BAP in POI and control groups.

Research results

The d-ROMs level and the oxidase stress index were significantly higher in the POI than in the control group. However, the BAP level did not significantly differ between the two groups.

Research conclusions

Oxidative stress (d-ROMs, OSI) in the POI group was significantly higher than in the control group, suggesting that the oxidative stress state may be a factor in POI and a potential biomarker. Therefore, it may be useful for early intervention for treatment, including infertility treatment.

Research perspectives

Oxidative stress was significantly higher in patients with POI than in healthy controls, suggesting the use of this measurement as a biomarker of POI. In the future, we plan to investigate whether these markers are useful for the early diagnosis of POI and how the state of oxidative stress affects the pathology of POI.

FOOTNOTES

Author contributions: Kakinuma K and Kakinuma T contributed to the methodology, software design, validation, and formal analysis, writing-original draft preparation, writing-review and editing, visualization, supervision, and project administration.

Institutional review board statement: The present study was approved by the Institutional Review Board of the International Health and Welfare Hospital (approval No. 21-Im-075, approved on 3/22/2022).

Informed consent statement: All study participants or their legal guardian provided informed written consent about

personal and medical data collection prior to study enrolment.

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

Data sharing statement: The original anonymous dataset is available on request from the corresponding author at tokakinuma@gmail.com.

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Surgical management of pituitary adenoma during pregnancy

Xin-Yu Jia, Xiao-Peng Guo, Yong Yao, Kan Deng, Wei Lian, Bing Xing

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Abstract

BACKGROUND

Although conservative treatment is typically recommended for pregnant patients with pituitary adenoma (PA), surgical treatment is occasionally necessary for those with acute symptoms. Currently, surgical interventions utilized among these patients is poorly studied.

AIM

To evaluate the surgical indications, timing, perioperative precautions and postoperative complications of PAs during pregnancy and to provide comprehensive guidance.

METHODS

Six patients with PAs who underwent surgical treatment during pregnancy at Peking Union Medical College Hospital between January 1990 and June 2021 were recruited for this study. Another 35 pregnant patients who were profiled in the literature were included in our analysis.

RESULTS

The 41 enrolled patients had acute symptoms including visual field defects, severe headaches or vision loss that required emergency pituitary surgeries. PA apoplexies were found in 23 patients. The majority of patients (55.9%) underwent surgery in the second trimester of pregnancy. A multidisciplinary team was involved in patient care from the preoperative period through the postpartum period. With the exception of 1 patient who underwent an induced abortion and 1 fetus that died due to a nuchal cord, 39 patients delivered successfully. Among them, 37 fetuses were healthy until the most recent follow-up.

CONCLUSION

PA surgery during pregnancy is effective and safe during the second and third trimesters. Pregnant patients requiring emergency PA surgery require multidisciplinary evaluation and healthcare management.

Key Words: Pituitary adenoma; Pregnancy; Surgery; Surgical indication; Surgical timing

Core Tip: Although clinicians generally recommend conservative treatment for patients with pituitary adenomas (PAs), surgical treatment is occasionally necessary. Currently, surgical interventions utilized among these patients is poorly studied. This study investigated the surgical interventions utilized for patients with PAs occurring during pregnancy. We found that in the second and third trimesters transsphenoidal PA surgery is a safe and effective approach for emergency conditions arising during pregnancy and may be conducted after a multidisciplinary team evaluation. These strategies may open up new avenues for the treatment of PAs during pregnancy in the future.

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INTRODUCTION

Pituitary adenoma (PA) is the second most common primary brain tumor, accounting for 15% to 17% of brain tumors and 25% of benign brain tumors[1]. Although PAs can occur at any age, those occurring in pregnant patients have unique characteristics. Pregnancy can cause the enlargement of pre-existing PAs that may compress the meningeal, contributing to acute symptoms such as severe headache and visual defects. These symptoms can affect maternal health and fetal development[2]. In addition, hormone-secreting PAs may lead to increased levels of hormones, such as adrenocorticotropic hormone (ACTH) and thyroid-stimulating hormone (TSH), resulting in poor prognoses[1,3].

During pregnancy, some PAs can be controlled by conservative treatment. For example, patients with prolactinomas are treated with oral dopamine agonists (DAs)[1,4-6]. Although there is no evidence that somatostatin analogues (SSAs) are safe for the fetus during pregnancy, SSAs are effective in reducing tumor size and decreasing growth hormone (GH) and insulin-like growth factor 1 (IGF1) levels in acromegaly[7,8]. However, some pregnant patients with acute compression symptoms, such as visual defects and severe headache, as well as non-prolactinoma patients with pathologically high hormone levels may accept surgical treatment in clinical practice. Surgical treatment may also be chosen if the problem cannot be solved by conservative treatment or potential side effects rule out pharmacological treatment. These patients pose a challenge to neurosurgeons in terms of surgical timing, surgical indications, anesthesia risk and perioperative treatment. At present, few case reports on the surgical treatment of pregnant PA patients are available, and adequate knowledge and experience regarding this surgical intervention are lacking.

The pituitary specialty at the Peking Union Medical College Hospital (PUMCH) has a long history[9], and the Neurosurgery Department of PUMCH is the founding unit of the China Pituitary Adenoma Specialist Council and the China Pituitary Disease Registry Network. The endocrinology department at PUMCH is known as a leader in endocrinology[10]. In this study, we summarized the clinical presentation, imaging features, surgical indications, perioperative management and other vital considerations of 6 pregnant PA patients surgically treated at our hospital. We also included 35 similar patients reported in the literature. Our goal was to provide suggestions for the management of pregnant PA patients to physicians in neurosurgery, endocrinology, obstetrics/gynecology, ophthalmology, and

other related specialties.

MATERIALS AND METHODS

Patient enrolment at PUMCH

Six pregnant patients with PAs admitted to the neurosurgery department of PUMCH between January 1990 and June 2021 were retrospectively analyzed. All patients underwent surgery for PAs during pregnancy. The data collected included clinical symptoms, imaging features, perioperative treatment, pathological classification, and postoperative follow-up. All procedures involving human participants were performed in accordance with the ethical standards of the Institutional Ethics Committee of Peking Union Medical College Hospital at the Chinese Academy of Medical Sciences and Peking Union Medical College and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Informed consent was obtained from all participants included in the study.

Additional cases from the literature and data extraction

We performed a literature search using PubMed to identify relevant studies published between January 1990 and June 2021. Our search used the MeSH terms "pituitary adenoma," "pregnancy" and "surgery." Citation indices were used to expand the search for relevant studies. The search was limited to studies written in English and were included only when sufficient data were available. Some studies without details of cases, such as those describing clinical symptoms, imaging findings, surgical timing and specific pathology, were not included[11].

After reading and reviewing relevant literature, only patients with PAs who underwent surgery during pregnancy were included. Patients treated with conservative treatment alone as well as those who received treatment for pathological non-PA were excluded.

Patients with duplicate reports due to multiple articles published by the same clinical center at different times were manually removed. Based on the above criteria, 30 studies screened, resulting in the inclusion of 35 patients.

Statistical analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) software (version 22.0; IBM Corp., Armonk, NY, United States). Measurement data conforming to a normal distribution were represented by. Enumeration data were expressed as percentages or ratios. Paired-sample *t* -tests were used for preoperative and postoperative comparisons. Statistical significance was set at $P < 0.05$.

RESULTS

Clinical characteristics

Forty-one patients with PAs who underwent surgery during pregnancy were included. A summary of their clinical characteristics is provided in Table 1, which includes 6 cases from our center and 35 cases from the PubMed database. The ages of 3 patients were not reported. The age of the remaining 38 patients ranged from 21 years to 41 years, with a mean age of 29.7 ± 5.3 years.

The clinical presentations of the 41 patients were as follows: visual field defects in 28 cases (68.3%) (bitemporal hemianopsia in 23 cases, unilateral temporal hemianopia in 5 cases; Figure 1); headaches in 27 cases (65.9%); vision loss in 20 cases (48.8%) (15 cases binocular, 5 cases monocular); Cushing syndrome in 7 cases (17.1%); acromegaly in 6 cases (14.6%); oculomotor paralysis in 4 cases (9.8%); diabetes insipidus in 2 cases (4.9%); and hyperthyroidism in 2 cases (4.9%).

Image data

The imaging data of the 41 patients are shown in Supplementary Table 1. Magnetic resonance imaging (MRI) was obtained for 37 of the patients (90.2%). Contrast-enhanced MRI was performed in 3 cases (7.3%), in which 1 case was obtained before pregnancy and 2 cases were obtained during pregnancy. Cranial enhanced computed tomography was performed in 1 case (2.4%) without MRI. The tumor sizes in the 27 patients with available data ranged from 0.4 cm to 4.0 cm (average: 2.1 ± 0.9 cm). Pituitary microadenomas were found in 2 patients. Up to 92.6% of patients (25 cases) had pituitary macroadenoma.

Twenty-seven patients underwent T1 weighted imaging (T1WI), yielding hypointensity in 11.1% of cases (3/27), isointensity in 37.0% of cases (10/27), isointensity and hypointensity in 3.7% of cases (1/27), isointensity and hyperintensity in 29.6% of cases (8/27), and hyperintensity in 18.5% of cases (5/27). Three types of T1WI for cases with pituitary apoplexy were shown in Figure 2. None of the images showed hypointensity on T1WI.

Table 1 Basic information and clinical symptoms of pregnant patients who underwent surgery for pituitary adenoma

Data source	Case	Age, yr	Sex	Clinical symptoms							
				Headache	Vision loss	Visual field	OP	DI	HT	CS	Acromegaly
Peking Union Medical College Hospital	1	29	F	No	Bi	BTH	No	No	No	No	No
	2	36	F	Yes	Bi	BTH	No	No	No	No	No
	3	34	F	No	Bi	BTH	Yes	Yes	No	No	No
	4	32	F	No	No	No	No	No	Yes	No	No
	5	37	F	Yes	Mo	BTH	No	No	No	No	No
	6	28	F	Yes	Bi	BTH	No	No	No	No	No
Jallad *et al*[16]	7	25	F	Yes	No	BTH	No	No	No	No	Yes
	8	27	F	Yes	No	BTH	No	No	No	No	Yes
	9	27	F	Yes	No	BTH	No	No	No	No	Yes
Chaiamnuay *et al*[17]	10	39	F	Yes	No	UTH	No	No	Yes	No	No
Guven *et al*[18]	11	32	F	No	Bi	BTH	No	No	No	No	Yes
Zhong *et al*[38]	12	29	F	No	Bi	No	No	No	No	No	No
Jemel *et al*[19]	13	35	F	Yes	No	BTH	No	No	No	No	No
	14	30	F	Yes	Bi	BTH	No	No	No	No	No
Xia *et al*[20]	15	25	F	Yes	Bi	BTH	No	No	No	No	No
Yamaguchi *et al*[21]	16	35	F	Yes	Bi	UTH	No	No	No	No	No
Tandon *et al*[22]	17	27	F	Yes	Mo	BTH	No	No	No	No	No
Parihar *et al*[36]	18	22	F	Yes	Bi	No	No	No	No	No	No
Gondim *et al*[23]	19	29	F	Yes	Mo	UTH	Yes	No	No	No	No
Witek *et al*[24]	20	25	F	Yes	Bi	BTH	No	No	No	No	No
Kita *et al*[25]	21	26	F	Yes	No	BTH	No	No	No	No	No
Nossek *et al*[26]	22	29	F	No	Bi	No	No	No	No	No	No
	23	34	F	No	No	BTH	No	No	No	No	No
Iuliano and Laws[27]	24	28	F	Yes	No	No	No	No	No	No	No
	25	35	F	Yes	Mo	UTH	Yes	No	No	No	No
Hayes *et al*[28]	26	41	F	Yes	No	BTH	No	No	No	No	No
Boronat *et al*[52]	27	26	F	No	No	No	No	No	No	Yes	No
Abbassy *et al*[37]	28	38	F	Yes	No	No	No	No	No	Yes	No
Coyne *et al*[53]	29	22	F	No	No	No	No	No	No	Yes	No
Pinette *et al*[54]	30	33	F	No	No	No	No	No	No	Yes	No
Ross *et al*[55]	31	24	F	No	No	No	No	No	No	Yes	No
Mellor *et al*[51]	32	40	F	No	No	No	No	No	No	Yes	No
Karaca *et al*[15]	33	NA	F	No	No	No	Yes	No	No	No	Yes
Jolly *et al*[56]	34	30	F	No	No	No	No	No	No	Yes	No
Galvão *et al*[29]	35	NA	F	Yes	Bi	BTH	No	No	No	No	No
Abid *et al*[30]	36	25	F	Yes	Bi	BTH	No	No	No	No	No
Barraud *et al*[31]	37	NA	F	Yes	No	BTH	No	No	No	No	No
Freeman *et al*[32]	38	22	F	Yes	Mo	BTH	No	Yes	No	No	No
Lunardi *et al*[33]	39	21	F	Yes	Bi	BTH	No	No	No	No	Yes

Oguz *et al*[34]	40	26	F	Yes	No	UTH	No	No	No	No	No
O'Neal[35]	41	27	F	Yes	No	BTH	No	No	No	No	No

Bi: Binocular; BTH: Bitemporal hemianopsia; CS: Cushing syndrome; DI: Diabetes insipidus; F: Female; HT: Hyperthyroidism; Mo: Monocular; OP: Oculomotor paralysis; NA: Not available; UTH: Unilateral temporal hemianopia.

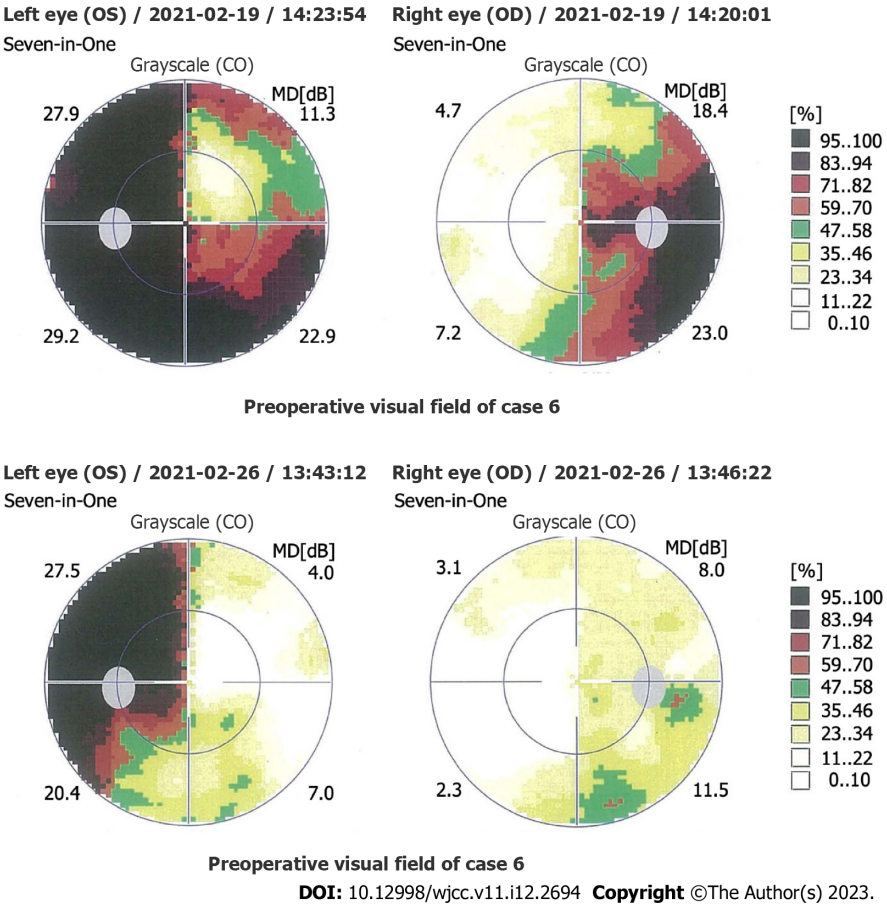

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Figure 1 Comparison of the preoperative and postoperative visual fields for Case 6. Preoperative visual field examination showed bitemporal hemianopsia, which was more severe in the left eye. Three days after surgery, examination revealed a partial temporal visual field defect in the left eye and a standard visual field in the right eye.

Ten patients underwent T2 weighted imaging, yielding hypointensity in 10.0% of cases (1/10), hyperintensity in 40.0% of cases (4/10) and isointensity and hyperintensity in 50.0% of cases (5/10). Three of the four patients who underwent contrast-enhanced MRI showed no enhancement. The remaining case showed inhomogeneous enhancement.

The Knosp classification was reported in 20 patients. In 5 cases (25.0%), the classification was invasive (Knosp classification III or IV). In 15 cases (75.0%), the classification was non-invasive. Five patients were in the highest unilateral Knosp classification IV (25.0%). Two patients (10.0%) were in Knosp classification II. Nine patients (45.0%) were in Knosp classification I, and four patients (20.0%) were in Knosp classification 0.

Hormone levels

Changes in hormone levels in the 41 patients were shown in Supplementary Table 2. Complete hormone monitoring was performed in 8 of 13 patients with prolactinoma. Prolactin levels decreased after operation, and the difference was statistically significant ($P < 0.05$).

GH levels in 4 patients with complete hormone monitoring decreased postoperatively, although without statistical significance ($P = 0.085$). One patient (Case 11) had higher IGF1 on the 2nd day after surgery. However, the IGF1 level returned to normal after 6 mo. The IGF1 difference in the other 3 patients was not statistically significant ($P = 0.115$).

ACTH levels of the 3 patients completing hormone monitoring increased preoperatively and sharply decreased postoperatively. The difference was statistically significant ($P < 0.05$). However, among 2

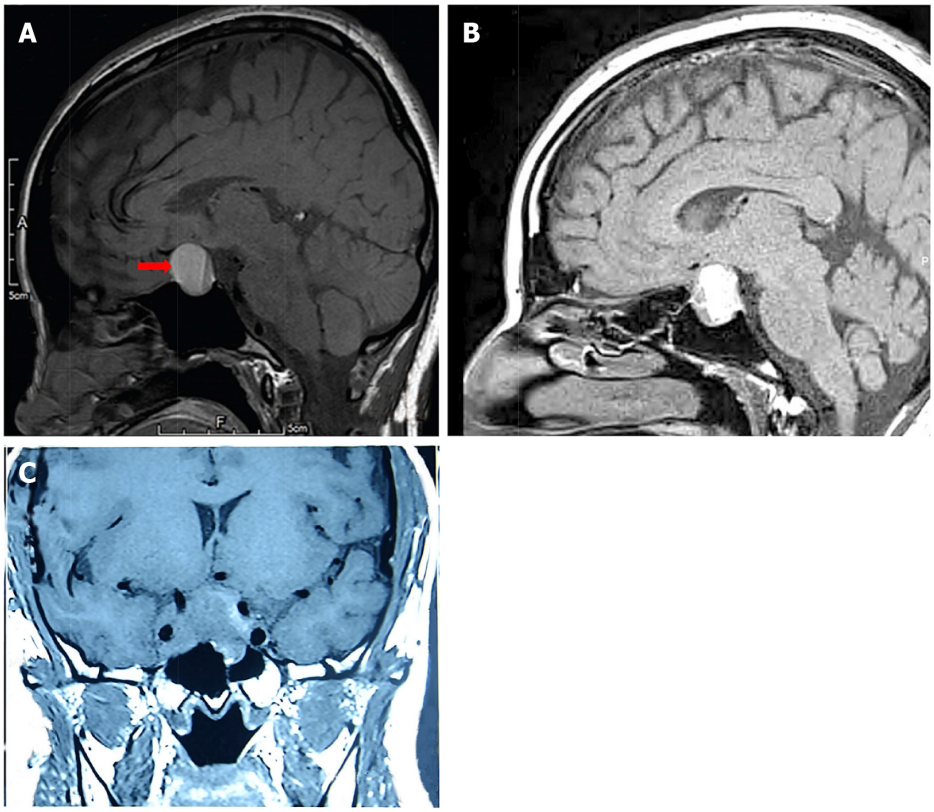

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Figure 2 Three typical images of pituitary adenoma apoplexy. A: Sagittal T1 weighted imaging (T1WI) showed isointensity and hyperintensity with a visible liquid level (Case 15); B: Sagittal T1WI showed mixed intensity (mainly hyperintensity) (Case 40); C: Coronal T1WI showed isointensity (Case 5).

patients with decreased TSH levels postoperatively, the difference was not statistically significant (P = 0.308).

Perioperative conservative treatment

Perioperative conservative treatments for the 41 patients are shown in Table 2. Twenty-two patients did not receive conservative treatment. Among the remaining 19 patients, bromocriptine was used most frequently (57.9%, 11/19), including for 6 patients with prolactinoma, 3 patients with non-functioning PA, 1 patient with TSH-secreting PA, and 1 patient without pathological classification. The second most frequent preoperative drug group was glucocorticoids, including 5 patients with non-functioning PA, 1 patient with prolactinoma and 1 patient without pathological classification. Cabergoline, also a DA, ranked third with only 2 patients, including 1 patient with non-functioning PA and 1 patient with GH-secreting PA. Drugs also used for preoperative medication included sandostatin, thyroxine, propyl-thiouracil, alpha-methyldopa and 1-desamino-8-D-arginine vasopressin. Postoperatively, 30 patients received conservative treatment, comprising 13 cases of glucocorticoid treatment, 7 cases of thyroxine treatment, 5 cases of arginine-vasopressin treatment, and 5 cases of desmopressin treatment.

Operations and pathological classifications

All 41 patients underwent transsphenoidal surgery under general anesthesia. No patients were treated with craniotomy. With the exception of 7 patients who did not report their specific gestation, the surgical gestation of the other 34 patients ranged from 11 wk to 36 wk, with an average of 25.1 ± 7.1 wk. Two cases were in the first trimester (gestation < 14 wk; 5.9%), 19 cases in the second trimester (14 wk ≤ gestation < 28 wk; 55.9%, 19/34), and 13 cases in the third trimester (gestation ≥ 28 wk; 38.2%, 13/34).

Three cases (from PubMed) did not have pathologic classification reported. There were 13 cases (34.2%) of prolactinoma, 10 cases (26.3%) of non-functioning PA, 7 cases (18.4%) of ACTH-secreting PA, 6 cases (15.8%) of GH-secreting PA, and 2 cases (5.3%) of TSH-secreting PA.

Follow-up information

Ten patients with non-functioning PA were not in remission, and twenty-six patients (63.4%) were in endocrine remission. Four patients (9.8%) were in endocrine control, and one patient (2.4%) relapsed. In terms of pregnancy outcomes, 1 patient underwent an induced abortion at 16 wk, and 1 fetus died due to a nuchal cord at 33 wk of gestation. The remaining 39 patients delivered 37 healthy fetuses successfully. One fetus died of a congenital diaphragmatic hernia within 36 h after caesarean section at

Table 2 Treatment and follow-up outcomes of pregnant patients who underwent surgery for pituitary adenoma

Ref.	Case	Treatment				Pathology	Follow up	
		Medical therapy		Operation	Delivery		M	I
		Pre	Post					
Peking Union Medical College Hospital	1	Bromocriptine	No	12th W TSS	40th W CS	NF PA	ER	H
	2	No	No	32nd W TSS	Full term CS	NF PA	ER	H
	3	No	No	22nd W TSS	38th W CS	NF PA	ER	H
	4	Sandostatin	No	26th W TSS	38th W CS	TSH PA	ER	H
	5	Bromocriptine	No	35th W TSS	35th W CS	PRL PA	ER	H
	6	Prednisone, thyroxine	Prednisone, thyroxine	30th W TSS	39th W CS	NF PA	ER	H
Jallad *et al*[16]	7	No	No	3rd Mon TSS	38thW CS	GH PA	ER	H
	8	No	No	4th Mon TSS	16th W A	GH PA	EC	A
	9	Cabergoline	No	4th Mon TSS	39th W CS	GH PA	ER	H
Chaiamnuay *et al*[17]	10	Propylthiouracil, bromocriptine	No	27th W TSS	39th W CS	TSH PA	ER	H
Guven *et al*[18]	11	No	Octreotide	34th W TSS	34th W CS	GH PA	EC	H
Zhong *et al*[38]	12	No	Cortisone, thyroxine	22nd W TSS	40th W VD	NF PA	ER	H
Jemel *et al*[19]	13	Cabergoline, hydrocortisone	No	22nd W TSS	37th W VD	NF PA	ER	H
	14	Corticosteroids	No	24th W TSS	38th W VD	NF PA	ER	H
Xia *et al*[20]	15	No	No	24th W TSS	38th W CS	PRL PA	ER	H
Yamaguchi *et al*[21]	16	No	Methyl prednisolone	36th W TSS	37th W CS	PRL PA, Optic neuritis	ER	H
Tandon *et al*[22]	17	Bromocriptine	Desmopressin	36th W TSS	37th W CS	PRL PA	ER	H
Parihar *et al*[36]	18	No	No	20th W TSS	Full term VD	PRL PA	ER	H
Gondim *et al*[23]	19	Bromocriptine	Thyroxine, hydrocortisone	32nd W TSS	39th W VD	PRL PA	EC	H
Witek *et al*[24]	20	Bromocriptine	Hydrocortisone	20th W TSS	38th W CS	PRL PA	ER	H
Kita *et al*[25]	21	No	DDAVP	27th W TSS	40th W VD	NF PA	ER	H
Nossek *et al*[26]	22	No	No	33rd W TSS	35th W CS	PA	ER	LAS
	23	No	No	31st W TSS	40th W VD	PA	ER	H
Iuliano and Laws[27]	24	Bromocriptine, dexamethasone	No	30th W TSS	39th W CS	NF PA	ER	H
	25	Bromocriptine, dexamethasone	Levothyroxine, hydrocortisone	33rd W TSS	39th W CS	NF PA	ER	H
Hayes *et al*[28]	26	Corticosteroids	No	18th W TSS	Full term VD	PRL PA	ER	H
Boronat *et al*[52]	27	Alpha-metildopa	Metyrapone	16th W TSS	34th W VD	ACTH PA	R	H
Abbassy *et al*[37]	28	No	Hydrocortisone, desmopressin	18th W TSS	39th W VD	ACTH PA	ER	H
Coyne *et al*[53]	29	No	Hydrocortisone, desmopressin	14th W TSS	38th W VD	ACTH PA	ER	H
Pinette *et al*[54]	30	No	Atenolol	16th W TSS	-	ACTH PA	ER	D
Ross *et al*[55]	31	No	Dexamethasone	18th W TSS	37th W CS	ACTH PA	ER	H
Mellor *et al*[51]	32	No	Hydrocortisone	Mid-trimester TSS	34th W CS	ACTH PA	ER	H
Karaca *et al*[15]	33	No	No	11th W TSS	39th W CS	GH PA	ER	H
Jolly *et al*[56]	34	No	Hydrocortisone,	23rd W TSS	38th W CS	ACTH PA	ER	D

			metformin, labetalol, nifedipine					
Galvão *et al*[29]	35	No	No	2nd trimester TSS	-	PRL PA	ER	H
Abid *et al*[30]	36	Bromocriptine	Lisuride hydrogen	27th W TSS	39th W VD	PRL PA	ER	H
Barraud *et al*[31]	37	Bromocriptine	No	4th Mon TSS	-	PRL PA	ER	H
Freeman *et al*[32]	38	DDAVP	Hydrocortisone, thyroxine, DDAVP	32nd W TSS	39th W VD	PRL PA	ER	H
Lunardi *et al*[33]	39	No	No	6th Mon TSS	Full term VD	GH PA	EC	H
Oguz *et al*[34]	40	No	Levothyroxine	23rd W TSS	37th W CS	PRL PA	ER	H
O'Neal[35]	41	Hydrocortisone, bromocriptine	No	29th W TSS	37th W VD	PA	ER	H

A: Abortion; ACTH: Adrenocorticotropic hormone; CS: Cesarean section; D: Death; DDAVP: 1-Desamino-8-D-arginine vasopressin; EC: Endocrine control; ER: Endocrine remission; GH: Growth hormone; H: Healthy; I: Infant; LAS: Low Apgar score; M: Maternal; NA: Not available; NF: Nonfunctional; PA: Pituitary adenoma; Post: Postoperatively; Pre: Preoperatively; PRL: Prolactin; R: Recurrence; TSH: Thyroid stimulating hormone; TSS: Transsphenoidal surgery; VD: Vaginal delivery.

38 wk of gestation, and one fetus survived with a low Apgar score after caesarean section at 35 wk of gestation. Twenty-two patients underwent caesarean section (59.5%), and fifteen patients chose vaginal delivery (40.5%). The method of delivery was unknown for 2 patients.

Delivery gestation was not reported in 6 of the 39 patients. Of the remaining 33 patients, gestation ranged from 34 wk to 40 wk, averaging 37.8 ± 1.7 wk. Premature delivery (28 wk ≤ gestation < 37 wk) occurred in 5 cases (15.2%), and full-term delivery (37 wk ≤ gestation < 42 wk) occurred in 28 cases (84.8%).

DISCUSSION

During pregnancy, physicians may face many challenges when diagnosing and treating PAs. Although conservative treatment is recommended for most pregnant patients with PAs, some patients must accept surgery due to visual defects, severe headaches and high hormone secretion levels that cannot be alleviated after conservative treatment[7,12-15]. We summarized the data of 41 patients with PAs who underwent surgery during pregnancy. To our knowledge, this is the most comprehensive report of surgical treatment of PAs in pregnant patients.

Clinical characteristics

Here, the three most common clinical symptoms of these patients were visual field defects (68.3%), headaches (65.9%) and vision loss (48.8%). Previous studies showed that the two most common clinical symptoms of PA patients with apoplexy during pregnancy were headaches and visual impairment[19,34], which is similar to our study.

The pituitary gland and pre-existing PAs may enlarge during pregnancy[2,39], and the risk is greater in patients with macroadenomas than in those with microadenomas[1]. This observation was confirmed here. In prolactinomas, the most common type of PA, the risk of symptomatic tumor enlargement during pregnancy was 27.9% for patients with macroadenomas and only 2.2% for patients with microadenomas[40]. Although 2 patients in our study had pituitary microadenomas, their surgical indications were intractable diabetes insipidus and Cushing syndrome rather than symptomatic tumor enlargement[15,37].

Conservative treatment during pregnancy

Conservative treatment during pregnancy primarily includes DA treatment for prolactinomas[1] and SSA treatment for GH-secreting PAs[1,7]. Although there is no evidence that SSAs increase the risk of fetal malformation[6,41-43], discontinuation of all medication except DAs during pregnancy is recommended to ensure fetal health to the maximum extent possible[7,8,44]. Resuming other treatments is recommended only when symptoms leading to poor prognoses, such as visual defects or severe headaches, occur. When patients do not achieve significant remission after conservative treatment, clinicians should consider surgical treatment as soon as possible following a multidisciplinary evaluation[8,12,44]. Additionally, to ensure maternal health and fetal development, hormone deficiencies, such as glucocorticoid or thyroxine, should be treated[45].

Indications for surgery during pregnancy

Patients with macroadenomas have a higher risk of symptomatic progression during pregnancy[1]. However, the size of the PA is not the criterion. The severity of visual defects and headaches should be used as surgical indications for PA during pregnancy[12,13]. Some microadenomas are also associated with adverse effects on maternal and fetal health due to high hormone levels[46]. Based on our results, the surgical indications during pregnancy are summarized as follows.

Visual defects: PAs are more likely to compress the optic chiasm during pregnancy, leading to visual defects[2]. When conservative treatment cannot relieve visual impairment, clinicians should conduct a multidisciplinary evaluation to balance visual defects with pregnancy safety and decide whether to treat surgically as soon as possible. Although the recovery rate of the visual field can be as high as 80%[47] to 95.7%[48], the severity and duration of visual impairment are essential factors for postoperative visual prognosis. Irreversible adverse effects caused by severe visual impairment during pregnancy should be avoided[48].

Severe headache: Sudden, severe headache is the most common symptom of PA with apoplexy, primarily due to the enlargement of the PA during pregnancy, increased pressure on the sella turcica, and dural pressure[45]. Headache is often accompanied by nausea, vomiting, eye muscle paralysis and impairment of consciousness. Because severe headache can induce contractions, surgery is indicated if the multidisciplinary evaluation considers that the headache is due to mass effect and that pain medication would affect fetal health[49].

Hormonal abnormalities: Some PAs, such as ACTH-secreting PA and TSH-secreting PA, can cause ovulation disorders in women of reproductive age[50]. This type of patient should be treated before pregnancy as early as possible. Nevertheless, a few patients have unintended pregnancies after diagnosis[37,51,52] or are diagnosed during pregnancy[53-56]. High hormone secretion during pregnancy is closely related to several complications and poor prognoses[46,50]. Surgical treatment with appropriate timing is the most effective method for reducing hormone levels in such patients[12,17,44].

Operative timing during pregnancy

The timing of transsphenoidal surgery depends on the potential risks and benefits, including maternal symptoms, fetal safety and gestational weeks, which is the most critical indicator. The spontaneous abortion rate in the first trimester is approximately 12.0% *vs* 5.0% in the second and third trimesters[13]. The overall malformation incidence in pregnancy is 2.0% compared with 3.9% in the first trimester. The incidence of neural tube defects and preterm delivery is highest in the third trimester[57]. In our study, most patients also underwent surgery in the second trimester. Therefore, the second trimester is the best time for PA surgery[12-14,58,59].

For patients in the first trimester, the surgery should be postponed until the second trimester if possible[14,15]. For patients in the third trimester, Lynch *et al*[60] recommended delaying surgery to 30 wk of gestation if possible because fetal survival can reach 90% after 27 wk of gestation. In comparison, Priddy *et al*[14] suggested induction of labor or caesarean section at 34 wk of gestation followed by surgical treatment, if possible. However, among the 13 patients in this study who underwent surgeries in the third trimester, 12 patients and fetuses were healthy. One fetus survived with a low Apgar score, but the mother was healthy. In this regard, we suggest that the balance of symptom severity and gestational weeks should be considered in the third trimester when glucocorticoids can be administered to promote fetal lung maturation. If symptoms do not worsen significantly, a caesarean section should be performed first. However, surgical treatment should then be performed promptly if symptoms progress significantly (Figure 3).

Precautions for surgery during pregnancy

Preoperative: A professional multidisciplinary team should be established to conduct individualized evaluations prior to surgery for pregnant patients with PAs indicated for surgical treatment. The team should include neurosurgeons, endocrinologists, obstetricians, gynecologists, pediatricians and anesthesiologists[20,59]. MRI must be acquired before the surgery. Although fetal toxicity of gadolinium is not established, MRI without gadolinium enhancement is preferred and is sufficient to make a definitive diagnosis and plan the surgery. Given the teratogenicity of X-rays, computed tomography should be avoided[61].

Preoperative ophthalmic examination is also essential, including examinations of visual acuity, visual field, fundus and retinal nerve fiber layer, and optical coherence tomography of the ganglion cell complex[12]. The ophthalmic examination can roughly predict the postoperative recovery rates for visual impairment[48]. The possible visual sequelae include severe visual impairment, severe visual field defects and severe degeneration of the retinal nerve fiber layer/ganglion cell complex[12].

Preoperative fetal ultrasonography should be performed routinely to evaluate fetal health. Continuous fetal heart rate monitoring is feasible under the proper conditions[12]. The endocrine examination can assess pituitary function. If necessary, relevant deficient hormones should be supplemented. Preoperative operations such as enemas that can induce contractions should be avoided. After

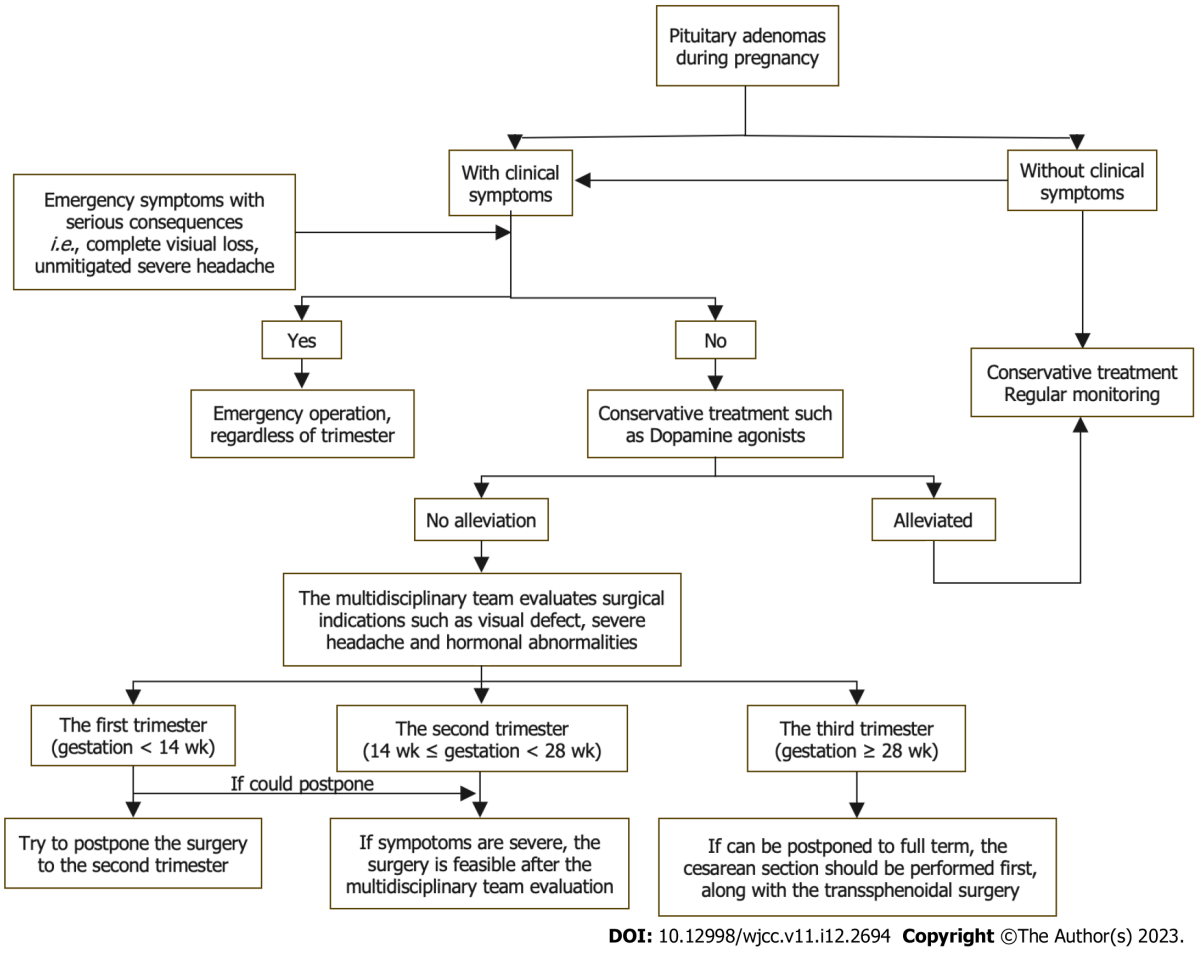

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Figure 3 Flow diagram of treatment procedures for pituitary adenoma during pregnancy.

evaluation, patients and their families should be fully informed of the risks and benefits of surgery. Written informed consent should be obtained after weighing the advantages and disadvantages.

Perioperative: Inhaled anesthetics can reduce uterine tension and increase bleeding risk and cerebral perfusion pressure in a concentration-dependent manner[62]. Total intravenous anesthesia, which is preferred during pregnancy, does not affect uterine tension and can constrict the cerebrovascular system and maintain cerebral perfusion pressure[63]. The United States Food and Drug Administration Class B drugs such as propofol are recommended. However, Class C drugs, which have potential risks but can be used given sufficient expected benefit, should be carefully used after considering the advantages and disadvantages[58].

Intraoperative reduction of cardiac return can lead to severe complications such as hypotension, placental insufficiency and cerebral insufficiency. Therefore, surgeons should lower the left side of the patient below the right side to avoid compression of the inferior vena cava[12,13]. Although there is no optimal cerebral perfusion pressure target, it seems reasonable to control the mean arterial pressure 20% above the baseline[13]. During surgery, the use of diuretics and anticonvulsants should be avoided. If necessary, contractions should be suppressed to protect the fetus[12].

Postoperative: Fetal heart rate variation is an essential indicator of fetal health and can indicate fetal distress. Therefore, continuous fetal heart rate monitoring should be performed after the surgery[13]. If postoperative reactions such as nausea, vomiting and headache occur, Class B drugs such as pethidine can be used for symptomatic treatment. Routine ophthalmic examinations should be conducted postoperatively to evaluate visual defect recovery. If no significant improvement is observed, differential diagnoses with other diseases leading to visual impairment, such as optic neuritis, should be considered[21]. Hormone stoss therapy, neurotrophic drugs and other treatments can also be administered.

Limitations

Although this report is the largest case series of patients undergoing surgical treatment for pituitary tumors during pregnancy, limitations of this study include biases due to the retrospective study design and follow-up differences. In addition, although we have tried to include all cases, the number of cases

is still relatively small. Therefore, we were unable to engage in analysis and discussion according to pathological classification. Prospective and multicenter studies with more cases are needed to further understand the surgical management of pituitary tumors during pregnancy.

CONCLUSION

The surgical treatment and perioperative management of PAs during pregnancy is complex. The surgical indications and timing issues must be well understood and carefully considered with the cooperation of neurosurgery, endocrinology, obstetrics, anesthesiology, neonatology and other related specialties. In the second and third trimesters, transsphenoidal surgery is a safe and effective approach for emergency treatment during pregnancy after evaluation by a multidisciplinary team. Additionally, for patients with irregular menstrual cycles, pituitary screening is necessary. Women of reproductive age who have been diagnosed with PAs should follow the advice of their endocrinologists and neurosurgeons before pregnancy.

ARTICLE HIGHLIGHTS

Research background

Although conservative treatment is recommended for pregnant patients with pituitary adenomas (PAs), surgical treatment is occasionally necessary for those with acute symptoms.

Research motivation

Surgical intervention among pregnant patients with PAs has been poorly studied.

Research objectives

To evaluate the surgical indications, timing, complications and perioperative precautions of surgical treatment of PAs during pregnancy and to provide comprehensive guidance.

Research methods

Six patients with PAs who underwent surgical treatment during pregnancy at Peking Union Medical College Hospital between January 1990 and June 2021 were included. Another 35 pregnant patients with PAs reported in the literature were also included. The surgical indications, timing of surgery, improvement of symptoms, postoperative complications and fetal condition were analyzed.

Research results

The 41 enrolled patients had acute symptoms including visual field defects, severe headaches or vision loss requiring emergency pituitary surgeries. PA apoplexies were found in 23 patients. The majority (55.9%) of patients underwent surgery in the second trimester of pregnancy. With the exception of 1 patient who underwent an induced abortion and 1 fetus who died due to a nuchal cord, 39 patients delivered successfully, and 37 of the fetuses were healthy at the most recent follow-up.

Research conclusions

PA surgery during pregnancy is effective and safe during the second and third trimesters. Pregnant patients requiring emergency PA surgery require multidisciplinary evaluation and healthcare management.

Research perspectives

Multicenter, large sample, randomized controlled clinical trials are still needed to improve the standardized guidelines for the surgical treatment of pituitary tumors during pregnancy.

FOOTNOTES

Author contributions: All authors contributed to the study conception and design; Jia XY, Guo XP, Yao Y, Deng K, Lian W and Xing B contributed to material preparation, data collection and analysis; Jia XY wrote the first draft of the manuscript; all authors contributed to critical revision of the manuscript; all authors read and approved the final manuscript.

Institutional review board statement: The Institutional Review Board of Peking Union Medical College Hospital provided approval for this study (IRB: I-23PJ338).

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment. Informed written consent was obtained from the patients for publication of this report and any accompanying images.

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ORIGINAL ARTICLE

Retrospective Study

Role of pre-existing incomplete intestinal metaplasia in gastric adenocarcinoma: A retrospective case series analysis

Inga Bogdanova, Inese Polaka, Ilona Aleksandraviča, Zane Dzērve, Linda Anarkulova, Vita Novika, Ivars Tolmanis, Marcis Leja

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Abstract

BACKGROUND

Risk stratification for patients with gastric precancerous lesions for endoscopic surveillance remains controversial.

AIM

To analysis of patients having developed gastric adenocarcinoma during the period of follow-up.

METHODS

We conducted a retrospective study on patients having undergone upper endoscopy prior to the development of gastric adenocarcinoma. The presence and stage of precancerous lesions as well as subtype of intestinal metaplasia at the baseline endoscopy got evaluated. Literature mini-review was performed.

RESULTS

Out of 1681 subjects in the Biobank, gastric adenocarcinoma was detected in five cases in whom previous endoscopy data with biopsies either from the corpus or antral part were available. All of the patients had incomplete intestinal metaplasia

during the baseline endoscopy; all three subjects in whom intestinal metaplasia subtyping was performed according to Filipe *et al*, had Type III intestinal metaplasia. Two of the five cases had low Operative Link on Gastritis Assessment (OLGA) and Operative Link on Gastritis Intestinal Metaplasia Assessment (OLGIM) stages (I-II) at the baseline.

CONCLUSION

The presence of incomplete intestinal metaplasia, in particular, that of Type III is a better predictor for gastric adenocarcinoma development than OLGA/OLGIM staging system. Subtyping of intestinal metaplasia have an important role in the risk stratification for surveillance decisions.

Key Words: Minireview; Gastric adenocarcinoma; Precancerous lesions; Retrospective study; Subtypes of intestinal metaplasia; OLGA/OLGIM staging

Core Tip: We present a retrospective case series and analysis of the available literature evidence on gastric mucosal precancerous lesion characteristics preceding gastric adenocarcinoma development. The obtained data are strongly suggesting that subtyping of gastric intestinal metaplasia, in particular that of Type III is an important predictor for the development of adenocarcinoma. The subtype of intestinal metaplasia appears to be a better predictor for cancer than Operative Link on Gastritis Assessment and Operative Link on Gastritis Intestinal Metaplasia Assessment staging system, however larger studies would be required to confirm this.

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INTRODUCTION

Atrophy, intestinal metaplasia and dysplasia are defined as precancerous lesions for gastric cancer, however the magnitude of risk for developing cancer may be substantially variable[1]. Surveillance strategies, *i.e.* repeated endoscopies in patients with such lesions is recommended in Europe[2]; yet substantial differences between the currently existing guidelines have to be noted[3]. The Operative Link on Gastritis Assessment (OLGA) and Operative Link on Gastritis Intestinal Metaplasia Assessment (OLGIM) have been suggested for easier use, and claimed to be a tool for better risk-stratification[4,5].

Based on a long-term follow-up study on 7436 patients in Italy, OLGA staging system was suggested to be a good predictor for gastric cancer development since most of the overall 28 incident neoplasia occurred in stages III and IV[6]. In another cohort study by the Italian investigators involving 1755 consecutive patients incident neoplastic lesions (prevalence - 0.4%; low-grade intraepithelial neoplasia - 4; high-grade intraepithelial neoplasia - 1; gastric cancer - 2) developed exclusively in patients with OLGA stages III-IV. A prospective, longitudinal multicenter study in Singapore involving 2980 subjects undergoing screening upper endoscopy with standardized gastric mucosal biopsy sampling has suggested patients with OLGIM III-IV lesions to be the highest risk-group for gastric neoplasia development (adjusted hazard ratio 20.7; 95%CI: 5.04-85.6) whereas OLGIM II group was identified to bear an intermediate risk[7].

A meta-analysis of six case-control studies and two cohort studies, comprising 2700 subjects has also demonstrated a significant association between the OLGA/OLGIM stages III/IV and gastric cancer risk [8].

The potential role of gastric intestinal metaplasia subtyping has been debated for decades. The landmark study by Filipe *et al*[9] has suggested the role of a specific high-iron diamine alcian-blue (HID-AB) staining technique for assessing the presence of sialomucins and sulfomucins. However, currently the HID-AB method is available only in a few specialized laboratories. Intestinal metaplasia can be more broadly subtyped in complete and incomplete metaplasia based on the standard hematoxylin and eosin (H&E) staining method. Incomplete intestinal metaplasia corresponds to Type II and Type III intestinal metaplasia by Filipe taken together (Figure 1).

Based on the above, we have decided to check in our retrospective surveillance cohort the role of intestinal metaplasia subtypes in gastric cancer development as well as to review the studies in the literature that have assessed subtypes of intestinal metaplasia prior to cancer development. The

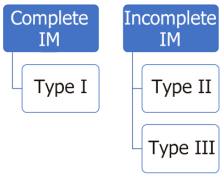

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Figure 1 Relationships between subtypes of intestinal metaplasia. (complete/incomplete; subtypes I, II, III according to Filipe *et al*[9]).

secondary objective was to assess the correlation to high-risk OLGA/OLGIM stages for assuring whether OLGA and/or OLGIM staging system could serve as the single reliable parameter for risk assessment.

MATERIALS AND METHODS

General design

We requested data on gastric cancer (C16) entries to the Cancer Registry of Latvia from individuals having been enrolled to the Biobank of the Clinical and Preventive Medicine, University of Latvia and having undergone upper endoscopy in the Digestive Diseases Centre GASTRO, Riga, Latvia. Patient enrolment to the biobank was initiated in 2007, the follow-up period according to the Registry data was ending December 2020. At the time of enrolment to the Biobank all the study subjects have provided their signed consent allowing their data to be analysed following the enrolment.

For the selected cases, the medical history available in the Digestive Diseases Centre GASTRO was analysed; this included preceding and follow-up endoscopy data. Only patients having undergone upper endoscopy prior to the diagnosis of gastric cancer and having been biopsied from the corpus and antrum during the endoscopy were included to the analysis. Those having been diagnosed with other type of malignancies than gastric adenocarcinoma were excluded.

Consequently, in the selected group of patients, endoscopy biopsy results were re-evaluated in the Academic Histology Laboratory, Riga, Latvia.

Assessment of gastric precancerous lesions

Only cases with biopsies available from the corpus and antrum were included to the analysis; incisura biopsy was also available as the standard. Routinely, staining with H&E was used for the clinical work-up. Whenever available, all the slides from the selected cases were re-analysed. Whenever the paraffin blocks were available, additional slides for HID-AB staining were produced, and the subtypes of intestinal metaplasia according to Filipe *et al*[9] were analysed.

Approaches for subtyping gastric intestinal metaplasia

Complete intestinal metaplasia is known also as small intestinal type, is characterized by the presence of absorptive cells with brush borders, goblet cells and occasionally Paneth cells, while incomplete intestinal metaplasia, known also as colonic type intestinal metaplasia – by the presence of hybrid mucous cells with large vacuoles of different sizes, without features of absorptive cells or goblet cells [10]. When both subtypes are present (mixed intestinal metaplasia), the case is classified according the lesions of the highest risk, *i.e.* incomplete metaplasia.

According to the HID-AB stain, in Type I intestinal metaplasia sialomucins are present in goblet cells with no mucins in columnar cells; in Type II – sialomucins are present in goblet and columnar cells, while in Type III - sulfomucins predominate in columnar cells, and goblet cells may contain sialomucins or sulfomucins[11].

RESULTS

Out of 1681 subjects in the Biobank (median age 59 years, 68% women, *Helicobacter pylori* (*H. pylori*) positivity – 56.8% according to histology, 13% had reported gastric cancer among the 1st degree relatives, median follow-up period 9.1 years), gastric adenocarcinoma was detected in five cases fulfilling the inclusion criteria described above. Of those, 4 were women, 1 man, one woman was a current smoker, while another one – past smoker; three have reported modest use of alcohol, one had a first degree relative with a gastric cancer; the mean age at cancer development was 75.6 years (range 53-90 years). The mean period of cancer detection was 52 mo (range 25-70 mo) following the initial endoscopy. In all, but one case several upper endoscopies have been performed during the follow-up period. Four of the five cases were *H. pylori* positive according to the histology of the preceding endoscopy, the only *H.*

pylori – negative subject was not self-reporting previous eradication therapy. For more details, see Table 1.

Patient No. 2 was the only case in which early gastric cancer was diagnosed, got the diagnosis set within a surveillance program, and was successfully managed by endoscopic submucosal resection.

At the reference endoscopy, *i.e.* an endoscopy prior to the cancer diagnosis with the highest-risk lesion, two patients were diagnosed with a high-grade dysplasia while the remaining three did not have any degree of dysplasia. One of the two with high-grade dysplasia was also classified as OLGA and OLGIM Stage III, while the other one – OLGA and OLGIM Stage I only. In the entire group, only two patients were stages as OLGA III (one of them – OLGIM II), whereas the majority, *i.e.* three cases were low OLGA and OLGIM risk stages (I and II).

In three cases in the group the material was available for an additional HID-AB staining: All three cases were diagnosed as Type III intestinal metaplasia according to Filipe *et al*[9].

DISCUSSION

Our retrospective cohort analysis was suggesting that incomplete intestinal metaplasia of the stomach mucosa, in particular, that of Type III according to Filipe *et al*[9], is a key predictor of gastric adenocarcinoma development.

The results in our case series of five patients having developed gastric cancer during the follow-up period is confirming the rationale for endoscopic surveillance strategies of patients with gastric precancerous lesions as suggested by the current guidelines[2]. Three of these patients had clearly high-risk precancerous lesions (high grade dysplasia in two cases, and an addition subject with a high-risk OLGA/OLGIM stage) at the initial investigations, whereas in two cases surveillance would not been indicated unless considering the subtype of intestinal metaplasia. Both were diagnosed as OLGA and OLGIM II stage cases at the enrolment. In all the five cases incomplete intestinal metaplasia was present at the enrolment, and in all the subjects in whom HID-AB staining was available – the intestinal metaplasia was subtyped as Type III. Therefore, based on this very small cohort, subtyping of intestinal metaplasia seems to be a more important factor for risk stratification that OLGA and OLGIM staging.

Increasing evidence is becoming available on the role of intestinal metaplasia subtyping for gastric cancer risk stratification. A 20-year follow-up study of the population-based cohort in Colombia has suggested that the presence of incomplete intestinal at baseline substantially increased the risk (OR, 13.4; 95%CI: 1.8-103.8) for gastric cancer development when compared to subjects with a complete intestinal metaplasia at the enrolment[12].

In the Spanish multi-center study having involved 649 patients with gastric precancerous lesions at baseline 24 patients had developed gastric adenocarcinoma during the mean follow-up period of 12 years. The hazards ratio of progression to gastric cancer was 2.75 (95%CI: 1.06-6.26) for those with incomplete compared with those with complete intestinal metaplasia at baseline, after adjusting for sex, age, smoking, family history of gastric cancer and the use of non-steroidal anti-inflammatory medication[10]. HID-AB staining was not used in the study.

These observations are supported by other studies. In France, a low gastric cancer risk country, progression towards gastric cancer was observed in two cases, both of them – had antrum limited disease (one was OLGA II, the other, - OLGA III stage), but incomplete intestinal metaplasia at the initial endoscopy[13].

In a study from Japan altogether 4 patients have been progressing to gastric cancer during the observational period following *H. pylori* eradication; all of these patients had incomplete intestinal metaplasia in the antral part of the stomach at the enrolment[14]. This group of researchers were using immunohistochemical staining for differentiating between the subtypes of intestinal metaplasia. Interestingly, the key objective of the study was addressing the reversibility of intestinal metaplasia; the obtained results were suggesting that incomplete intestinal metaplasia in the antrum was regressing within a 10-year period following the eradication whereas complete intestinal metaplasia did not regress either in the antrum or corpus[14].

The study that has been conducted by our group in healthy individuals from Kazakhstan, a country with high incidence of gastric cancer, has suggested that limiting the patient surveillance of those with high OLGA or OLGIM stages may result in substantial downgrading of the risk, and therefore missing patients with high risk for surveillance as a substantial proportion of subjects with low stages according to the above classifications had incomplete intestinal metaplasia[15].

Recently two meta-analysis on the subtypes of gastric intestinal metaplasia and neoplasia risk have been published by researchers from China – Du *et al*[16] has been including cohort studies (published until May 15, 2021) while Wei *et al*[17] included also case-control studies, and the analysis period was ending March 2020. Both analysis obtained similar findings. Pooled relative risk for gastric cancer development of incomplete intestinal metaplasia when compared to complete type was 5.16 (95%CI: 3.28-8.12) in the study by Du *et al*[16], and 4.96 (95%CI: 2.72-9.04) in the study by Wei *et al*[17] Both studies revealed the highest risk of progression to cancer in Type III intestinal metaplasia, *i.e.* 6.27 (95%CI: 1.89-20.77) in the analysis by Wei *et al*[17] when compared Types I and II combined, while 6.42

Table 1 Characteristics of the subjects having developed gastric adenocarcinoma following a previous upper endoscopy with biopsies

No.	Gender	Age at cancer development	Year of enrolment	Year of cancer diagnosis	Year of death	No. of preceding upper endoscopies	Number of months of the reference endoscopy prior to cancer development	Reference endoscopy (highest risk lesion in the case of several preceding endoscopies)					Grade of the cancer
								Dysplasia	OLGA stage	OLGIM stage	Complete/incomplete intestinal metaplasia	Intestinal metaplasia according to Filipe *et al*[9] (highest grade)	
1	Female	88	2008	2012	2013	1	52	No	II	II	Incomplete	NA	NA
2	Male	53	2011	2016	Alive	3	70	High-grade	III	III	Incomplete	III	Grade 1
3	Female	72	2010	2014	2015	3	48	High-grade	I	I	Incomplete	NA	Grade 3
4	Female	90	2008	2019	2020	4	65	No	III	II	Incomplete	III	Grade I
5	Female	75	2007	2021	Alive	2	25	No	II	II	Incomplete	III	Grade 1

NA: Not available; OLGA: Operative Link on Gastritis Assessment; OLGIM: Operative Link on Gastritis Intestinal Metaplasia Assessment.

(95%CI: 3.03-13.62) in the analysis by Du *et al*[16] when compared to Type I intestinal metaplasia.

There are certain limitations to our and other studies. The numbers of study subjects either in our case series or in other cohorts, including the study from France[13], are low. Besides, there is a very limited number of laboratories that are currently using the HID-AB staining method; also in some of our patients the material was not available to apply this staining method in all. Larger series would be required for definite conclusions; European-level data collaborative for pooling the results from various studies whether published or unpublished, would be a powerful tool for the purpose.

Finally, the relevance of intestinal metaplasia subtyping has been gradually acknowledged by international guidelines. There is limited awareness among gastroenterologists of the potential prognostic value of the histological subtyping of IM[11], and therefore, the pathologists are frequently not reporting the subtypes even though this would be important for setting the most appropriate surveillance endoscopy intervals. The latest version of MAPS (II) guideline acknowledges the role of incomplete intestinal metaplasia[2], while this was discouraged in the initial version[18]. Although referring to MAPS II, the recent Maastricht VI guideline suggests subtyping of intestinal metaplasia is clinically redundant if using OLGA/OLGIM staging systems[5], which actually contradicts our findings and the above discussed evidence. We expect that increasing knowledge in the field should result in changes to upcoming editions of these guidelines.

CONCLUSION

Proper risk stratification of precancerous lesions of the stomach mucosa is important for determining the optimal surveillance strategies. The presence of incomplete intestinal metaplasia, in particular that of Type III is a better predictor for gastric adenocarcinoma development than OLGA/OLGIM staging system. Subtyping of intestinal metaplasia may have an important role in the risk stratification for surveillance decisions. Large-scale international data collaborative may be of importance to address the above issues.

ARTICLE HIGHLIGHTS

Research background

Gastric cancer is still remaining an important burden of the global health. Proper stratification of precancerous lesions is of significant importance for scheduling surveillance endoscopic investigations.

Research motivation

To address the role of intestinal metaplasia subtyping in clinical settings.

Research objectives

To investigate the subtypes of intestinal metaplasia during an endoscopy that was performed prior to cancer development in a retrospective cohort.

Research methods

Retrospective analysis of patients having been diagnosed with gastric cancer following a past endoscopic assessment (without cancer).

Research results

Incomplete type intestinal metaplasia was present in all patients having developed cancer. In all three patients in whom the subtyping of intestinal metaplasia was performed according to Filipe *et al*, Type III intestinal metaplasia was present.

Research conclusions

Subtyping of gastric intestinal metaplasia is important for clinical practice.

Research perspectives

Larger-scale case-controlled studies would be required to support the conclusions.

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FOOTNOTES

Author contributions: Bogdanova I designed the outline and performed all the pathology evaluation, including specific staining for intestinal metaplasia subtypes, performed the analysis of the obtained results and design of the tables; Aleksandravičа I coordinated the biobanking activities and data acquisition; Tolmanis I reviewed the endoscopy reports; Leja M coordinated the research and participated in the outline design and writing of the paper, all authors were involved in writing and final approval of the manuscript.

Institutional review board statement: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Medical and Biomedical Research Ethics Committee of the Riga East University Hospital Support Foundation, protocol 18-A/16, October 6, 2016.

Informed consent statement: Signed consent was obtained form all the study subjects at the time of their recruitment to the Biobank.

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

Data sharing statement: No additional data available.

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ORIGINAL ARTICLE

Observational Study

Severe/critical COVID-19 early warning system based on machine learning algorithms using novel imaging scores

Qiu-Yu Li, Zhuo-Yu An, Zi-Han Pan, Zi-Zhen Wang, Yi-Ren Wang, Xi-Gong Zhang, Ning Shen

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Abstract

BACKGROUND

Early identification of severe/critical coronavirus disease 2019 (COVID-19) is crucial for timely treatment and intervention. Chest computed tomography (CT) score has been shown to be a significant factor in the diagnosis and treatment of pneumonia, however, there is currently a lack of effective early warning systems for severe/critical COVID-19 based on dynamic CT evolution.

AIM

To develop a severe/critical COVID-19 prediction model using a combination of imaging scores, clinical features, and biomarker levels.

METHODS

This study used an improved scoring system to extract and describe the chest CT characteristics of COVID-19 patients. The study also took into consideration the general clinical indicators such as dyspnea, oxygen saturation, alternative lengthening of telomeres (ALT), and androgen suppression treatment (AST), which are commonly associated with severe/critical COVID-19 cases. The study employed lasso regression to evaluate and rank the significance of different disease characteristics.

RESULTS

The results showed that blood oxygen saturation, ALT, IL-6/IL-10, combined

score, ground glass opacity score, age, crazy paving mode score, qsofa, AST, and overall lung involvement score were key factors in predicting severe/critical COVID-19 cases. The study established a COVID-19 severe/critical early warning system using various machine learning algorithms, including XGBClassifier, Logistic Regression, MLPClassifier, RandomForestClassifier, and AdaBoost Classifier. The study concluded that the prediction model based on the improved CT score and machine learning algorithms is a feasible method for early detection of severe/critical COVID-19 evolution.

CONCLUSION

The findings of this study suggest that a prediction model based on improved CT scores and machine learning algorithms is effective in detecting the early warning signals of severe/critical COVID-19.

Key Words: COVID-19; Clinical prediction model; Electron computed tomography; Machine learning

Core Tip: The computed tomography (CT) score is a relatively objective and clinically accessible semiquantitative assessment tool for patients with coronavirus disease 2019 (COVID-19). The CT scores of common, severe, and critically ill patients showed different trends, and there were differences between the groups of patients as the disease progressed. Patients who are recovering from the disease can be monitored *via* CT at reduced intervals to reduce their radiation exposure and financial burden. The 2 wk CT scores of the patients were important for predicting disease deterioration in hospitalized patients who have an average admission severity rating. The qSOFA score, aspartate aminotransferase, oxygenation, and dyspnea were important for the prediction of severe/critical COVID-19 disease.

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INTRODUCTION

Since the outbreak of novel coronavirus pneumonia (COVID-19) in late December 2019, approximately 521 million more patients worldwide have been infected as of late May 2022, and over 6 million patients could have died from COVID-19. Some COVID-19 patients are not critical at the time of initial diagnosis, but their conditions may deteriorate, leading to severe illness. Currently, case reports in China show that most COVID-19 patients have mild disease, but 15% and 5% develop severe disease and become critically ill, respectively. The intensive care unit (ICU) mortality rate for critically ill patients is as high as 50%-60%. Hence, early identification of the warning signs of severe/critical COVID-19 cases and prompt intervention and treatment can help reduce mortality and improve cure rates[1,2]. At present, CT chest examination is an important part of the diagnosis and treatment of COVID-19 pneumonia and has been used to diagnose patients clinically. Its significance in indicating patient deterioration has been confirmed. However, there is still a lack of means to predict the early progression of severe/critical cases based on the dynamic evolution of CT, and how to determine the progression of CT lesions objectively and quantitatively has become an urgent clinical issue that needs to be addressed[3,4]. During the progression of COVID-19, the occurrence of an inflammatory storm plays a crucial role and the alteration of related inflammatory factors can directly damage the pulmonary capillary mucosa, promoting alveolar edema and inactivating surface active proteins, leading to diffuse alveolar damage and ventilation dysfunction. Inflammatory storms are also a major cause of acute respiratory distress syndrome and multiple organ dysfunction syndrome[5,6]. Numerous prognostic studies on COVID-19 have shown that the trends in related cytokines are crucial for early identification and treatment of critical cases[7,8]. Therefore, exploring the trends in biomarkers, such as cytokines, is important for further understanding the mechanisms of disease progression and regression in COVID-19 patients[9].

Identifying patients at the time of initial diagnosis and providing timely and aggressive interventions are currently the main challenges in treating COVID-19. There are several COVID-19 warning and scoring systems[9], such as the MuLBSTA scoring system, a mortality risk prediction model for COVID-

19 that integrates four ML algorithms[10], the National Early Warning Score and Rapid Emergency Medicine Score for ER COVID-19 patients, and NEWS+age[11,12]. To optimize patient treatment and recovery using limited healthcare resources, early detection of prognostic biomarkers is crucial in distinguishing patients who may develop severe COVID-19 and assessing their associated mortality risk during a global pandemic. A model that combines multiple variables for early prediction of the prognosis in COVID-19 patients would help allocate healthcare resources effectively and reduce mortality. In this study, we aim to develop a severe/critical COVID-19 prediction model based on imaging scores, patient clinical features, and biomarker levels (Table 1).

MATERIALS AND METHODS

Study design and study population

A retrospective analysis was used to examine the medical records of adult COVID-19 patients who were admitted to the infectious disease wards of three medical centers in Beijing, Wuhan, and Nanchang. The retrospective cohort collected primary clinical data and CT imaging data, as well as collected the patients' clinical data, including the patients' demographic data, medical history, laboratory tests after admission, inflammatory markers and cytokine levels, and CURB65 scores. All data were collected and obtained from the electronic medical record system, and if the electronic medical record system lacked relevant data records, these records were obtained by communicating with the attending physicians. This study was reviewed by the Ethics Committee of Peking University Third Hospital.

Case diagnostic criteria and clinical staging criteria

The case diagnostic criteria and clinical typing criteria included the following. All of the deceased patients were confirmed to have COVID-19 based on the pneumonia diagnosis and treatment protocol for novel coronavirus infection (trial version 7) that was issued by the National Health and Wellness Commission. 10 Confirmed cases were required to conform to the clinical manifestations in the diagnosis and treatment protocols, and pharyngeal swabs, sputum, and lower respiratory secretions were tested by real-time fluorescence RT–PCR using the Wuhan Centers for Disease Control and Prevention's 2019-nCoV nucleic acid test. The clinical typing criteria included the following: (1) Light: The clinical symptoms are mild, and no pneumonia manifestations are seen on imaging; (2) Common type: Fever and respiratory symptoms are present, and pneumonia is visible on imaging; (3) Severe disease: Any of the following are present: respiratory distress, a respiratory rate ≥ 30 breaths/min; a resting state oxygen saturation of ≤ 93%; and a PaO2/FiO2 ≤ 300 mmHg (1 mmHg = 0.133 kPa); and (4) Critical type: One of the following conditions is present: Respiratory failure requiring mechanical ventilation; shock, which may combined with other organ failure that requires ICU monitoring and treatment.

Chest CT scoring

The CT images were independently interpreted by two emergency physicians with more than 10 years of experience, and the CT images were interpreted based on the Fleischner Society definition[13]. The training of the artificial intelligence was by respiratory and radiology specialists. If the scores were inconsistent, they were reassessed, and if an agreement could not be reached, the closer score was used to calculate the mean value. A new scoring system was developed based on the previous lung CT severity score 12, which is widely used in patients with interstitial lung disease, and this scoring system was modified by experts from the departments of respiratory medicine, radiology, critical care medicine, and emergency medicine: (1) The partitioning of the lung field was performed as follows. The lung field was divided into upper, middle, and lower parts, and a total of 6 regions were portioned on the left and right sides by the plane of the tracheal bulge and the plane of inferior pulmonary veins; (2) The target lesion types were defined as follows: (a) Ground glass opacity (GGO): Widespread, blurred increased density of the lung parenchyma with visible bronchial and vascular textures; (b) Pulmonary solidity: Uniformly increased density of the lung parenchyma, obscuring the bronchial and vascular shadows within it, with bronchial inflation signs; (c) Paving stone sign: Ground glass opacity combined with lobular septa; and (d) Pavement stone sign: The combination of lobular septum thickening with a ground glass shadow. The other types of lesions were not analyzed because they were relatively rare and were noncharacteristic[6]; and (3) Scoring: The overall extent of the involvement of the lesions, the extent of the ground glass shadows, and the extent of solid lesions in each region were scored separately: (a) 0: Normal lung tissue; (b) 1: The extent of the lesions is < 25%; (c) 2: The extent of lesions is 26%-50%; (d) 3: The extent of the lesions is 51%-75%; and (e) 4: The extent of the lesions is > 75%. The regional scores were accumulated (the total scores for the overall extent of the involvement, ground glass shadows, and solid lesions were 0-24 for each region). The total score of each was 0 to 24 points. The pavement stone sign was scored as 0 or 1 for the presence or absence of this sign, and the 6 area scores were also cumulative (total score 0 to 6)[13].

Table 1 Demographics and clinical features of patients

Variable		Classification	Overall (*n* = 153)	Common (*n* = 48)	Severe/critical (*n* = 105)	*P* value
Basic information and vital signs	Age, median (IQR)		69 (66, 74)	69.0 (66.0, 74.0)	69.0 (66.0, 76.0)	0.79
Comorbidity	Sex, *n* (%)	Male	78 (50.980)	19 (39.583)	59 (56.190)	0.057
		Female	75 (49.020)	29 (60.417)	46 (43.810)	
	Heart rate, median (IQR)		90 (79, 102)	87.0 (79.0, 98.0)	91.0 (79.0, 104.0)	0.329
	Temperature, median (IQR)		36.7 (36.3, 37.1)	36.7 (36.4, 37.0)	36.7 (36.3, 37.2)	0.576
	Body mass index, mean (SD)		20.290 (9.929)	20.789 (7.825)	20.041 (10.819)	0.715
	Respiratory rate, median (IQR)		21 (20, 24)	20.0 (20.0, 22.0)	22.0 (20.0, 25.0)	*P* < 0.001
	Blood oxygen saturation, median (IQR)		94 (90, 97)	98.0 (96.0, 99.0)	92.0 (85.0, 95.0)	*P* < 0.001
	Coronary heart disease, *n* (%)	No	126 (82.353)	38 (79.167)	88 (83.810)	0.485
		Yes	27 (17.647)	10 (20.833)	17 (16.190)	
	Pulmonary disease, *n* (%)	No	124 (81.046)	37 (77.083)	87 (82.857)	0.398
		Yes	29 (18.954)	11 (22.917)	18 (17.143)	
	Diabetes, *n* (%)	No	99 (64.706)	30 (62.500)	69 (65.714)	0.699
		Yes	54 (35.294)	18 (37.500)	36 (34.286)	
Laboratory tests	Platelet, mean (SD)		225.125 (86.792)	215.563 (73.367)	229.538 (91.997)	0.359
	Neutrophil, mean (SD)		5.469 (3.729)	3.821 (1.999)	6.230 (4.080)	*P* < 0.001
	Lymphocyte, mean (SD)		0.929 (0.418)	1.028 (0.373)	0.883 (0.429)	0.047
	Hemoglobin, mean (SD)		125.151 (17.785)	117.958 (16.285)	128.471 (17.464)	*P* < 0.001
	Alanine aminotransferase, median (IQR)		24 (15, 40)	16.0 (11.0, 24.0)	27.0 (19.0, 44.0)	*P* < 0.001
	Aspartate aminotransferase, median (IQR)		29 (21, 42)	21.0 (17.0, 27.0)	36.0 (26.0, 49.0)	*P* < 0.001
	Albumin, median (IQR)		32.6 (30.1, 35.5)	35.1 (31.5, 38.2)	31.9 (29.6, 34.4)	*P* < 0.001
	Total bilirubin, median (IQR)		10.0 (7.4, 14.2)	9.5 (6.9, 12.5)	10.7 (8.2, 14.6)	0.066
	Direct bilirubin, median (IQR)		4.4 (3.3, 6.2)	3.7 (3.1, 5.1)	4.9 (3.6, 7.0)	0.005
	Lactate dehydrogenase, median (IQR)		294 (239, 398)	251.0 (224.0, 284.0)	341.0 (266.0, 464.0)	*P* < 0.001
	Urea, median (IQR)		4.8 (3.6, 6.6)	4.0 (3.2, 5.0)	5.2 (4.0, 7.8)	0.002
	Creatinine, median (IQR)		72 (59, 88)	68.0 (59.0, 80.0)	75.0 (59.0, 91.0)	0.115
	Prothrombin time, median (IQR)		14.2 (13.6, 14.9)	14.1 (13.5, 14.5)	14.3 (13.8, 15.1)	0.019
	Activated partial thromboplastin time, median (IQR)		40.0 (36.0, 44.5)	38.9 (35.6, 42.9)	40.6 (36.3, 45.4)	0.035
	Fibrinogen, mean (SD)		5.208 (1.495)	4.640 (1.236)	5.468 (1.531)	0.001
	D-Dimer, mean (SD)		3.394 (5.451)	1.827 (3.304)	4.125 (6.065)	0.003
	C-Response Protein, mean (SD)		61.199 (66.732)	24.943 (30.023)	77.583 (72.082)	*P* < 0.001
	calcitoninogen, mean (SD)		0.483 (3.484)	0.047 (0.053)	0.678 (4.177)	0.305
	Ferritin, mean (SD)		956.507 (874.540)	486.000 (328.994)	1170.374 (957.550)	*P* < 0.001

Cytokines	IL-1, mean (SD)	3.639 (5.076)	2.853 (1.351)	3.996 (6.019)	0.213
	IL-2R, mean (SD)	895.375 (630.955)	621.844 (321.241)	1019.707 (694.756)	$P <$ 0.001
	IL-6, mean (SD)	48.628 (88.255)	13.359 (15.597)	64.691 (101.986)	$P <$ 0.001
	IL-10, mean (SD)	6.464 (8.108)	3.907 (5.734)	7.626 (8.738)	0.003
	IL-8, mean (SD)	22.083 (22.814)	13.900 (15.389)	25.802 (24.600)	0.004
	TNF, mean (SD)	10.424 (8.969)	9.158 (13.597)	11.000 (5.649)	0.256
Scores	IL6/IL10, mean (SD)	9.051 (15.654)	3.848 (3.570)	11.417 (18.241)	$P <$ 0.001
	CURB65, median (IQR)	1 (1, 2)	1.0 (1.0, 1.0)	1.0 (1.0, 2.0)	0.035
	qSOFA, median (IQR)	1 (0, 1)	0.0 (0.0, 1.0)	1.0 (0.0, 1.0)	$P <$ 0.001

To understand the changes in the CT scores over time (time series), the median interval time between the recheck lung CTs was used as a cutoff point to segment the disease course time axis and to compare the differences in the lung CT scores among patients with common, severe, and critical disease at different periods within the course of the disease. The mean values of the 2 CT scores were taken within the same time period. To understand the spatial distribution characteristics (spatial sequence) of the intrapulmonary lesions, the lung fields were divided based on the aforementioned methods to compare the differences in the CT scores in the upper, middle and lower lung field regions (Table 2).

Statistical methods

Cronbach's alpha index was used to evaluate the reliability of the scores of the two reviewers. The measurement data are expressed as the median and interquartile range, and the count data are expressed as the frequency (percentage). The Mann–Whitney U test was used to evaluate the continuous variables, and the chi-square test or Fisher exact test was used to evaluate the rank variables. The Wilcoxon test or the Friedman test was used to compare two/multiple samples of interest. To evaluate the predictive validity of the CT scores, receiver operating characteristic (ROC) curves were traced, and the area under the curve (AUC) was calculated. The statistical analysis was performed using SPSS 22.0 software. MedCalc 19.1 software was used for the comparison of the AUCs of the ROC curves. All of the tests were two-sided; the significance level was set at $P < 0.05$.

RESULTS

General clinical characteristics

A cohort of 153 COVID-19 patients was included in the study, with 105 patients in severe or critical condition and 48 with common disease. The median age of the patients was 89 years and 50.98% were male. The results of the chi-square test, Mann–Whitney U test, and t test showed that there was no significant difference between the two groups in terms of basic information and vital signs, such as age, sex, heart rate, blood pressure, maximum body temperature, and body mass index. However, the respiratory rate and oxygenation index were significantly different. No significant difference was found between the two groups in terms of underlying diseases, such as coronary artery disease, pulmonary disease, and diabetes mellitus. Clinical symptoms were not significantly different between the two groups, except for dyspnea. Significant differences were found between the two groups in terms of absolute neutrophil values, hemoglobin, liver function tests, albumin, urea, blood coagulation tests, CRP, ferritin, glucose, and T3. The qSOFA score and CURB-65 score were also significantly different between the groups. Significant differences were also found in the characteristics of lung CT scores for patients with different types of COVID-19. Of the 110 patients who underwent CT scans, 114 (94.6%) had GGOs, 68 (61.9%) had solid lesions, and 43 (39.1%) had paving stone signs. Bilateral involvement was seen in 103 (93.6%) of the patients. The CT scans were performed at intervals of 3 to 25 d, with a median interval of 7 d. Disease progression was segmented by week, with the CT scores of common and severe patients peaking during the 3rd to 4th week, while the CT scores of critically ill patients progressed more rapidly, peaking during the 2nd to 3rd week. During the first week, only the GGO score differed between common and critical patients. From the second week onward, the GGO score, solid lesion score, paving stone sign score, and overall extent of involvement score differed between the patients with different degrees of criticality. The spatial distribution of the lesions showed that the upper lung region involvement extent scores were lower for common and severe patients compared to the middle and lower lung regions, while for critically ill patients, there was no statistically significant

Table 2 Characteristics of computed tomography scans

	Computed tomography scoring item	Overall (*n* = 110)	Common (*n* = 41)	Severe/Critical (*n* = 69)	*P* value
Right upper area	Crazy-paving pattern score, median (IQR)	0.000 (0.000, 0.000)	0.000 (0.000, 0.000)	0.000 (0.000, 0.000)	0.1
	Consolidation score, median (IQR)	0.000 (0.000, 0.000)	0.000 (0.000, 0.000)	0.000 (0.000, 1.000)	0.027
	GGO, median (IQR)	1.000 (1.000, 2.000)	1.000 (1.000, 1.000)	2.000 (1.000, 3.000)	0.003
	Overall lung involment score, median (IQR)	1.000 (1.000, 3.000)	1.000 (1.000, 1.000)	2.000 (1.000, 3.000)	0.006
Left upper area	Crazy-paving pattern score, median (IQR)	0.000 (0.000, 0.000)	0.000 (0.000, 0.000)	0.000 (0.000, 0.000)	0.071
	Consolidation score, median (IQR)	0.000 (0.000, 0.000)	0.000 (0.000, 0.000)	0.000 (0.000, 1.000)	0.019
	GGO, median (IQR)	1.000 (1.000, 2.000)	1.000 (0.000, 1.000)	2.000 (1.000, 2.000)	$P < 0.001$
	Overall lung involment score, median (IQR)	1.000 (1.000, 2.000)	1.000 (1.000, 1.000)	2.000 (1.000, 3.000)	$P < 0.001$
Right medium area	Crazy-paving pattern score, median (IQR)	0.000 (0.000, 0.000)	0.000 (0.000, 0.000)	0.000 (0.000, 1.000)	0.085
	Consolidation score, median (IQR)	0.000 (0.000, 1.000)	0.000 (0.000, 0.000)	0.000 (0.000, 1.000)	0.007
	GGO, median (IQR)	2.000 (1.000, 3.000)	1.000 (1.000, 2.000)	2.000 (1.000, 3.000)	0.002
	Overall lung involment score, median (IQR)	2.000 (1.000, 3.000)	1.000 (1.000, 2.000)	2.000 (2.000, 3.000)	$P < 0.001$
Left medium area	Crazy-paving pattern score, median (IQR)	0.000 (0.000, 0.000)	0.000 (0.000, 0.000)	0.000 (0.000, 1.000)	0.279
	Consolidation score, median (IQR)	0.000 (0.000, 1.000)	0.000 (0.000, 0.000)	0.000 (0.000, 2.000)	0.006
	GGO, median (IQR)	2.000 (1.000, 3.000)	1.000 (1.000, 1.000)	2.000 (1.000, 3.000)	0.001
	Overall lung involment score, median (IQR)	2.000 (1.000, 3.000)	1.000 (1.000, 2.000)	2.000 (1.000, 3.000)	$P < 0.001$
Right lower area	Crazy-paving pattern score, median (IQR)	0.000 (0.000, 1.000)	0.000 (0.000, 0.000)	0.000 (0.000, 1.000)	0.122
	Consolidation score, median (IQR)	0.000 (0.000, 1.000)	0.000 (0.000, 0.000)	0.000 (0.000, 2.000)	0.002
	GGO, median (IQR)	1.000 (1.000, 3.000)	1.000 (1.000, 2.000)	2.000 (1.000, 3.000)	0.004
	Overall lung involment score, median (IQR)	2.000 (1.000, 3.000)	1.000 (1.000, 2.000)	2.000 (1.000, 3.000)	$P < 0.001$
Left lower area	Crazy-paving pattern score, median (IQR)	0.000 (0.000, 0.000)	0.000 (0.000, 0.000)	0.000 (0.000, 0.000)	0.357
	Consolidation score, median (IQR)	0.000 (0.000, 1.000)	0.000 (0.000, 0.000)	0.000 (0.000, 1.000)	0.007
	GGO, median (IQR)	1.000 (1.000, 3.000)	1.000 (1.000, 1.000)	2.000 (1.000, 3.000)	$P < 0.001$
	Overall lung involment score, median (IQR)	2.000 (1.000, 3.000)	1.000 (1.000, 1.000)	2.000 (1.000, 3.000)	$P < 0.001$

IQR: Interquartile range.

difference in the CT scores of the upper, middle, and lower lung regions.

The machine learning-based risk factor mining for severe/critical COVID-19 disease

To explore the possible risk factors for severe/critical COVID-19 disease, this study used Lasso regression for the variable importance analysis based on machine learning, and the model parameters were as follows: cv (cross-validation fold): 10; max_iter (number of iterations): 1000; tol (convergence measure): 0.0001; alpha (L1 regularization factor): 0.01. By Lasso regression, the 10 variables with the highest importance (from highest to lowest) were found to be the blood oxygen saturation, ALT, IL-6/IL-10, consolidation score, GGO score, age, crazy-paving pattern score, qSOFA, AST, and overall lung involvement score (Figure 1).

The development and validation of a machine learning-based clinical prediction model for severe/critical COVID-19 disease

A combination of the results of variable importance analysis and other factors, such as clinical experience, age, IL-6/IL10 Levels, ALT levels, oxygen saturation, qSOFA score, and consolidation score, were selected to be included in the model. A classification task for the data sample was conducted using several machine learning models, including XGBClassifier, RandomForestClassifier, LogisticRegression, LGBMClassifier, and MLPClassifier. A forest plot displays the ROC results of each model for the prediction of severe/critical COVID-19 cases, with the error lines representing the mean and standard deviation of the ROC (Table 3). The means and standard deviations of the ROC were computed by repeating the sampling five times, with each resampled training set accounting for 20% of the overall sample and 80% of the training set. Among the models tested, the best performer in the validation set

Table 3 Comparison prediction performances of different models

	Model	AUC (95%CI)	Accuracy	Sensitivity	Specificity	PPV	NPV	F1
Mean	XGBoost	0.841 (0.690-0.987)	0.745	0.768	0.88	0.92	0.572	0.823
SD	XGBoost	0.044 (0.066-0.018)	0.052	0.122	0.16	0.098	0.169	0.033
Mean	RandomForest	0.843 (0.709-0.974)	0.731	0.698	0.975	0.988	0.554	0.809
SD	RandomForest	0.081 (0.139-0.025)	0.105	0.145	0.05	0.025	0.147	0.097
Mean	logistic	0.892 (NaN-NaN)	0.828	0.88	0.848	0.932	0.666	0.896
SD	logistic	0.069 (NaN-NaN)	0.079	0.119	0.189	0.087	0.177	0.066
Mean	LightGBM	0.813 (0.690-0.937)	0.324	0.671	0.956	NaN	0.324	NaN
SD	LightGBM	0.067 (0.098-0.038)	0.071	0.092	0.058	NaN	0.071	NaN
Mean	MLP	0.617 (0.397-0.829)	0.655	0.634	0.764	NaN	0.503	NaN
SD	MLP	0.219 (0.228-0.212)	0.162	0.326	0.172	NaN	0.099	NaN

AUC: Area under the curve; PPV: Pulse pressure variation; NPV: Nucleopolyhedroviruses.

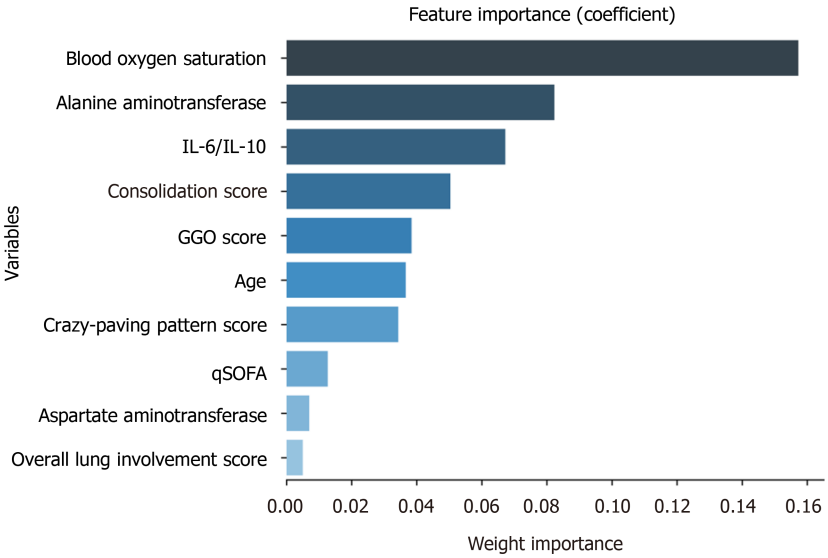

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Figure 1 Feature importance derived from the RandomForestClassifier model. The plot shows the relative importance of the variables in the RandomForestClassifier model.

was the RandomForestClassifier (sorted by AUC), while the best performer in the test set was the LogisticRegression (sorted by AUC). The performance of the algorithms was inconsistent between the training and validation sets. The RandomForestClassifier was more prone to overfitting, while the LogisticRegression appeared to be relatively more stable and was ultimately chosen for the final modeling (Figure 2).

The machine learning models' performances for predicting severe/critical COVID-19 cases

The calibration plots also confirmed good consistency between the "LogisticRegression" algorithm that was predicted and the observed actual risk of severe/critical COVID-19 (Figure 3). A further decision curve analysis was performed, and this analysis showed that the present model provides an excellent net benefit when the clinical decision threshold is between 0% and 100% (Supplementary Figure 1).

DISCUSSION

Most of the warning scoring systems only use the clinical measurements, such as the level of consciousness and the patient's vital signs or laboratory testing and do not include the imaging features

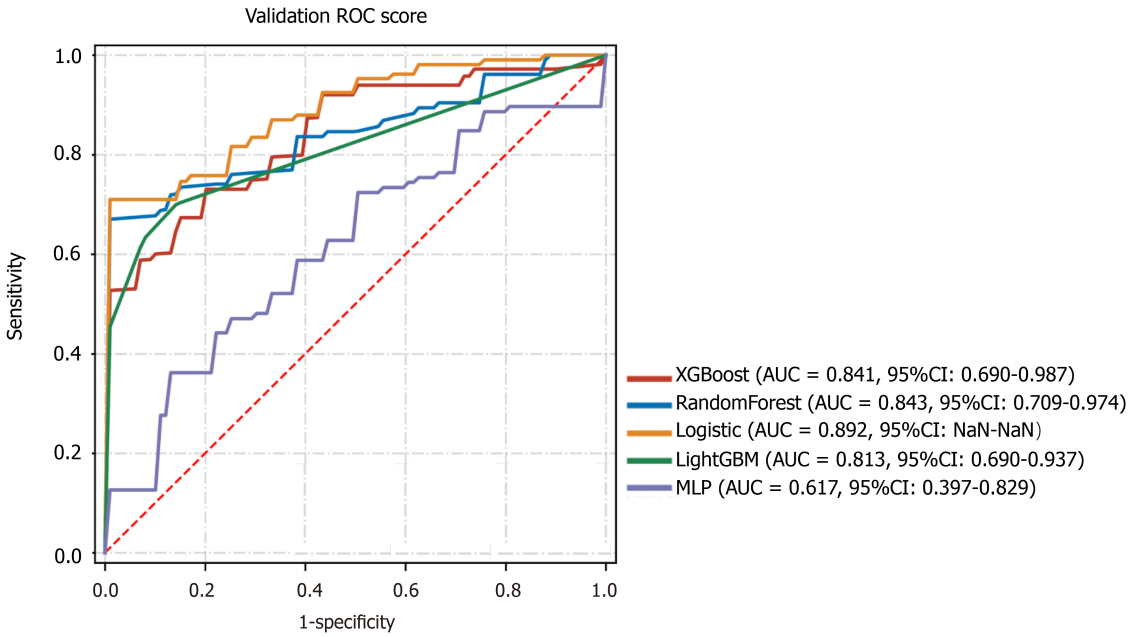

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Figure 2 The receiver operating characteristic curves of the different machine learning models that were used in predicting critical/severe coronavirus disease 2019 patents in the validation cohort.

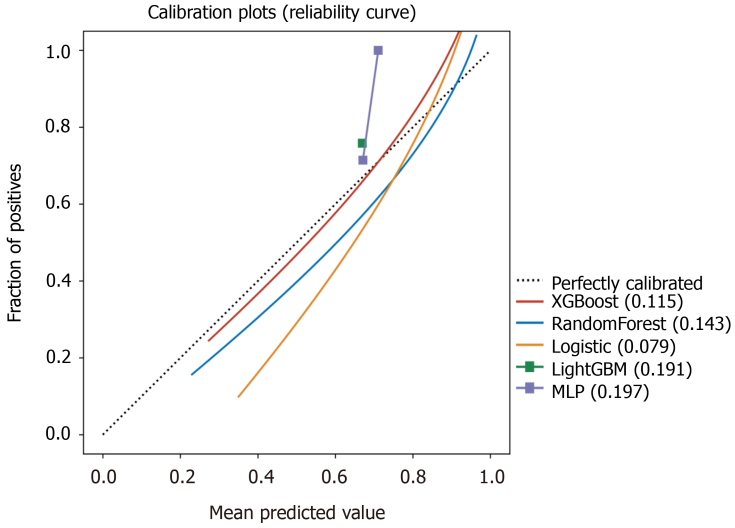

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Figure 3 Calibration plot of the different models. The model-predicted probability was plotted on the x-axis; the actual risks were plotted on the y-axis. An ideal calibration plot is indicated by a 45° diagonal line.

[1,9,10,12,14]. Since SARS-CoV-2 mainly invades the lungs, a lung CT can often be the best indicator for the severity of the disease and can provide further guidance for the development and prognosis of COVID-19 disease. Several studies have used the CT findings as important indicators to assess the prognosis of COVID-19 patients[15-21]. The prognosis of COVID-19 patients has been predicted by scoring factors, such as the presence of gross glassy shadows on CT images, bronchial and pleural involvement, the presence of a lobular septum, and the lesion morphology, distribution, and size[18, 19]. The present study differs from previous studies because the current study used a modified CT severity score that had been previously used in patients with interstitial lung disease, and this score has also been used in patients with COVID-19. This study was the first study that adjusted for complex anatomical localizations by selecting easily recognizable anatomical landmarks for the partitioning and simplification. In this study, the main manifestations of the lung CTs in patients with COVID-19 included GGOs in both lungs, thickening of the lobular septa in the form of the "pavement sign", solid changes, fibrous cords, *etc*. Multiple signs could exist simultaneously, and a "white lung" could be seen in severe cases. In contrast, pleural effusion, lymph node enlargement, cavitation, and nodular lesions

were less common. Therefore, only the typical lesion types, such as GGOs, solid lesions and paving stone signs, were selected for the modified score, and this simplified the lesion types. Furthermore, the modified imaging score was not time-consuming, and the reliability of the two reviewers' scores for each type of lesion was high. Thus, the improved scoring increased the ability of clinicians to make rapid judgments. In addition, the overall extent of the involvement score downplays the identification of the lesion type, and the upper lung regional involvement score narrows the target area. Both of these scores have a statistically similar predictive validity, as compared to the GGO score, and both of the former scores reduce the complexity and sensitivity of the assessment. Therefore, these novel scores could be a relatively simple alternative to the GGO score. Regarding the predictive value of the lung CT score, this study found that a GGO score of more than 5 on the lung CT at week 2 could be used as a significant indictor for severe COVID-19, even before the development of oxygen reserve depletion, clinical decompensation, and sudden deterioration. In conclusion, clinicians should perform a comprehensive evaluation in COVID-19 patients, which should be used in conjunction with the patient's lung CT score, in order to provide enough respiratory support to the patient as early as possible. The inclusion of the CT score in the clinical severity grading criteria may be considered in the future. In addition to the imaging findings, a variety of clinical features and laboratory indicators have been included in in the models of different studies to develop appropriate predictive models. These factors mainly included age, sex, the patient's vital signs (temperature, arterial systolic blood pressure, respiration, heart rate), and the patient's laboratory indicators (neutrophil count, platelet count, CRP, arterial partial pressure of oxygen, blood creatinine value, eGFR, serum albumin value)[16,17,20,22,23]; in addition, the patients' underlying diseases (hypertension, COPD, *etc*.) have also been included in some risk prediction models[17,23]. In this study, qSOFA, aspartate aminotransferase, oxygenation, and dyspnea were found to have a good predictive value for the prediction of patients with severe/critical COVID-19.

The qSOFA score is an important diagnostic tool for organ failure. Current studies on the role of inflammatory factors in organ failure have suggested that, compared with COVID-19 patients who were not admitted to the ICU for treatment, critically ill COVID-19 patients in the ICU have higher levels of IP-10, macrophage inflammatory protein 1A (MIP-1A), serum granulocyte colony-stimulating factor (GSCF), GCSF and TNF-α expression levels, suggesting a positive correlation between the inflammatory storm and the disease severity[5,24,25]. It is known that the levels of cytokines, including interleukin, play a crucial role in the progression of COVID-19. During an inflammatory storm, a sustained increase in the expression of proinflammatory factors, produced by the body's immune system, can exacerbate the disease progression, while anti-inflammatory factors can promote pathogen clearance and tissue repair. Monitoring the levels of both pro- and anti-inflammatory cytokines early in the course of COVID-19 is important for determining the patient's condition, treatment plan, and prognosis. Multiple studies have shown that the trends of relevant cytokines are essential for early identification and treatment of critical COVID-19 cases[5,6,24,26]. Above all, this study not only simplifies the complex anatomical location of the lesions that are seen on lung CT but also combines the findings on medical imaging with the patient's clinical features and laboratory indicators, and the inclusion of all of these factors will more accurately predict the prognosis of COVID-19 patients during the early course of the disease. In this study, there are several limitations to consider. Firstly, it is a retrospective study, which may introduce bias in the results and difficulties in the statistical analysis due to the absence of CT data from the first examination and from critical patients. Secondly, not all of the CT scans included in the analysis were high-resolution scans, which could affect the accuracy of the readings. Finally, the low proportion of deaths in the sample size limited the ability to analyze the predictive value of CT on in-hospital patient outcomes. To address these limitations, future studies could consider expanding the sample size and conducting prospective studies.In the future, it is necessary to evaluate data and perform statistics from multiple medical centers to further evaluate adult COVID-19 confirmed cases, to establish a "COVID-19 clinical-imaging database", and to systematically analyze the patients' clinical information, laboratory tests and imaging data of admitted and discharged patients with the help of imaging and histological analysis methods. These methods can also help to more accurately assess the lesion progression, establish a quantitative assessment criteria, determine the early warning signals for severe/critical COVID-19 disease, and establish a predictive model for early warning for the progression and development of severe/critical COVID-19 disease, based on the dynamic evolution of CT, and all of these factors can help in the early intervention and treatment of COVID-19 patients clinically [3,27]. In addition, the relationship between the occurrence of inflammatory storms and CT information features is currently unclear. In recent years, big data analysis technology and artificial intelligence have become important tools for evaluating the findings of CT using clinical precision judgment. By using imagingomics technology to extract high-dimensional quantitative features from the CT images of COVID-19 patients, we can conduct in-depth mining of the CT information features to evaluate the lesions, screen the CT information features with high sensitivity and specificity, and observe the dynamic evolution of the CT information features and related cytokines. It is scientifically important to further explore the mechanisms that are involved with COVID-19 disease progression and regression [28-30]. The identification of the associations between the dynamic changes in the patient's imaging and histological findings and the trends of the patient's related cytokines, the mining of the CT information features that reflect the trends in related pro/anti-inflammatory factors, and the exploration of the

potential inflammation based on the associated features in COVID-19 will all provide an important basis for an early and accurate clinical judgment. The development of these projects will provide an objective basis for the effective prevention and control of COVID-19. Validity studies that are based on chest CT should be performed, and these studies can provide strong support for the application of imaging and histological tests, especially when combined with artificial intelligence technology, in the diagnosis and treatment of COVID-19[31].

CONCLUSION

In conclusion, CT scores provide a valuable and objective measure of the progression of COVID-19 in patients. The trends of CT scores differed between common, severe, and critical patients, and monitoring these scores over time can help reduce unnecessary exposure to radiation and cost. The 2-wk CT scores of patients can also be useful in predicting disease deterioration in hospital patients with an average admission severity. Factors such as qSOFA score, aspartate aminotransferase, oxygen saturation, and dyspnea were found to be significant predictors of severe or critical COVID-19.

ARTICLE HIGHLIGHTS

Research background

coronavirus disease 2019 (COVID-19) is a global pandemic that requires early identification and intervention to reduce morbidity and mortality. Chest computed tomography (CT) score has been shown to be a factor in the diagnosis and treatment of COVID-19 pneumonia. However, there is currently a lack of effective early warning systems for severe/critical COVID-19.

Research motivation

To develop a severe/critical COVID-19 prediction model using a combination of imaging scores, clinical features, and biomarker levels.

Research objectives

To identify key factors in predicting severe/critical COVID-19 cases using improved chest CT scores and machine learning algorithms.

Research methods

The study used an improved scoring system to extract chest CT characteristics of COVID-19 patients, and considered general clinical indicators such as dyspnea, oxygen saturation, alanine aminotransferase, and aspartate aminotransferase. Lasso regression was employed to evaluate the significance of different disease characteristics.

Research results

A COVID-19 severe/critical early warning system was established using machine learning algorithms including XGBClassifier, Logistic Regression, MLPClassifier, RandomForestClassifier, and AdaBoost Classifier.

Research conclusions

The prediction model based on improved CT scores and machine learning algorithms is effective in detecting early warning signals of severe/critical COVID-19.

Research perspectives

The findings suggest that this method is a feasible solution for early detection of severe/critical COVID-19 evolution and may help reduce morbidity and mortality.

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FOOTNOTES

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ORIGINAL ARTICLE

Observational Study

Mediating effect of mindfulness level on the relationship between marital quality and postpartum depression among primiparas

Jian Yang, Xin-Zhu Lin, Qian-Wen Guo, Cheng-Ling Wang, Ren-Yan Yang, Jun-Wen Zhang, Yan Zeng

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Abstract

BACKGROUND

Postpartum depression refers to a depressive episode or depressive symptoms up to 12 mo after delivery. Trait mindfulness has presented a protective factor for postpartum depressive symptoms and proved efficient in improving relationship satisfaction among couples.

AIM

To investigate the correlations among mindfulness, marital quality, anxiety, and depression in a large city in western China during the post-corona virus infectious disease-2019 era and determine whether trait mindfulness mediates the relationship between marital quality and postpartum anxiety and depression among primiparas.

METHODS

A cross-sectional study was conducted. The self-administered questionnaire was submitted online through smartphones. The levels of mindfulness, anxiety, depression, and marital quality were respectively investigated by the mindful attention awareness scale (MAAS), the self-rating anxiety scale (SAS), the self-rating depression scale (SDS), and the marriage perception scale (MPS) in these enrolled Han and Tujia primiparas.

RESULTS

No statistical significance was observed in the prevalence of postpartum anxiety and depression, nor scores of MAAS and MPS-Total in different regions or ethnicities ($P > 0.05$). However, MPS-Marital interaction ($P < 0.05$), MPS-Family relationship (MPS-FR) ($P < 0.01$), and MPS-Marital conflict (MPS-MC) ($P < 0.01$) scores of urban primiparas were higher than those of rural primiparas. The MPS-MC score of Han primiparas was higher than that of Tujia primiparas ($P < 0.05$). Negative correlations were observed between MAAS and SAS (r = -0.457, $P < 0.01$), and MAAS and SDS (r = -0.439, $P < 0.01$). SAS has revealed a highly positive correlation with SDS (r = 0.720, $P < 0.01$) and a weak negative correlation with MPS (r = -0.200, $P < 0.05$). Besides, a weak negative correlation was observed between MAAS and MPS-MC (r = -0.184, $P < 0.05$), and a weak positive correlation was noticed between SAS and MPS-MC (r = -0.225, $P < 0.01$). Mediation analysis demonstrated a full mediation effect of mindfulness level on the relationship between MPS-FR and postpartum anxiety ($P < 0.05$, 95%CI: -0.384 to 0.033), MPS-MC and postpartum anxiety ($P < 0.01$, 95%CI: 0.027-0.193), MPS-FR and postpartum depression ($P < 0.05$, 95%CI: -0.365 to 0.031), and MPS-MC and postpartum depression ($P < 0.01$, 95%CI: 0.022-0.206).

CONCLUSION

Mindfulness demonstrates negative correlations with marital conflict, postpartum anxiety and depression, and it may have cross-ethnic and trans-regional characteristics. Although the mindfulness levels have revealed no significant mediating effect between the total score of marital quality and postpartum depression in this study, it demonstrates a full mediation effect on the relationships between family relationships, marital conflict, and postpartum anxiety and depression.

Key Words: Mediating effect; Mindfulness; Marital quality; Postpartum depression; Postpartum anxiety; Primiparas

Core Tip: Postpartum depression is a common mental complication during the postpartum period. This cross-sectional observational study aimed to investigate the correlations among mindfulness, marital quality, anxiety, and depression in different regions and ethnicities in a large city in western China during the post-corona virus infectious disease-2019 era and determine whether trait mindfulness mediates the relationship between marital quality and postpartum anxiety and depression among primiparas. Mindfulness is closely related to the mental health conditions of primiparas, and it may have cross-ethnic and trans-regional characteristics. Although the mindfulness levels revealed no significant mediating effect between the total score of marital quality and postpartum depression in this study, it demonstrated a full mediation effect on the relationship between family relationships, marital conflict, and postpartum anxiety and depression. Our findings can provide a reference for further application of mindfulness in Chinese postpartum mental disorders.

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INTRODUCTION

The number and proportion of disability-adjusted life-years (DALYs) due to mental disorders have increased since 1990[1], and depressive and anxiety disorders have been listed among the top three causes of DALYs in females[2]. Postpartum depression, a common mental complication during the postpartum period, refers to a depressive episode or depressive symptoms up to 12 mo after delivery[3,4]. Postpartum depression may lead to long-term cognitive impairment, emotional difficulties, and behavioral problems in both mother and child[5], and its prevalence in China has presented a significantly increasing trend in recent years[6]. Therefore postpartum depression has been a hot spot for research and intervention[6,7].

Each individual's mental health, including that of a primipara, has always been influenced by unique social and environmental factors[8], and accumulating evidence suggests that marital quality plays an essential role in postpartum depression[9,10]. Meanwhile, trait mindfulness has proved efficient in improving relationship satisfaction among couples[11].

Mindfulness refers to moment-to-moment awareness, and it is based on our inner capacities for relaxation, paying attention, awareness, and insight[12]. Mindfulness helps promote relief from depressing thoughts and feelings, and mindfulness-based therapy has been developed as an effective psychological intervention for depressive individuals[13]. Moreover, trait mindfulness has presented a protective factor for postpartum depressive symptoms[14]. However, there is scant evidence on the mediating effect of mindfulness levels on the relationship between marital quality and postpartum depression among primiparas.

The prevalence of postpartum depression across Mainland China varied in different provinces[3,6], and southwest China has been among the regions suggested to pay more attention[3]. Thus, this observational study aims to investigate the mediating effect of mindfulness levels on relationships between marital quality and postpartum depression among primiparas in southwestern China and provide a reference for future application of mindfulness in Chinese postpartum mental disorders.

MATERIALS AND METHODS

Ethics statement

Ethics approval for the study was granted by the Ethics Committee of the Second Affiliated Hospital of Chongqing Medical University (2021-288). All participants provided informed consent.

Study design and participants

Participants in this cross-sectional study were a subset of the Chongqing Science and Health Joint Medical Research Project (No. 2021MSXM034), with an estimated sample size of 120 subjects[15]. Two tertiary hospitals from a large city in western China were enrolled in this study, including one from a developed main urban area and the other from an underdeveloped Tujia ethnic area. Primiparas who gave birth in or visited these hospitals within 4 wk postpartum were randomly sampled and consecutively recruited between November 2021 and June 2022, with no compensation or honoraria. Primiparas with different lifestyles and cultural customs have no difference in access to medical services. The inclusion criteria were: (1) Primiparas aged from 18 to 40 years old; (2) proficiency in spoken Chinese; (3) good compliance with completing online questionnaires; and (4) providing informed consent.

The exclusion criterion was as follows: (1) Severe physical disease; (2) gestational hypertension or gestational diabetes mellitus; (3) premature delivery or multiple pregnancies; (4) mental disorder or personality disorder; (5) previous history of labor or labor induction; (6) previous mindfulness training; and (7) non-local resident. A total of 132 primiparas were initially included. All enrolled participants underwent an initial interview to confirm their eligibility for this study, during which seven primiparas were excluded. Three primiparas withdrew from the study, and one primipara returned incomplete questionnaires. Thus, 121 individuals were eventually enrolled (71 from developed and 50 from underdeveloped areas). All participants received a full explanation of this study from the researchers and volunteered to participate. After signing the informed consent, the questionnaire was completed and submitted online through smartphones. Socio-demographic characteristics were obtained through interviews and personal reports. The levels of mindfulness, anxiety, depression and marriage perception were respectively investigated in these enrolled primiparas. All data is encrypted to ensure privacy.

Instruments

The mindful attention awareness scale (MAAS): MAAS is an effective and reliable instrument for measuring mindfulness levels[16,17]. The MAAS score has proven a significant and inverse association with various mental health indicators, including depression, anxiety, stress, hostility, and negative affect, and also a positive relationship with psychological and physical health, including optimism, self-esteem, self-control, and life satisfaction, in contrast[16,18]. The Chinese version of MAAS presents a Cronbach's α coefficient of 0.89 and a two-week test-retest reliability of 0.82, indicating good reliability, similar results to the original English version, and acceptable psychometric quality in the Chinese population[19].

The self-rating anxiety scale (SAS) and self-rating depression scale (SDS): Depression and anxiety were assessed *via* the SDS and SAS[20,21]. The reliability and validity of SDS and SAS have been examined in the Chinese population[22,23]. Higher scores of SDS or SAS indicate a higher level of depression or anxiety, respectively. According to the Chinese norm, a score of 50 or above indicates anxiety or depression[24].

The marriage perception scale (MPS): MPS is an effective tool to assess the perception of marriage in urban and rural China, and MPS takes participants' subjective evaluations and feelings about their own marital life as the leading indicator of marital quality evaluation. MPS presents a Cronbach's α coefficient of 0.889 and a four-week test-retest reliability of 0.758, indicating good reliability and stability [25].

Statistical analysis

Statistical analysis was performed using SPSS 26.0 software (IBM SPSS 26.0, SPSS Inc.) and SPSSAU (version 22.0, online application software, https://www.spssau.com). Continuous variables were compared *via* the *t*-test or Wilcoxon test, and categorical variables were compared using Chi-square tests or Fisher exact tests. Correlation analysis was performed using Pearson correlation analysis, and the mediating effects were tested by the bootstrap method. Statistical significance was considered if $P < 0.05$.

RESULTS

Descriptive analysis

The study sample consisted of 121 participants, among which 71 (58.68%) were from rural areas, and 61 (50.41%) were Tujia primiparas. Age ranged from 18 to 40, with a mean of 27.26 years (SD = 3.60). Sixty-eight primiparas (56.20%) have an educational experience of junior college or below, while 53 primiparas (43.80%) have experienced undergraduate or above. These results are summarized in Table 1.

Anxiety and depression levels of primiparas in different areas and ethnicities

Anxiety and depression presented in 19 (15.70%) and 62 (51.24%) primiparas, respectively, among which 10 (20.00%) of anxiety and 33 (66.00%) of depression were in urban primiparas, 9 (12.68%) of anxiety and 29 (40.85%) of depression in rural primiparas, while 9 (15.00%) of anxiety and 33 (55.00%) of depression in Han ethnicity, 10 (16.39%) of anxiety and 29 (47.54%) of depression in Tujia ethnicity. No statistical significance was observed in the prevalence of postpartum anxiety and depression in different regions or ethnicities (Table 2).

Mindfulness and marital quality of primiparas in different regions and ethnicities

No significant differences were observed in MAAS or MPS-Total between different regions ($P > 0.05$); however, MPS-Marital interaction (MPS-MI) ($P < 0.05$), MPS-Family relationship (MPS-FR) ($P < 0.01$), and MPS-Marital conflict (MPS-MC) ($P < 0.01$) scores of urban primiparas were significantly higher than those of rural primiparas (Table 3). In contrast, no significant differences between Han and Tujia primiparas were noticed in MAAS, MPS-Total, MPS-MI, or MPS-FR ($P > 0.05$); however, the MPS-MC score of Han primiparas was higher than that of Tujia primiparas ($P < 0.05$) (Table 4).

Correlations among mindfulness, postpartum depression, postpartum anxiety, and marital quality

Significant but moderate negative correlations were observed between MAAS and SAS (r = -0.457, $P < 0.01$), and MAAS and SDS (r = -0.439, $P < 0.01$). SAS has revealed a highly positive correlation with SDS ($r = 0.720$, $P < 0.01$), and a weak negative correlation with MPS (r = -0.200, $P < 0.05$). Besides, a weak negative correlation was observed between MAAS and MPS-MC (r = -0.184, $P < 0.05$), and a weak positive correlation was noticed between SAS and MPS-MC (r = -0.225, $P < 0.01$) (Table 5).

Mediating effect of mindfulness level

MPS-MI, MPS-FR, and MPS-MC were analyzed as independent variables X1, X2, X3, postpartum anxiety and depression as dependent variables Y1, Y2, and mindfulness level as mediating variable M. Three types of mediation analysis model are established: Firstly, the regression model of independent variable X (X1, X2, X3) and dependent variable Y (Y1, Y2); secondly, the regression model of independent variable X (X1, X2, X3) and mediating variable M; thirdly, the regression model of the independent variable X (X1, X2, X3) and the mediating variable M together with the dependent variable Y (Y1, Y2) (Figure 1). Mediation analysis demonstrated a full mediation effect of mindfulness level on the relationships between MPS-FR and postpartum anxiety ($P < 0.05$, 95%CI: -0.384 to 0.033), MPS-MC and postpartum anxiety ($P < 0.01$, 95%CI: 0.027-0.193) (Table 6), MPS-FR and postpartum depression ($P < 0.05$, 95%CI: -0.365 to 0.031), and MPS-MC and postpartum depression ($P < 0.01$, 95%CI: 0.022-0.206) (Table 7).

Table 1 Demographic characteristics of the sample

Variables	*n*	%
Age (yr)		
18-25	37	30.58
26-30	66	54.54
31-35	14	11.57
36-40	4	3.31
Regions		
Urban	50	41.32
Rural	71	58.68
Ethnicity		
Han	60	49.59
Tujia	61	50.41
Educational Status		
Junior high school or below	13	10.74
Senior high school	23	19.01
Junior college	32	26.45
Undergraduate	49	40.5
Postgraduate	4	3.3

Table 2 Anxiety and depression levels of primiparas in different regions and ethnicities

	SAS (*n*)		χ^2	*P* value	SDS (*n*)		χ^2	*P* value
	Normal	Abnormal			Normal	Abnormal		
Urban	40	10	0.084	0.772	17	33	0.674	0.412
Rural	62	9			42	29		
Han	41	9	0.044	0.833	17	33	0.674	0.412
Tujia	61	10			42	29		

SAS: Self-rating anxiety scale; SDS: Self-rating depression scale.

DISCUSSION

The prevalence of postpartum depression has been affected by numerous factors, including marital quality, life stress, social support, income, and region[9]. This study of Han and Tujia primipara in a large southwestern city of China has demonstrated the prevalence of postpartum anxiety and depression as 15.70% and 51.24%, respectively. The prevalence of postpartum anxiety among primiparas in Chongqing is similar to the previous data from other Chinese cities[26]. However, the elevation in the prevalence of postpartum depression may be related to economic and regional differences, varied instruments and cut-off scores, selection bias due to voluntary enrollment, and the research period during corona virus infectious disease-2019 (COVID-19) rather than the non-pandemic period[3,27]. This study has provided a reference for currently limited data on postpartum anxiety and depression among Tujia primiparas and comparisons with Han primiparas. This study revealed no statistical significance in the prevalence of postpartum anxiety and depression between Tujia and Han ethnicities, while another survey before COVID-19 presented varied incidences between Kazak and Han women[28]. These differences may be related to different regions, comparisons between ethnicities, instruments used, and research periods. The prevalence of postpartum anxiety and depression in this study also suggests that mental disorders are postpartum complications worthy of attention and timely interventions.

Table 3 Levels of mindful attention awareness scale and marriage perception scale in different regions

	Region	mean ± SD	*t* value	*P* value
MAAS	Urban	63.86 ± 11.86	-0.416	0.678
	Rural	64.76 ± 11.63		
MPS-Total	Urban	62.78 ± 12.85	1.611	0.11
	Rural	58.35 ± 17.38		
MPS-MI	Urban	59.22 ± 9.81	2.626	0.01
	Rural	54.24 ± 1059		
MPS-FR	Urban	30.66 ± 4.22	3.965	< 0.001
	Rural	26.8 ± 6.47		
MPS-MC	Urban	27.1 ± 4.29	3.785	< 0.001
	Rural	22.69 ± 8.38		

MPS: Marriage perception scale; MAAS: Mindful attention awareness scale; MPS-MI: MPS-Marital interaction; MPS-FR: MPS-Family relationship; MPS-MC: MPS-Marital conflict.

Table 4 Levels of mindful attention awareness scale and marriage perception scale in different ethnicities

	Ethnicity	mean ± SD	*t* value	*P* value
MAAS	Han	64.6 ± 10.96	0.349	0.727
	Tujia	63.85 ± 12.5		
MPS-Total	Han	59.58 ± 14.71	-0.227	0.821
	Tujia	60.24 ± 16.67		
MPS-MI	Han	56.65 ± 10.62	-0.447	0.656
	Tujia	55.78 ± 10.62		
MPS-FR	Han	28.88 ± 5.5	0.975	0.332
	Tujia	27.81 ± 6.45		
MPS-MC	Han	25.95 ± 5.99	1.997	0.048
	Tujia	23.36 ± 8.01		

MPS: Marriage perception scale; MAAS: Mindful attention awareness scale; MPS-MI: MPS-Marital interaction; MPS-FR: MPS-Family relationship; MPS-MC: MPS-Marital conflict.

Previous studies have paid little attention to the influence of cultural differences in different regions and ethnicities in China on mindfulness levels. According to the results of this study, there is no statistically significant difference in trait mindfulness among different regions and ethnicities, which indicates that trait mindfulness may have cross-ethnic and trans-regional characteristics. Thus, further research in this field is necessary. This study has demonstrated significant negative correlations between mindfulness levels and postpartum anxiety and depression, which suggests trait mindfulness is closely related to mental health conditions of primiparas. Previous studies have also reached the same conclusion[29]. This study also shows that the trait mindfulness of primipara has no significant correlation with the overall score of marital quality. However, mindfulness negatively correlates with the marital conflict factor in marital quality, while marital conflict is positively correlated with postpartum anxiety. That is, the higher the level of mindfulness, the less marital conflict, and the lower the level of anxiety, the less marital conflict. We consider that the role of mindfulness in reducing marital conflict is related to its benefits in increasing happiness and relationship satisfaction[30].

Although the mindfulness levels revealed no significant mediating effect between the total score of marital quality and postpartum depression in this study, it demonstrated a full mediation effect on the relationships between family relationships, marital conflict, and postpartum anxiety and depression. Studies have shown that primiparity and good family relations, social support, and economic conditions are positive factors for the good quality of life of pregnant and postpartum women[31]. However, in the

Table 5 Correlations among mindfulness, postpartum depression, postpartum anxiety, and marital quality

		MAAS	SAS	SDS	MPS	MPS-MI	MPS-FR	MPS-MC
MAAS	Correlation coefficient	1	-0.457[b]	-0.439[b]	0.123	0.1	0.802	-0.184[a]
	N		121	121	121	121	121	121
SAS	Correlation coefficient		1	0.720[b]	-0.200[a]	-0.107	-0.066	0.225[a]
	N			121	121	121	121	121
SDS	Correlation coefficient			1	-0.157	-0.082	-0.069	0.164
	N				121	121	121	121

[a]$P < 0.05$.
[b]$P < 0.01$.
SAS: Self-rating anxiety scale; SDS: Self-rating depression scale; MPS: Marriage perception scale; MAAS: Mindful attention awareness scale; MPS-MI: MPS-Marital interaction; MPS-FR: MPS-Family relationship; MPS-MC: MPS-Marital conflict.

Table 6 Mediating effect of mindfulness level on marital quality and postpartum anxiety (*n* = 121)

Mediating relationship	c (Total effect)	a	b	a × b (ME value)	a × b (Boot SE)	a × b (*z* value)	a × b (*P* value)	a × b (95% Boot CI)	c' (Direct effect)
MPS→MAAS→SAS	-0.100[d]	0.091	-0.297[e]	-0.027	0.046	-0.592	0.554	-0.146-0.029	-0.073
MPS-MI→MAAS→SAS	-0.083	-0.304	-0.296[e]	0.09	0.08	1.128	0.259	-0.038-0.273	-0.173
MPS-FR→MAAS→SAS	-0.073	0.772[d]	-0.296[e]	-0.228	0.105	-2.182	0.029	-0.384-0.033	0.155
MPS-MC→MAAS→SAS	0.285[e]	-0.408[e]	-0.296[e]	0.121	0.042	2.84	0.005	0.027-0.193	0.164

[d]$P < 0.05$.
[e]$P < 0.01$.
a: Represents the regression coefficient of X to M; b: Represents the regression coefficient of M to Y; c: Represents the regression coefficient of X to Y, namely the total effect; c': Represents the regression coefficient of X to Y (when there is mediating variable M in the model), namely the direct effect; SAS: Self-rating anxiety scale; SDS: Self-rating depression scale; MPS: Marriage perception scale; MAAS: Mindful attention awareness scale; MPS-MI: MPS-Marital interaction; MPS-FR: MPS-Family relationship; MPS-MC: MPS-Marital conflict.

Table 7 Mediating effect of mindfulness level on marital quality and postpartum depression (*n* = 121)

Mediating relationship	c (Total effect)	a	b	a × b (ME value)	a × b (Boot SE)	a × b (*z* value)	a × b (*P* value)	a × b (95% Boot CI)	c' (Direct effect)
MPS→MAAS→SDS	-0.113	0.091	-0.414[e]	-0.038	0.044	-0.855	0.392	-0.143-0.026	-0.076
MPS-MI→MAAS→SDS	-0.034	-0.304	-0.413[e]	0.125	0.078	1.615	0.106	-0.039-0.267	-0.159
MPS-FR→MAAS→SDS	-0.204	0.772[d]	-0.413[e]	-0.319	0.101	-3.166	0.002	-0.365-0.031	0.115
MPS-MC→MAAS→SDS	0.317[d]	-0.408[e]	-0.413[e]	0.169	0.047	3.597	< 0.001	0.022-0.206	0.149

[d]$P < 0.05$.
[e]$P < 0.01$.
a: Represents the regression coefficient of X to M; b: Represents the regression coefficient of M to Y; c: Represents the regression coefficient of X to Y, namely the total effect; c': Represents the regression coefficient of X to Y (when there is mediating variable M in the model), namely the direct effect; SAS: Self-rating anxiety scale; SDS: Self-rating depression scale; MPS: Marriage perception scale; MAAS: Mindful attention awareness scale; MPS-MI: MPS-Marital interaction; MPS-FR: MPS-Family relationship; MPS-MC: MPS-Marital conflict.

years since the COVID-19 outbreak, the worldwide prevalence of postpartum depression has presented a significantly increasing trend due to numerous potential causes, including disease-related stress and anxiety and lack of social support[6,27]. The relative decline in social support due to decreased social interaction and the recent downturn in economic conditions during the post-COVID-19 era have made good marital quality and relationships increasingly important for primiparas' emotional stability and quality of life. Distress from intimate relationships has already been proven as a causal risk factor for depression[32], while close marital or cohabiting relationships have assisted in lower depression rates

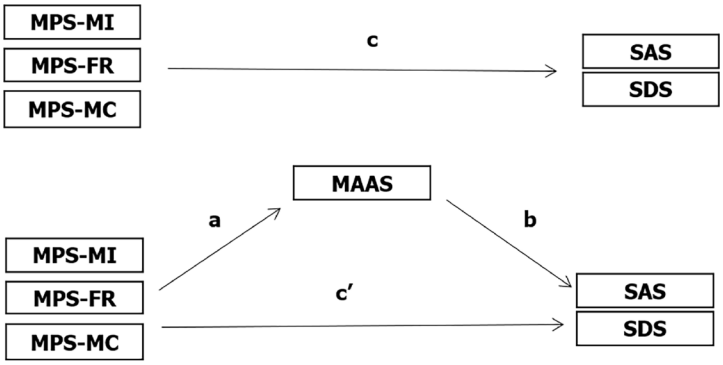

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Figure 1 Integrative model for the mediating role of the mindfulness level in the relationship between marital quality and postpartum mental disorders among primiparas. a: Represents the regression coefficient of X to M; b: Represents the regression coefficient of M to Y; c: Represents the regression coefficient of X to Y, namely the total effect; c': Represents the regression coefficient of X to Y (when there is mediating variable M in the model), namely the direct effect. MPS: Marriage perception scale; MAAS: Mindful attention awareness scale; SAS: Self-rating anxiety scale; SDS: Self-rating depression scale; MPS-MI: MPS-marital interaction; MPS-FR: MPS-Family relationship; MPS-MC: MPS-Marital conflict.

during the COVID-19 pandemic[33]. Mindfulness is a protective factor against depression, anxiety, and other psychological distress in the post-COVID-19 era[34]. Mindfulness may affect marital satisfaction by regulating psychological distress, emotional regulation, empathy, marital intimacy, and positive emotions[35], and higher mindfulness has presented an association with higher levels of happiness and reduced anxiety and depression symptoms through a connection with both a sense of purpose in life and positive outcomes[36]. Moreover, mindfulness has demonstrated benefits in promoting general health among couples in China[37], and smartphone-based mindfulness training has been proven effective in improving perinatal depression for those with a potential risk of depression[38]. Although higher trait mindfulness may not lead to better emotional recognition, it was positively associated with cognitive empathy and improved emotional skills[39]. In addition, the previous study has indicated that trait mindfulness can increase relationship satisfaction in couples by impacting their forgiving ability [11]. The above effects of mindfulness may be the potential reasons for mindfulness's positive full mediation effect on the relationship between family relationships, marital conflict, and postpartum anxiety and depression.

This study had some limitations. First, voluntary participation may have led to a selection bias, and self-administered questionnaires may also lead to a reporting bias. Second, this was a cross-sectional observational study, and further prospective studies are required to confirm the current findings. Third, although the results revealed a cross-ethnic characteristic of mindfulness, more participants from different ethnicities and regions need to be recruited in future studies to testify to current findings.

CONCLUSION

Mindfulness is closely related to the mental health conditions of primiparas due to negative correlations with both postpartum anxiety and depression, and it may have cross-ethnic and trans-regional characteristics. Mindfulness is also negatively correlated with marital conflict, while marital conflict is positively correlated with postpartum anxiety. Although the mindfulness levels have revealed no significant mediating effect between the total score of marital quality and postpartum depression in this study, it demonstrates a full mediation effect on the relationships between family relationships, marital conflict, and postpartum anxiety and depression.

ARTICLE HIGHLIGHTS

Research background

Postpartum depression is a common mental complication during the postpartum period, and it may lead to long-term cognitive impairment, emotional difficulties, and behavioral problems in both mother and child. Trait mindfulness has proved efficient in improving relationship satisfaction among couples, while marital quality is essential in postpartum depression.

Research motivation

This manuscript investigates the correlations among mindfulness, marital quality, anxiety, and

depression in different regions and ethnicities in a large city in western China during the post-corona virus infectious disease-2019 era and whether trait mindfulness mediates the relationship between marital quality and postpartum anxiety and depression among primiparas. Our findings can provide a reference for further application of mindfulness in Chinese postpartum mental disorders.

Research objectives

This observational study aims to investigate the mediating effect of mindfulness levels on relationships between marital quality and postpartum depression among primiparas in southwestern China and provide a reference for the future application of mindfulness in Chinese postpartum mental disorders.

Research methods

This cross-sectional study was conducted in Chongqing, China, from November 2021 and June 2022. The self-administered questionnaire was completed and submitted online through smartphones. The levels of mindfulness, anxiety, depression, and marital quality were respectively investigated by the mindful attention awareness scale, the self-rating anxiety scale, the self-rating depression scale, and the marriage perception scale in these enrolled Han and Tujia primiparas. In contrast, previous studies have paid little attention to the influence of cultural differences in different regions and ethnicities in China on mindfulness levels.

Research results

This observational study found no statistically significant difference in trait mindfulness among different regions and ethnicities. Significant negative correlations have been observed between mindfulness levels and postpartum anxiety and depression. The marriage perception scale (MPS)-marital Interaction, MPS-family relationship (FR), and MPS-marital conflict (MC) scores of urban primiparas were higher than those of rural primiparas. Mediation analysis demonstrated a full mediation effect of mindfulness level on the relationship between MPS-FR and postpartum anxiety, MPS-MC and postpartum anxiety, MPS-FR and postpartum depression, and MPS-MC and postpartum depression.

Research conclusions

Mindfulness is closely related to the mental health conditions of primiparas due to negative correlations with both postpartum anxiety and depression, and it may have cross-ethnic and trans-regional characteristics. Mindfulness is also negatively correlated with marital conflict, while marital conflict is positively correlated with postpartum anxiety. This study demonstrates a full mediation effect on the relationships between family relationships, marital conflict, and postpartum anxiety and depression. Therefore, attempts can be made to improve postpartum anxiety and depression by increasing levels of mindfulness.

Research perspectives

Further prospective studies with more participants from different ethnicities and regions are required in future studies to testify to current findings.

FOOTNOTES

Author contributions: Zeng Y designed and supervised the research; Lin XZ, Guo QW, Wang CL, and Yang RY enrolled participants and performed the data collection and initial analysis; Yang J and Zhang JW analyzed and interpreted the data; Yang J performed the literature search and drafted the initial manuscript; Zeng Y and Zhang JW revised the final manuscript; All authors have read and approved the final manuscript.

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ORIGINAL ARTICLE

Observational Study

Ferric carboxymaltose for anemia in Crohn's disease patients at a tertiary center: A retrospective observational cohort study

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Abstract

BACKGROUND

Although the gastrointestinal tract is the most affected by Crohn's disease (CD), the condition triggers other consequent manifestations, and iron deficiency anemia (IDA) is one of the most common. Intravenous (IV) iron replacement is currently available through several drugs, such as ferric hydroxide sucrose and ferric carboxymaltose (FCM). However, the clinical management of these conditions can be challenging.

AIM

To elucidate the drug's effectiveness, the present study analyzed, through medical records, the clinical and epidemiological data of a cohort of patients with active CD who received IV FCM for the IDA treatment.

METHODS

This retrospective observational study included 25 patients with active CD, severe anemia, and refractory to previous conventional treatments. Patients were evaluated two times: During the last treatment with ferric hydroxide sucrose and treatment with FCM.

RESULTS

After treatment with FCM, parameters of IDA assessment significantly improved, serum hemoglobin (Hb) levels increased in 93% of patients ($P < 0.0001$), and in

44%, there was an increase of ≥ 2 g/dL in a single application. In addition, 86% of the patients showed an increase in serum iron ($P < 0.0001$) and ferritin ($P = 0.0008$) and 50% in transferrin saturation ($P = 0.01$). The serum iron levels at baseline showed a negative association with the ileal and colonic CD and use of biologics and a positive association with patients who developed CD later in life after the age of 40 (A3) and with a stenosing (B2) and fistulizing (B3) phenotype. The values of Hb and hematocrit after ferric hydroxide sucrose treatment remained similar to those found before treatment.

CONCLUSION

This study demonstrated that FCM is an important therapeutic strategy for treating IDA in CD patients, achieving satisfactory results in refractory cases.

Key Words: Ferric carboxymaltose; Iron deficiency anemia; Crohn's disease; Inflammatory bowel disease; Anemia; Clinical management

Core Tip: In this observational cohort study, treatment with a single dose of ferric carboxymaltose demonstrated a significant improvement in the hematological parameters evaluated for the treatment of iron deficiency anemia in Crohn's disease patients at a tertiary center of a developing country. These results may contribute to guiding clinical treatment of this condition, mainly in cases of refractoriness to ferric hydroxide sucrose.

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INTRODUCTION

Crohn's disease (CD) is an inflammatory bowel disease (IBD) characterized by a chronic inflammatory disorder of the gastrointestinal tract[1,2]. Although the gastrointestinal tract is the most affected section in CD, the affection may occur under other manifestations[3,4], such as anemia, among the most common in IBD[5-7]. This condition is commonly defined by the World Health Organization (WHO) as when hemoglobin (Hb) is below average values (less than 12 g/dL in women and 13 g/dL in men)[8]. Its prevalence varies widely, depending on the evaluated CD patients (hospitalized or outpatients).

Iron deficiency anemia (IDA) is usually determined by a negative balance in serum iron levels, where more iron is lost than is consumed in the diet[9]. In CD patients, chronic blood loss from the ulcerated intestinal mucosa associated with diarrhea, decreased iron intake due to dietary restriction, and deficiency in transluminal iron absorption during disease activity plays an important role in causing iron deficiency[10]. Erythropoiesis and iron metabolism may also be affected by increased serum hepcidin levels in high systemic inflammation, impairing dietary iron absorption and resulting in low serum iron levels[11].

Treatment of IDA aims to increase levels of Hb, serum ferritin (s-ferritin), and transferrin saturation (TSAT) levels above the lower threshold of normal to restore iron stocks to prevent recurrent anemia and not just to restore the short-term hematopoietic state[10]. Oral iron supplementation is usually the first choice for treatment, but intestinal absorption in CD patients can be compromised by the activity of the inflammatory process, which limits the effectiveness of treatment[3,12]. In addition, unabsorbed iron results in increased clinical activity in IBD patients due to gastrointestinal side effects, decreasing treatment adherence[13,14]. On the other hand, administering intravenous (IV) iron has helped in the correction of IDA of these patients and the maintenance of iron stocks in a faster and more prolonged response to treatment. Moreover, IV iron administration avoids gastrointestinal side effects, positively influencing treatment adherence and consequently improving quality of life[15,16].

Currently, IV iron replacement for treating IDA is available through several drugs distinguished by their complex chemistry, such as iron hydroxide sucrose and iron dextran[17]. Recent pharmacology progress has led ferric carboxymaltose (FCM) to correct the IDA through its pharmacokinetic characteristics[18,19]. FCM has a robust molecular structure containing stable iron in the form of a non-dextran iron complex with an iron hydroxide core (III) with a carbohydrate ligand. The structure is similar to ferritin's, allowing for iron absorption without releasing free iron in the body. Therefore, administration

can be performed in high doses (with a maximum dose of up to 1000 mg) in a safe and clinically well-tolerated manner[20,21]. Given the above, this study was designed to evaluate the effectiveness of FCM in treating IDA in CD patients in a tertiary center in Brazil, where IBD has become increasingly frequent, mainly in the last two decades[22].

MATERIALS AND METHODS

Study design and Study population

In this observational retrospective cohort study, 25 patients with active CD who were followed at the IBD Unit of the Clinical Hospital of the University of Campinas (Unicamp) were included sequentially from October 2014 to November 2021. The patient's clinical information was evaluated through outpatient database electronic records. Disease activity was determined by the CD Activity Index (CDAI), CD Endoscopic Index of Severity (CDEIS), magnetic resonance imaging enterography, and clinical and laboratory exams.

All patients presented severe anemia (Hb ≤ 10 g/dL and hematocrit < 41% for men and < 36% for women), according to the WHO[8], and they were refractory to previous conventional treatments. Iron deficiency was determined by TSAT < 20%, ferritin ≤ 100 ng/mL, and serum iron < 60 μg/dL.

Clinical characteristics and laboratory results were collected twice from the patient's past clinical history: During the previous treatment with ferric hydroxide sucrose (a subgroup of the total cohort) and the therapy with FCM.

Analysis of the treatment effect after ferric carboxymaltose and ferric hydroxide sucrose

All laboratory parameters were evaluated before and after treatment with a single IV administration of FCM (500 mg) and after treatment with IV ferric hydroxide sucrose to elucidate the effectiveness of medication in this group of patients. The primary analysis parameters for anemia correction were Hb ≥ 12 g/dL in women and ≥ 13 g/dL in men or an increase of Hb ≥ 1 g/dL. Secondary analyses included increased serum levels of iron, s-ferritin, and TSAT.

Statistical analysis

All results are reported as the median ± SEM. The D'Agostino & Pearson and Shapiro-Wilk tests were used to investigate whether the data followed a normal *Gaussian* distribution ($P > 0.1$). The data were analyzed using Person's χ^2 and paired *t*-test, Wilcoxon matched pair test or Mann-Whitney Test. Data were analyzed using GraphPad Prism® 8, with a critical *P*-value of 5%. Finally, univariate and multiple regression analyses using generalized linear models were performed to investigate the association of the hematological parameters with the clinical and demographic characteristics of the patients. For this performance, the significant variables or the ones that adjusted other variables < 0.20 were maintained in multiple models, and data were analyzed using Stata® 14, with a critical value of 5%.

RESULTS

Patient characteristics and clinical outcomes

The clinical and demographic characteristics of the entire cohort are reported in Table 1. A total of 25 CD patients were included in the study, 12 males (48%) and 13 females (52%), with a median age of 37 (20-67) years. The median duration of CD was 144 (6-312) mo. According to the Montreal classification, one patient was diagnosed before the age of 16 years (A1, 4%), 22 patients between 17 and 40 years (A2, 88%), and 2 patients over 40 years old (A3, 8%). Five patients had terminal ileal location (L1, 20%), 4 colonic location (L2, 16%), and 16 ileal and colonic locations (L3, 64%). Regarding the behavior of CD, 8 patients had a non-penetrating pattern (B1, 32%), 13 had stenosing disease (B2, 52%), and the remaining 4 patients had a penetrating disease (B3,16%). Eleven patients had the concomitant perianal disease (44%), and 20 underwent previous surgeries because of CD complications, such as abscesses, stenosis, and fistula.

Almost all recruited patients were under biological therapy (23 patients, 92%), and 14 were using immunosuppressive therapy (56%). Regarding the treatment of IDA, all patients had previously used other medications, and 10 (40%) had a history of blood transfusion because of severe anemia.

Of the total patients, a subgroup of 16 used ferric hydroxide sucrose previously for the treatment of IDA; 9 males (56.3%) and 7 females (43.7%), with a median age of 37 (25-67) years. The median duration of CD was 144 (24-312) mo and, according to the Montreal classification, one patient was diagnosed before the age of 16 years (A1, 6.25%), 14 patients between 17 and 40 years (A2, 87.5%), and one patient over 40 years old (A3, 6.25%). Four patients had ileal location (L1, 25%), 3 colonic location (L2, 18.7%), and 9 ileal and colonic location (L3, 56.3%). Regarding the CD behavior, 4 patients had a non-penetrating pattern (B1, 25%), 8 stenotic disease (B2, 50%), and the remaining 4 patients had penetrating disease (B3, 25%). Eight patients had concomitant perianal disease (50%), and 15 had undergone

Table 1 Demographic and clinical characteristics of the patients included in the study

Variables	Ferric carboxymaltose	Iron sucrose	*P* value
Sex (M/F)	12/13	9/7	0.606[a]
Age (yr)	37 (20-67)	37 (25-67)	0.989[b]
Disease duration (mo)	144 (6-312)	144 (24-312)	0.718[b]
Age at the diagnostic A1/A2/A3[1]	1/22/2	1/14/1	0.931[a]
Disease location L1/L2/L3/L4[1]	5/4/16/0	4/3/9/0	0.882[a]
Behavior B1/B2/B3[1]	8/13/4	4/8/4	0.750[a]
Perianal disease (yes/no)	11/14	8/8	0.707[a]
Prior Surgery (yes/no)	20/05	15/1	0.224[a]
Biologic therapy (yes/no)	23/2	15/1	0.962[a]
Immunosuppressive therapy (yes/no)	14/11	13/3	0.242[a]
Previous blood transfusion (yes/no)	10/15	8/8	0.529[a]

[1]Montreal classification.
[a]Pearson's χ^2 test.
[b]Unpaired *t*-test (Mann Whitney) with $P < 0.05$.
Numerical variables are described in median (minimum and maximum), and the categorical variables in absolute frequency. $n = 25$. CD: Crohn's disease; M: Male; F: Female.

previous surgeries for CD complications.

All recruited patients with a history of ferric hydroxide sucrose injection for the ADF treatment were under treatment for CD: 15 patients were under biological therapy (93.7%), and 13 were under immunosuppressive therapy (81.3%). Eight patients (50%) of this subgroup needed a blood transfusion because of severe anemia.

Disease activity

Patients with CD who received iron replacement therapy with FCM had their disease activity determined by nuclear magnetic resonance (presence of ulcers, mucosal enhancement of contrast, or alteration of mesentery associated with the affected intestinal area), colonoscopy with median CDEIS of 16.9 (5.6–26) and/or fecal calprotectin 1000 (104–1000) μg/g at baseline.

The median CDAI at baseline was 303.5 (128–537.6), and at the end of treatment, it decreased in most patients (61%), 235.8 (13.5–470), but without statistical significance ($P = 0.21$). Regarding other inflammatory biomarkers, most patients included in the study (64%) had serum C-reactive protein (CRP) levels > 3 mg/L (reference value lower than 3 mg/L), with a median of 5.91 (0.16-114) mg/L; and the ERS median was 30 (3-120) mm/h.

Evaluation of laboratory parameters before and after treatment with ferric carboxymaltose

Hb levels increased in 93% of patients after treatment with FCM. The median Hb concentration increased from 8.5 g/dL (5.8–10) to 10.1g/dL (7.8–13.7) ($P < 0.0001$) (Figure 1A). In addition, correction of anemia and/or Hb increase ≥ 1 g/dL was achieved in 84% of patients with just one dose of medication. Eleven patients (44%) had an increase in Hb ≥ 2 g/dL. Hematocrit values were within normal parameters in 16% of patients after treatment with FCM, and there was a significant increase in 88% of patients with a median concentration from 27.8% (19.7–32.29) to 33% (25.9–42.8) ($P < 0.0001$) (Figure 1B, Table 2).

Moreover, serum iron levels increased in 18 patients (86%) after FCM injection. The median serum iron improved from 15 μg/dL (4–43) up to 26 μg/dL (10–64.52), demonstrating the satisfactory effect of the medication in only one application ($P < 0.0001$) (Figure 1C). Ferritin increased in 86% of patients after FCM: 23.79 ng/mL (0.5–475.4) at baseline and 100.38 ng/mL (4.26–826.1) after treatment, 77% of patients showed normalization of this parameter after treatment ($P = 0.0008$) (Figure 1D). Concerning the TAST, it increased under treatment with FCM, from 3.5 at the beginning of treatment (1–21) up to 9 (2–26.3) after injection ($P = 0.01$) (Figure 1E, Table 2).

After a single application with iron carboxymaltose, all patients had an increase in mean corpuscular volume levels, and most reached normalization in the parameter (59%) after treatment ($P = 0.05$) (Table 2). No statistical significance was found regarding the levels of Mean Corpuscular Hemoglobin, Mean Corpuscular Hemoglobin Concentration, and platelets analyzed after treatment (Table 2).

Table 2 Evaluation of the laboratory parameters in the patients who received ferric carboxymaltose

Variables	Pre-therapy	Post-therapy	*P* value
Hemoglobin (mg/dL)	8.5 (5.8-10)	10.1 (7.8-13.7)	< 0.0001
Haematocrit (%)	27.8 (19.7-32.29)	33 (25.9-42.8)	< 0.0001
Ferritin (ng/dL)	23.79 (0.5-475.4)	100.38 (4.26-826.1)	0.0008
Iron (mcg/dL)	15 (4-43)	26 (10-64.52)	< 0.0001
STAT (mcg/dL)	3.5 (1-21)	9 (2-26.3)	0.01
MCV (fL)	74.6 (57.8-92.9)	80.8 (64.4-97.8)	0.05
HCM (pg)	22.3 (14.4-37.2)	23.6 (18.5-30.7)	0.15
MCHC (g/dL)	30.1 (24.9-38.8)	30.65 (26.4-33.9)	0.48
Platelets (× 10^3/μL)	410 (200-888)	321 (201-708)	0.19

Numerical variables are described in the median (minimum and maximum). n = 25. Unpaired t-test (Mann Whitney) with $P < 0.05$. MCV: Mean Corpuscular Volume; HCM: Mean Corpuscular Hemoglobin; MCHC: Mean Corpuscular Hemoglobin Concentration; STAT: Transferrin saturation.

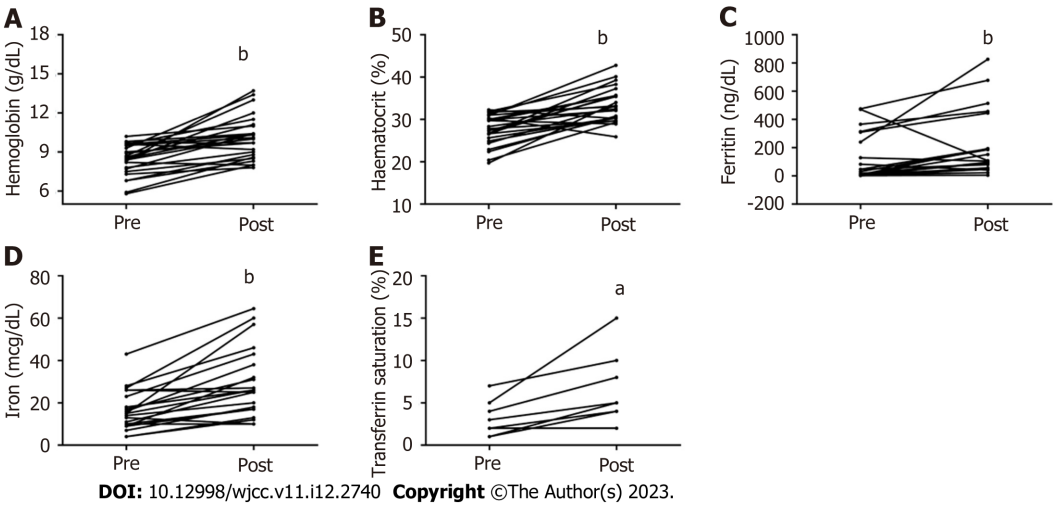

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Figure 1 Hematological variables at baseline and after ferric carboxymaltose treatment. A: Median of hemoglobin; B: Hematocrit; C: Ferritin; D: Serum iron; E: Transferrin saturation. n = 25. Paired t-test with $^aP < 0.05$; $^bP < 0.001$.

Concerning the hematimetric parameters and profile of iron, ferritin, and STAT, we analyzed the associations with the clinical variables under investigation. As observed in Table 3, although all patients included in the study had baseline serum iron levels below the normal range, the baseline serum iron levels were negatively associated with patients with an ileal and colonic CD (L3) who took biologics, but positively associated with patients who developed CD later in life after the age of 40 (A3) and with a stenosing (B2) and fistulizing (B3) phenotype. The highest level of ferritin after the application of FCM occurred in patients who presented colonic location (L2) and fistulizing phenotype (B3). The baseline serum STAT levels were associated with patients with stenosing (B2) and fistulizing (B3) phenotypes and perianal disease (Table 3).

Results of previous ferric hydroxide sucrose injections in this cohort

Finally, the study aimed to assess the effects of FCM in CD patients, taking into account the previous treatment of ferric hydroxide sucrose in these patients. For this analysis, a subgroup of patients from the total cohort was included, and Hb and hematocrit levels were obtained from the medical charts. The median duration of the treatment with ferric hydroxide sucrose was 5.5 mo (1-30), and the number of applications was 12 (4-32).

The median Hb concentration increased from 8.9 g/dL (6.5-11.8) to 9.7 g/dL (7.5-13.2), and the median hematocrit levels increased from 30.4 (22.2-37.8) to 34.54 (24.8-39.29) after treatment with ferric hydroxide sucrose. However, with no statistically significant difference ($P < 0.05$), this cohort comprises refractory patients to traditional iron replacement as expected. When these patients were treated with FCM, we observed increased Hb (P = 0.0005) and hematocrit (P = 0.0001) compared to the values

Table 3 Multiple linear regression analysis of clinical and demographic characteristics associated with serum iron, ferritin, and transferrin saturation in Crohn's disease patients

Variables	β value	95%CI	*P* value
Serum iron levels at baseline			
Age at the diagnostic[1]			
A3	50.119	(15.778, 84.459)	0.004
Disease location[1]			
L3	-16.328	(-30.601, -2.055)	0.025
Behavior[1]			
B2	18.357	(4.711, 32.002)	0.008
B3	21.961	(2.931, 40.992)	0.024
Biologic therapy			
Yes	-27.271	(-53.623, -0.919)	0.043
Serum ferritin levels after FCM injection			
Disease location[1]			
L2	348.460	(56.087, 640.833)	0.019
Behavior[1]			
B3	335.922	(57.389,614.454)	0.018
STAT at baseline			
Behavior[1]			
B2	8.033	(1.974, 14.091)	0.009
B3	13.866	(5.762, 21.971)	0.001
Perianal disease			
Yes	10.5	(3.907, 17.092)	0.002

[1]Montreal classification.

Analysis of multiple linear regression with $P < 0.05$. $n = 25$. FCM: Ferric carboxymaltose; STAT: Transferrin saturation.

obtained before treatment. (Figure 2A and B)

DISCUSSION

IDA is the most frequent clinical condition in CD patients. Usually, it is accompanied by the clinical and endoscopic activity of the disease, but at other times it can be the first manifestation that precedes the intestinal and abdominal symptoms and is one of the main causes of fatigue and poor quality of life. Our data demonstrated a significant improvement in Hb, iron, ferritin, and TAST levels after treatment with FCM. Although these findings have been previously proven in a few studies[10,20], our data showed significant improvement in the hematological parameters with a single dose of the medication.

Our results from the clinical practice confirmed the findings obtained by Sobrado *et al*[23], who evaluated FCM for the treatment of anemia in CD patients at a Brazilian center[23]. Although they performed a quite similar study, we included a larger number of patients treated at a tertiary center in selective and strictly defined disease activity criteria (endoscopic and/or radiological imaging). Furthermore, we compared the effects of FCM with previous ferric hydroxide sucrose treatment.

CD patients are at greater risk of developing anemia, especially with active disease[24,25]. To analyze the safety and efficacy of FCM for the anemia treatment of IBD patients, Stein *et al*[10] performed a prospective study. However, not only patients with severe CD activity were included, but also patients in remission, and the disease activity was based on rather unspecific criteria such as serum CRP, CDAI for patients diagnosed with CD, and Colitis Activity Index for patients with ulcerative colitis[11]. All patients in our study had severe disease activity determined by more specific criteria. 40% of our patients had severe activity determined by magnetic resonance enterography. The other 60% had CD activity determined by colonoscopy and fecal calprotectin. Furthermore, the median baseline CD

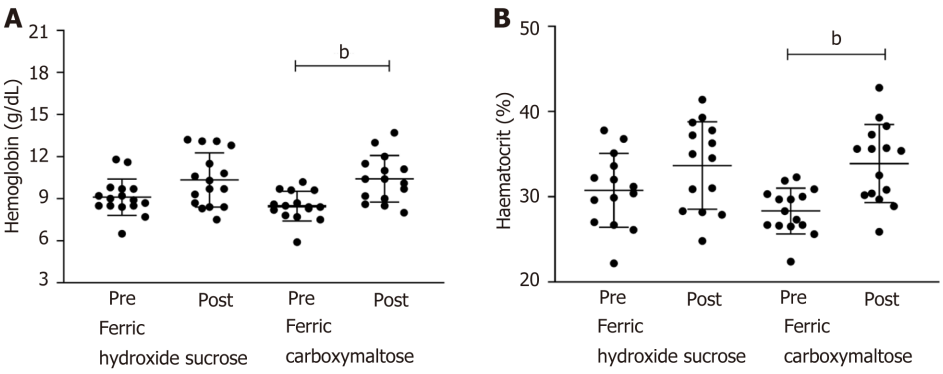

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Figure 2 Hematological variables at baseline and after the treatment with ferric carboxymaltose and ferric hydroxide sucrose. A: The median of hemoglobin; B: Hematocrit. $n = 16$. Paired *t*-test with $^{b}P < 0.001$.

activity assessed by the CDAI was 303.5, and CRP levels had a median of 5.91 before treatment with FCM.

Usually, assistant physicians who take care of these chronic patients neglect the importance of IDA and accept it as a consequence of CD, so they proceed without having an established protocol based on gathering information and assessing alternative resolutions that could assist the decision-making and treatment in their clinical practice. Coe *et al*[9] performed a retrospective study and concluded that gastroenterologists should consider treating patients with IBD and IDA with IV iron as it is safe and effective[9]. Our study confirms that IV medication has proved to be an important therapeutic strategy, which can help quickly and safely in the treatment of IDA when prescribed by physicians accompanying this group of patients. A suggested approach to managing patients with CD and IDA is illustrated in Figure 3.

It is important to point out that although other studies have resulted in an increase in Hb levels of ≥ 2 g/dL, the assessment was not done with just a single dose of medication[10,20,23]. Our study showed that 44% of patients had an increase of ≥ 2 g/dL with a single dose of 50 mg/mL, which demonstrates that FCM can be an important therapeutic strategy when a significant increase in parameters is needed in a short period of follow-up, either to relieve symptoms or to prepare CD patients for surgical procedures and post-surgical recovering.

Iron and ferritin serum levels increased in 86% of patients, and TAST levels increased by 50% after treatment. This early response is in agreement with previous studies that performed this assessment. However, these studies evaluated a complete response between 4 to 8 wk of treatment. Our data point to this response in most patients 15 d after treatment[20,26].

The effect of biological therapy on anemia in patients with IBD is seldom discussed in the literature. Demonstrated evidence showed a significantly improving in anemia in patients using biological therapy for other chronic inflammatory diseases such as arthritis and ankylosing spondylitis[27]. Due to chronic inflammation, anemia is usually characterized as anemia of chronic disease (ACD) in these conditions. However, although ACD is associated with IBD, the most prominent impact is due to iron deficiency, and patients have recurrent anemia even after treatment with immunomodulators[28].

A recent pediatric study showed no statistical difference in Hb levels between IBD patients who responded or did not respond to ant-Tumor necrosis factor treatment[29]. A study of adult patients with IBD demonstrated that although biological therapy had significant beneficial effects on disease activity, the research found no significant change in the prevalence of anemia. Furthermore, one-fifth of patients without anemia at baseline developed anemia after one year of therapy[30]. Our results are in agreement with these recent studies. We demonstrated that although patients had iron levels below normal at baseline, the use of biological therapy had a negative correlation with baseline serum iron levels, indicating that these patients had more severe anemia.

A study evaluating anemia in Korean patients with IBD found no significant association between patients' clinical characteristics and anemia[31]. Bergamaschi *et al*[32], in 2010, did not relate anemia in CD to the location or behavior of the disease[32]. In 2020, a study analyzed the prevalence and risk factors of anemia and iron deficiency in patients with IBD in Brazil and concluded that patients with the penetrating disease phenotype in CD were associated with a lower risk of anemia[33]. Our study demonstrates that patients with an ileal and colonic location correlate negatively with basal serum iron levels, demonstrating more severe anemia. Patients with stenosing and fistulizing phenotypes positively correlated with baseline serum iron levels and TAST.

We also compared treatment effects with FCM and previous treatment with ferric hydroxide sucrose. We observed no statistical difference in Hb and hematocrit levels after treatment with ferric hydroxide sucrose, while those levels showed a significant increase with a single dose of FCM. Although other studies evaluated the efficacy of the two medications[9,34], our study compared the efficacy of the

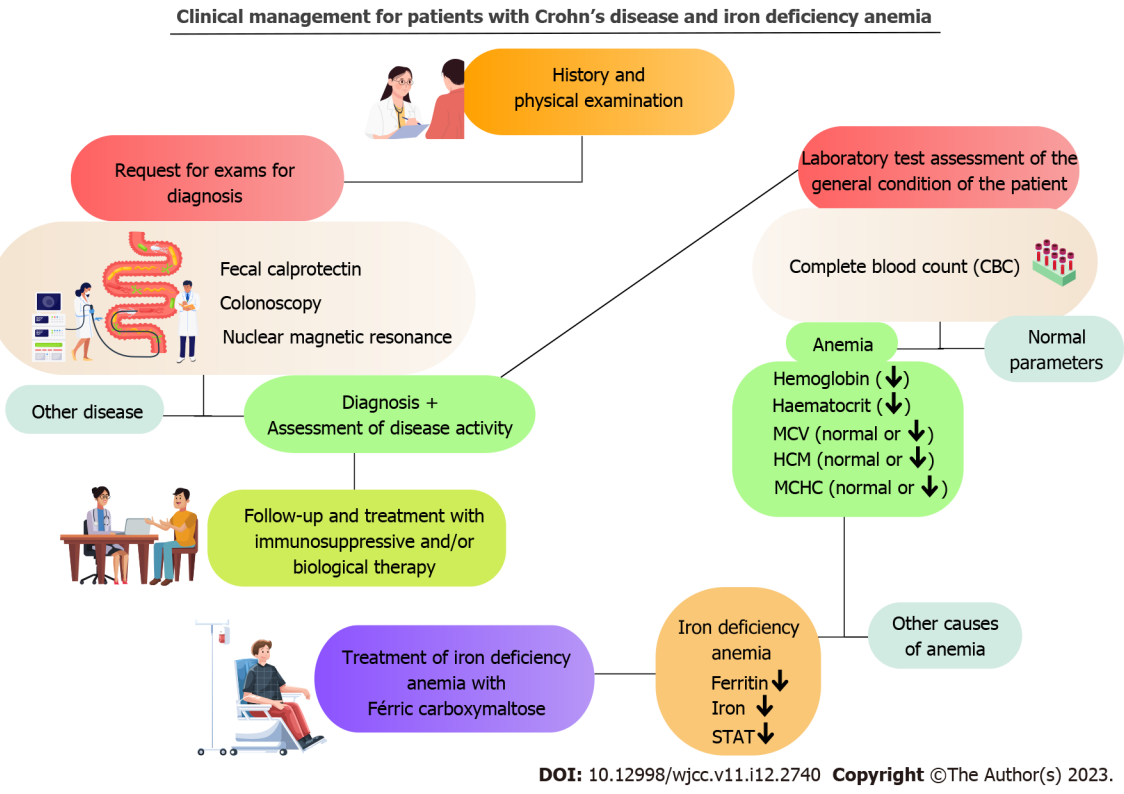

Figure 3 Suggested clinical management to the patient with Crohn's disease and iron deficiency anemia. MCV: Mean corpuscular volume; HCM: Mean corpuscular hemoglobin; MCHC: Mean corpuscular hemoglobin concentration; STAT: Transferrin saturation.

treatment in the same group of patients, demonstrating that FCM is an important therapeutic strategy in refractory patients who received ferric hydroxide sucrose.

The present study reported a median of 12 applications (4-35) with previous treatment with ferric hydroxide sucrose. However, when the same patients were treated with FCM, a single infusion guaranteed a significant increase in the hematological parameters. Evstatiev *et al*[34] reported in their study treatment with 1 to 3 infusions of FCM, while the ferric hydroxide sucrose treatment lasted 11 infusions[34]. Onken *et al*[35] also showed a similar result; patients treated with ferric sucrose received an average of 5 infusions, while patients treated with FCM underwent two infusions[35].

Thus, CD patients can be exposed to fewer interventions since FCM has better efficacy with a significant increase in hematological parameters, as well as iron, ferritin, and TAST levels with usually a single dose. The consequence is a decreased number of patients' visits to hospitals or private clinics, contributing to the quality of life and emotional well-being.

Currently, the value of an ampoule of FCM (+/- R$ 641.90 – Brazilian currency) is approximately 10 times more expensive than an ampoule of ferric hydroxide sucrose (+/- R$ 64.70 - Brazilian currency), which restricts patient adherence to treatment since this medication is not available by the Unified Health System through State Public Pharmacies in Brazil. However, studies indicate that as a final result of the treatment, FCM has a lower cost when compared to ferric sucrose. Vicente *et al*[36] concluded that the overall cost of FCM treatment is significantly advantageous compared to ferric hydroxide sucrose, such as the relatively lower number of infusions of FCM and the quick increase of serum Hb levels after iron replacement[36].

Toblli and Di Gennaro[24] in 2015, evaluated the economic impact of oral iron replacement treatment *vs* FCM in patients with chronic kidney disease. As a result, the study demonstrated that the cumulative cost during the 6 mo study period with FCM was United States $ 3.070 per patient, whereas compared to oral iron administration over the same period, the cost was US $ 17.670. The study also found that using FCM to treat IDA resulted in savings of US $ 14.600 (82.6%) per patient[24].

Another study published in 2021 by Aksan *et al*[37] analyzed and compared the cost-effectiveness of IV and oral iron treatment in patients with IDA associated with IBD and concluded that FCM is designed to be the most cost-effective IV iron therapy in Switzerland and with better clinical response to treatment[37]. Basha *et al*[25] in 2021 evaluated the efficacy and cost-effectiveness of FCM *vs*. iron sucrose. The retrospective study assessed patients who were followed up for 12 mo in a tertiary center, and as a result, although the cost of the medication FCM is 6.5 times higher than iron sucrose, at the end of the period, the treatment with FCM has a lower cost in bed or nursing[25]. Table 4 shows the main characteristics differentiating FCM from iron sucrose[38,39].

Table 4 Main features of ferric carboxymaltose versus iron hydroxide sucrose

	Ferric carboxymaltase[38]	Iron hydroxide sucrose[39]
Concentration	Up to 20 mL corresponding to 1000 mg of iron	10 mL corresponding to 200 mg of iron
Dosage	1 time a week	1 to 3 times a week (depending on hemoglobin level)
Infusion time	Up to 200 mg of iron - there is no established administration time from 200 mg to 500 mg of iron – the rate of 100 mg per minute above 500 mg up to 1000 mg of iron -66 mg per min	Up to 200 mg of iron - 6.6 mg per min, 300 mg of iron - 3.3 mg per min, 400 mg - 2.6 mg per min, 500 mg - 2.3 mg per min
Molecule	Stable iron is in the form of a complex of non-dextran iron with a polynuclear ferric hydroxide core with a carbohydrate linker. Because of the high stability of the complex, there is only a small amount of weakly bound iron (also called free iron). The structure of the nucleus is similar to that of ferritin, so the complex is intended to provide a controlled supply of usable iron for ferric transport and storage of proteins in the body	Trivalent form as a macromolecular colloidal complex of ferric hydroxide saccharate. The polynuclear ferric hydroxide core is superficially surrounded by a large number of non-covalently linked sucrose molecules, resulting in a complex whose molecular mass is approximately 43 kDa
Pharmacokinetics	After administration of a single dose of iron carboxymaltose of 100 to 1000 mg of iron in patients with anemia, peak serum iron concentrations were between 37 and 333 mcg per mL	After the injection of 100mg of iron in healthy individuals, the maximum plasma concentration, on average, of 538 μmol per L, 10 min after the injection
Volume of distribution	The volume of distribution of the central compartment corresponds to the plasma volume (approximately 3 L). It is retained mainly in the reticuloendothelial system of the bone marrow, liver, and spleen. The average residence time varied between 11 and 17 h	The central compartment volume of distribution correlates well with serum volume (approximately 3 L). The volume of distribution at a steady state was about 8 L, which indicates the low distribution of iron in body fluids
Half-life	7 and 12 h	6 h
Route of administration	Intravenous injectable solution	Intravenous injectable solution

The literature demonstrates the effectiveness of FCM in many diseases. Several studies have shown the important role that medication performs in cardiovascular diseases[40,41]. However, in the gastrointestinal tract, few studies have analyzed the effectiveness of FCM, especially in CD. Thus, our study contributed to a greater understanding of medication use in this disease, helping clinical practice.

The limitations of our study lay in the retrospective character of the research, as data collected through electronic medical records or outpatient databases may be scarce. As described above, we could only analyze the serum levels of Hb and hematocrit in comparing the two medications. Another limitation is that the study evaluated a small number of patients despite being larger than other Brazilian studies. In addition, it was neither possible to correlate the degree of CD activity through the CDAI, CRP, and erythrocyte sedimentation rate values with the severity of anemia nor to determine if the increase of the hematological parameters after FCM treatment correlates with an improvement in quality of life assessed by validated questionnaires, such as IBD Questionnaire[29].

CONCLUSION

From the analysis performed in this retrospective study, a better understanding of the effects of FCM in the treatment of IDA in CD patients has emerged. The study also showed that FCM is an important therapeutic strategy, as it achieves superior results compared to the administration of iron hydroxide sucrose in patients with refractory IDA. However, there are still many gaps to be addressed in future studies about the molecular mechanism of IDA in CD. We do not yet know if IV iron replacement, besides improving the patient's quality of life and well-being, can affect the activity of the disease and help the patient to enter clinical and endoscopic remission. Our findings support FCM as an important therapeutic strategy to treat anemia and improve CD patients' clinical status.

ARTICLE HIGHLIGHTS

Research background

Crohn's disease (CD) is a chronic inflammatory disorder of the gastrointestinal tract, and anemia is one of the clinical manifestations. Iron deficiency anemia (IDA) in CD is due to chronic blood loss from the ulcerated intestinal mucosa associated with diarrhea, decreased iron intake due to dietary restriction, and/or deficiency in transluminal iron absorption during the disease activity. Currently, intravenous (IV) iron replacement is the best option for the treatment of IDA in CD. Recent pharmacology progress has led ferric carboxymaltose (FCM) to correct the IDA through its pharmacokinetic characteristics.

Research motivation

The administration of FCM can be performed in high doses safely and well-tolerated. Given that, this study was designed to evaluate the effectiveness of FCM in the treatment of IDA in CD patients in a tertiary center in Brazil, where inflammatory bowel disease has become increasingly frequent. This clinical approach can make the quality of life of CD patients better.

Research objectives

The objective of this study was to analyze, through medical records, the clinical and epidemiological data of a cohort of patients with active CD who received IV FCM in the treatment of IDA to elucidate the effectiveness of the drug and compare it to iron hydroxide sucrose treatment.

Research methods

It is a retrospective, observational study, which included 25 patients with active CD, severe anemia, and refractory to previous conventional treatments. Patients were evaluated two times: During previous treatment with ferric hydroxide sucrose and treatment with FCM. Epidemiological and clinical data were analyzed, besides hematimetric parameters.

Research results

The parameters of IDA assessment significantly improve after treatment with FCM. Serum hemoglobin (Hb) levels increased in 93% of patients, and in 44%, there was an increase of ≥ 2 g/dL in a single application. Moreover, 86% of the patients showed increased serum iron and ferritin and 50% in transferrin saturation. The serum iron levels at baseline showed a negative association with the ileal and colonic CD and use of biologics and a positive association with patients who developed CD later in life after the age of 40 (A3) and with a stenosing (B2) and fistulizing (B3) phenotype. The Hb and hematocrit values after ferric hydroxide sucrose treatment remained similar to those found before treatment.

Research conclusions

FCM is an important therapeutic strategy for treating IDA in CD patients, achieving satisfactory results in refractory cases.

Research perspectives

The study showed that FCM is an important therapeutic strategy to treat IDA in CD patients. However, there are still many gaps to be addressed in future studies about the molecular mechanism of IDA in CD. We do not yet know if IV iron replacement, besides improving the patient's quality of life and well-being, can affect the activity of the disease and help the patient to enter clinical and endoscopic remission. Our findings support FCM as an important therapeutic strategy to treat anemia and improve the clinical status of CD patients.

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FOOTNOTES

Author contributions: Siqueira NSN, Castro MM, Martins ASC, and Araújo DOS were responsible for collecting the data; Siqueira NSN, Pascoal LB, Castro MM, and Gomes LEM plotted and analyzed the data; Siqueira NSN, Leal RF, Pascoal LB, and Castro MM contributed to interpreting the results; Leal RF conceived the study and performed the final revision of the manuscript; All authors contributed to the writing and revised the manuscript; All authors read and approved the final manuscript.

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Institutional review board statement: The study was approved by the University of Campinas Ethics Committee, No. CAAE:56915516.6.0000.5404.

Informed consent statement: Patients were informed, but written consent was waived due to the retrospective methodology of the study. All efforts were made to ensure data confidentiality, as required by the Ethics Committee. This study was performed in accordance with the Declaration of Helsinki, good clinical practice, and applicable

regulatory requirements.

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

Data sharing statement: The data used to support the findings of this study are included within the article. No additional data are available.

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

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META-ANALYSIS

Is metaphyseal ulnar shortening osteotomy superior to diaphyseal ulnar shortening osteotomy in the treatment of ulnar impaction syndrome? A meta-analysis

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Abstract

BACKGROUND

Although metaphyseal ulnar shortening osteotomy (MUSO) is safer for the treatment of ulnar impaction syndrome (UIS) than diaphyseal ulnar shortening osteotomy (DUSO), DUSO is widely used for UIS treatment.

AIM

To evaluate the effectiveness of DUSO and MUSO for UIS treatment and determine the factors that should be considered when choosing surgical treatment for UIS.

METHODS

Articles comparing the effectiveness of DUSO and MUSO for UIS treatment were systematically retrieved from MEDLINE (Ovid), PubMed, EMBASE, and Cochrane Library. The demography, incidence of complications, secondary operation rate, postoperative DASH score, wrist pain on the visual analogue scale, and grip strength improvement were also evaluated. In addition, the correlation between the improvement of grip strength and the shortening of osteotomy length of ulna was analyzed. The outcome of the patient was discontinuous, and the odds ratio, risk ratio (RR), and 95%CI were calculated and analyzed *via* RevMan5.3 software.

RESULTS
Six studies, including 83 patients receiving MUSO (experimental group) and 112 patients receiving DUSO (control group), were included in the meta-analysis. The second operation rate was significantly higher after DUSO than after MUSO. The DASH scores were slightly lower in the MUSO group than in the DUSO group. The patients receiving MUSO had slightly better pain relief effect than patients receiving DUSO. However, the incidence of complications and improvement of grip strength were not significantly different between the two groups.

CONCLUSION
Although DUSO and MUSO provide similar effects for UIS, MUSO is associated with a lower secondary operation rate, slightly lower postoperative DASH scores and slightly better pain relief effect than DUSO, indicating that MUSO can effectively be used for UIS treatment.

Key Words: Metaphyseal; Diaphyseal; Ulnar shortening osteotomy; Ulnar impaction syndrome; Meta-analysis

Core Tip: Ulnar impaction syndrome (UIS) is caused by overload of the ulnar wrist joint. This is the common cause of ulnar wrist pain. UIS is related to static or dynamic lateral positive change. If not treated in time, it may lead to the erosion and perforation of the triangular fibrocartilage complex, as well as the degeneration of the triangular, Lunate or ulnar head cartilage. Therefore, the basic treatment of UIS includes mechanical decompression of the overloaded ulnar wrist joint by reducing the ulnar variation. There are many surgical treatments that can reduce the excessive pressure on the ulnar side of the wrist joint, including diaphyseal ulnar shortening osteotomy (DUSO), thin section resection and metaphyseal ulnar shortening osteotomy (MUSO). The Wafer resection site of the distal ulna belongs to MUSO. Compare the effect of DUSO and MUSO ulnar shortening methods. In fact, both of these operations have specific advantages and disadvantages. It should be clear whether the treatment choice of UIS patients depends on the preferences of surgeons.

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INTRODUCTION

Ulnar impaction syndrome (UIS) is a common cause of ulnar-sided wrist pain caused by overload through the ulnocarpal joint. UIS is associated with static or dynamic ulnar positive variance[1,2] and may lead to erosion and perforation of triangular fibrocartilage complex (TFCC) and degeneration of triangular, lunate or ulnar head cartilage if not timely treated[3,4]. The basic UIS treatment involves mechanical decompression of overloaded ulnocarpal joint by decreasing ulnar variance. Many surgical treatments, including diaphyseal ulnar shortening osteotomy (DUSO), wafer resection, and metaphyseal ulnar shortening osteotomy (MUSO), can be used to reduce excessive pressure on the ulnar side of the carpus[5-11]. MUSO is usually performed at the Wafer resection site of the distal ulna. Nonetheless, both DUSO and MUSO have specific advantages and disadvantages[9-13].

Although UIS is usually associated with positive ulnar variance, UIS has been found in patients with neutral or negative ulnar variance. Furthermore, the thickness of TFCC is inversely associated with ulnar variance[1,2]. Previous studies have reported that TFCC debridement alone cannot relieve ulnar wrist pain caused by significant positive ulnar variance or other carpal lesions[14-16]. Besides, positive ulnar variance may increase the risk of TFCC wear or perforation. Bernstein *et al*[4] showed that arthroscopic TFCC debridement combined with USO can effectively treat UIS. However, Saito *et al*[17] indicated that ulnar variance may affect the results of TFCC debridement. Therefore, USO can biomechanically unload the ulnocarpal joint and relieve the ulnar wrist pain associated with UIS. Compared with arthroscopic TFCC debridement combined with USO, arthroscopic TFCC debridement combined with wafer distal ulna resection is a more minimally invasive treatment with less secondary surgery rate and tendonitis.

DUSO is a common USO widely used to treat UIS since it can satisfactorily relieve ulnar wrist pain [18,19]. Diaphyseal is the most common site of osteotomy. However, DUSO is associated with many complications, including implant removal[20], catastrophic delayed union or nonunion at the osteotomy site[20-25], postoperative tendinitis[26,27], and accidental residual positive variance[26]. Besides, the position of the plate on the surface of the metacarpal or dorsal ulna may cause different regional responses, such as postoperative tendinitis, symptomatic hardware, and hardware stimulation. Compared with DUSO, MUSO has fewer complications. Nonetheless, MUSO is associated with some complications. Some studies have also shown that DUSO and MUSO have similar treatment effects[1-6, 8]. The morphology of the inferior radioulnar joint (DRUJ) can affect the effect of USO for UIS treatment [3]. DRUJ arthritis after USO may cause ulnar wrist pain and even impair wrist function due to the incoordination of DRUJ[28-31]. MUSO is associated with better ulnar wrist pain relief, lower bone nonunion rate, and lower secondary operation rate. However, Claes *et al*[32] showed that metaphyseal and diaphysis fracture healing follows similar biomechanical progress. Smoking and the site of osteotomy also affect the outcome of postoperative pain relief[33]. Cha *et al*[34] recommend that patients with osteoporosis in UIS should avoid using DUSO since delayed union or nonunion occasionally occurs after DUSO.

However, it is unknown whether any factor should be considered when choosing DUSO or MUSO for UIS treatment or whether it should be based on surgeon's decision only. This meta-analysis aimed to assess the effects of DUSO and MUSO for UIS treatment and determine preoperative factors that surgeons should carefully consider when selecting DUSO and MUSO for UIS treatment.

MATERIALS AND METHODS

Literature search

Cochrane Library, MEDLINE (Ovid), PubMed, and EMBASE databases were searched on September 7, 2019, following the Reporting Items for Systematic Reviews and Meta-Analyses guideline[35]. A manual search was also conducted on the relevant research to ensure that no research was omitted.

Search strategies

The key words applied in the literature search are shown in Table 1. The abbreviations "AWP" and "USO" were also used during the search. The keywords were limited to titles and abstracts to ensure a more accurate search for target research.

Inclusion and exclusion criteria

Inclusion criteria: (1) Studies reporting treatment outcomes of UIS and comparing distal MUSO and DUSO for UIS treatment; (2) Studies with patients aged 15-80 years; and (3) Reports with at least one of the following results: ulnar variance, visual analog scale (VAS) pain score, Quick DASH score, contralateral grip strength, incidence of complications, and incidence of secondary surgery.

Exclusion criteria: (1) Studies not comparing distal MUSO and DUSO for UIS treatment; (2) Studies only reporting the results of UIS's DUSO or MUSO; and (3) Duplicates and studies on cadavers, animals, and children (below 14 years). Notably, all research designs were eligible, and exclusion was not based on methodological quality.

Types of participants in the included studies

UIS patients with or without degenerative TFCC tears and patients diagnosed with ulnocarpal abutment syndrome since ulnocarpal abutment syndrome has the same symptoms as UIS (Table 2).

Outcomes analyzed

The following information was analyzed: (1) Ulnar variance; (2) Pain score: VAS score; (3) Quick DASH score: quick disabilities of the arm, shoulder, and hand questionnaire scores; (4) Grip strength of the unaffected side; (5) Complication rates: Complication was defined as the need for a subsequent surgical procedure after the first operation. The complication rates were calculated by dividing the number of complications by the number of patients. The patients were treated using a Sauvé-Kapandji procedure. Nonunion patients were treated with iliac crest bone grafting, cubital tunnel release, tendon graft stabilization of the DRUJ. Some patients were treated with arthrolysis of the DRUJ, wrist arthrodesis, osteosynthesis for nonunion of the ulna, refixation for refracture of the ulna, removal of the fixation device for hardware-produced irritation, secondary surgery for unrelieved symptoms, and TFCC repair for iatrogenic rupture of the TFCC during the AWP. Additional complications included the requirement for hospital admission and antibiotics to treat an infection, the presence of an iatrogenic neurovascular deficit or tendinopathy, and the detection of arthritic changes *via* radiography combined with symptoms, extensor carpi ulnaris tendinitis, hardware loosening, and regional pain; and (6) Secondary procedure rate: Hardware removal, resection ulnocarpal scar, arthrolysis of the DRUJ, arthrodesis, refixation for refracture of the ulna.

Table 1 Search items

Search items
Metaphyseal osteotomy and diaphyseal osteotomy
Distal metaphyseal ulnar shortening osteotomy and diaphyseal ulnar shortening osteotomy
Arthroscopic wafer procedures and ulnar shortening osteotomy
Wafer procedures and ulnar shortening osteotomy
Arthroscopic distal ulna resections and ulnar shortening osteotomy

Table 2 General demographic characteristics

Ref.	Types of participants	Selected outcomes
Bernstein *et al*[4], 2004	MUSO *vs* DUSO	Ulnar variance; VAS; grip strength; complication rate; secondary procedure rate
Marquez-Lara *et al*[12], 2017	MUSO *vs* DUSO	Secondary procedure rate; complication rate; quick DASH score
Sennwald *et al*[10], 2013	MUSO *vs* DUSO	Ulnar variance; VAS
Constantine *et al*[41], 2000	MUSO *vs* DUSO	Secondary procedure rate; complication rate
Smet *et al*[11], 2014	MUSO *vs* DUSO	Secondary procedure rate; complication rate; quick DASH score
Oh *et al*[9], 2018	MUSO *vs* DUSO	Secondary procedure rate; complication rate; quick DASH score

MUSO: Metaphyseal ulnar shortening osteotomy; DUSO: Diaphyseal ulnar shortening osteotomy; VAS: Visual analog scale.

Data extraction and review

Two authors (Deng HL and Lu ML) conducted a systematic electronic search. Duplicates were excluded first, then the authors reviewed the titles and abstracts step by step. Finally, two other authors (Zhao JM and Tang ZM) conducted a full-text review of the identified articles following the inclusion and exclusion criteria. The following data were extracted: Year of publication, name of the author, type of article, average age and gender distribution, type of operation, type of enrollment (experimental group and control group), number of patients in each group, ulnar variance, pain score, Quick DASH score, grip strength, incidence of complications and incidence of secondary operation. In addition, factors that may affect healing (delayed union or nonunion) and pain relief, such as smoking status, osteoporosis, and preoperative use of painkillers, were recorded.

Only the literature related to the efficacy of DUSO and MUSO in IUS treatment was retrieved. The selection of the studies was performed step by step through title, abstract, and full-text review following the predetermined inclusion and exclusion criteria. Non-English published studies were translated before reviewing the reference part of the article. Two reviewers (Tang ZM and Mao QL) made research choices and resolved any differences in the inclusion of the articles through discussion and further review.

Statistical analysis

Discontinuous data were used for comparison analysis. Odds ratio (OR), risk ratio (RR), and 95%CI were used for (The Cochrane Collaboration, Oxford, UK) for final analysis *via* RevMan5.3 software. The sources of heterogeneity between studies were assessed in a step-by-step manner. In addition, heterogeneity was extracted for subgroup analysis. A random effects model was used for moderate to high heterogeneity (I^2 value > 50%), while fixed effects model was used for low heterogeneity (I^2 value < 50%). Pain relief between subgroups was also compared based on ulnar shortening osteotomy of different lengths. The pain score (VAS) and grip strength improvement were compared using a two-sample *t*-test. A two-sample *t*-test was also used to analyze the difference of grip strength improvement between different lengths of ulnar shortening osteotomy. The relationship between the length of ulnar osteotomy and grip strength improvement was evaluated using linear regression analysis. Data were expressed as mean ± SD, and the significance level was set at 0.05.

RESULTS

Search results

The search results are presented in Figure 1. A total of 80 articles were initially identified from the

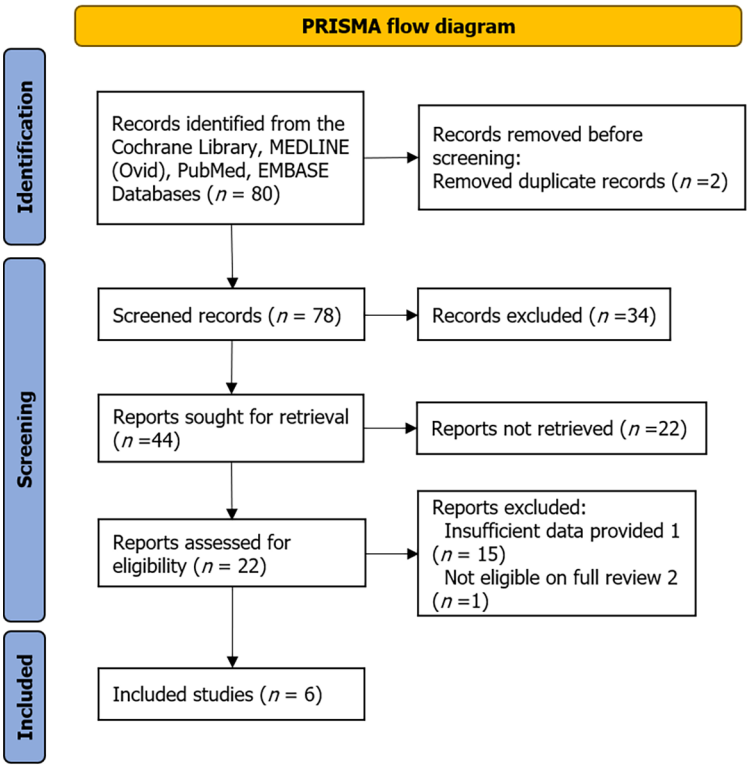

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Figure 1 PRISMA flow diagram.

electronic databases, of which only 44 were considered potentially relevant. A total of 22 of 44 potentially relevant articles were excluded after a careful evaluation of the title and abstract. Also, 15 of the remaining 22 studies were excluded after reviewing full-text studies because they did not provide sufficient data for meta-analysis, and 1 was excluded because it was a systematic review. Finally, six independent studies were included in the final analysis. The bias risk map is shown in Figure 2, and the summary of bias risk is shown in Figure 3.

Main characteristics of the included studies

The main features (study time, number of patients, gender, age, follow-up time, time since the first onset of clinical syndrome, and intervention of participants) are shown in Table 3. The included studies had 195 patients, of which 83 received MUSO (experimental group) and 112 received DUSO (control group) (Table 3). The six studies included 82 men and 113 women with an average age of 43.9 years. The average follow-up period of the included studies was about 31.7 mo. Three studies provided preoperative intervals (mo).

Baseline features

Some original studies did not provide baseline factors focusing on the comparison. The studies showed that the amount of ulnar shortening osteotomy had a linear relationship with the improvement of grip strength. However, the included studies did not provide raw data for analysis of the aspects of interest since each had different objectives. Therefore, the aspects were analyzed based on the information provided by the included studies. The preoperative ulnar variance, VAS, and contralateral grip strength are shown in Table 4. The preoperative ulnar variance, VAS, and grip strength improvement were not significantly different between the experimental and the control groups. The demographic characteristics of the production subgroup are shown in Table 5. These characteristics were used to analyze the selected results of VAS and grip strength between the MUSO and DUSO groups.

Complication rates

The incidence of complications was slightly higher in the DUSO group than in the MUSO group (Figure 4) (OR = 0.54, 95%CI: 0.13-2.25, $P > 0.05$, $I^2 = 53\%$). The funnel chart showing the incidence of complications is shown in Figure 5A.

Secondary procedure rate

The secondary operation rate was lower in the MUSO group than in the DUSO group (OR = 0.10, 95%CI: 0.01-0.70, $P < 0.05$, $I^2 = 65\%$) (Figure 6). Funnel plot showing the secondary procedure rate is

Table 3 General patient information of the included studies

Ref.	No. of patients	Gender (male/female)	Age (mean yr)	Follow-up time (mo)	After injury (mo)	No. of patients who underwent MUSO	No. of patients who underwent DUSO
Bernstein *et al*[4], 2004	27	13/14	37.6	17.4	13.8	11	16
Marquez-Lara *et al* [12], 2017	35	17/18	43.9	18.5	Not reported	14	21
Sennwald *et al*[10], 2013	29	45277	42.9	54	5.5	16	13
Constantine *et al* [41], 2000	22	45152	40.5	36	Not reported	11	11
Smet *et al*[11], 2014	40	45229	40.4	29	Not reported	12	28
Oh *et al*[9], 2018	42	17/25	53.6	35.5	29.5	19	23

MUSO: Metaphyseal ulnar shortening osteotomy; DUSO: Diaphyseal ulnar shortening osteotomy.

Table 4 General demographic characteristics

Ref.	Preoperative ulnar variance (mm)	Pain score (VAS)	Grip strength of the unaffected side (%)	Selected outcomes
Bernstein *et al*[4], 2004	1.5	Not reported	55.2	Ulnar variance; VAS; grip strength; complication rate; secondary procedure rate
Marquez-Lara *et al* [12], 2017	3.9	6.5	Not reported	Secondary procedure rate; complication rate; quick DASH score
Sennwald *et al*[10], 2013	2.6	8	Not reported	Ulnar variance; VAS
Constantine *et al*[41], 2000	2	Not reported	Not reported	Secondary procedure rate; complication rate
Smet *et al*[11], 2014	2	Not reported	Not reported	Secondary procedure rate; complication rate; quick DASH score
Oh *et al*[9], 2018	2.9	5.9	54.1	Secondary procedure rate; complication rate; quick DASH score

VAS: Visual analog scale.

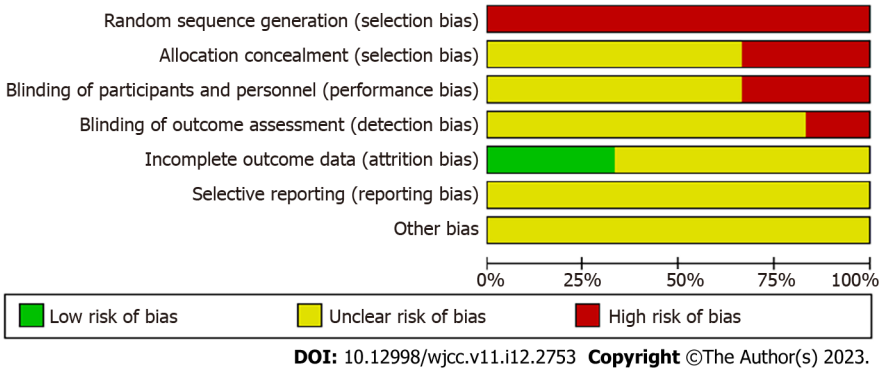

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Figure 2 Risk of bias graph.

shown in Figure 5B.

Postoperative DASH score

The postoperative DASH score was slightly lower in the MUSO group than in the DUSO group OR = -7.87, 95%CI: -22.04-6.31, $P > 0.05$, $I^2 = 97\%$) (Figure 7). Funnel chart showing Pos-op DASH score is

Table 5 Interval group demographic characteristics

Ref.	Preoperative ulnar variance (mm)	Pain score (VAS)	Grip strength of the unaffected side (%)	Selected outcomes
Bernstein *et al*[4], 2004	1	Not reported	54/56	Ulnar variance; VAS; grip strength; complication rate; secondary procedure rate
Marquez-Lara *et al* [12], 2017	1.285714	6.64/6.45	Not reported	Secondary procedure rate; complication rate; quick DASH score
Sennwald *et al*[10], 2013	0.666667	7.3/8.2	Not reported	Ulnar variance; VAS
Constantine *et al* [41], 2000	0.6	Not reported	Not reported	Secondary procedure rate; complication rate
Smet *et al*[11], 2014	1.588235	Not reported	Not reported	Secondary procedure rate; complication rate; quick DASH score
Oh *et al*[9], 2018	1.034483	5.8/6.0	51/ 59	Secondary procedure rate; complication rate; quick DASH score

VAS: Visual analog scale.

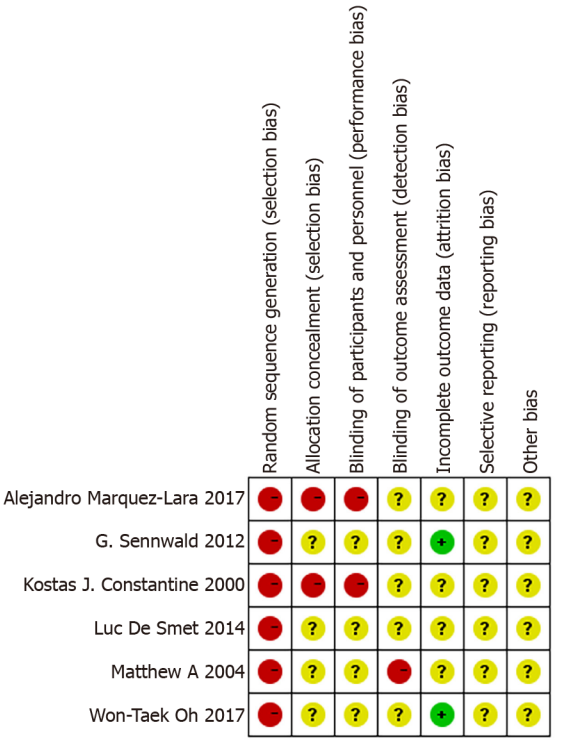

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Figure 3 Risk of bias summary.

shown in Figure 5C.

Pain VAS outcome

Two sample t-test showed that the postoperative VAS was slightly lower in the MUSO group than in the DUSO group (T = −0.978, $P > 0.05$).

Grip strength outcome

Two sample *t*-test showed that the postoperative grip strength of the unaffected extremity was not significantly different between the two groups (T = 0.252, $P > 0.05$). Two sample *t*-test was also applied to compare postoperative grip strength outcomes between two common lengths of ulnar shortening osteotomy (2.5-mm and 3.0-mm USO). The postoperative grip strength outcomes were not significantly different between the 2.5-mm and 3.0-mm groups ($P > 0.05$). However, the pre- and postoperative percentages of grip strength of the contralateral wrist were significantly different between the two

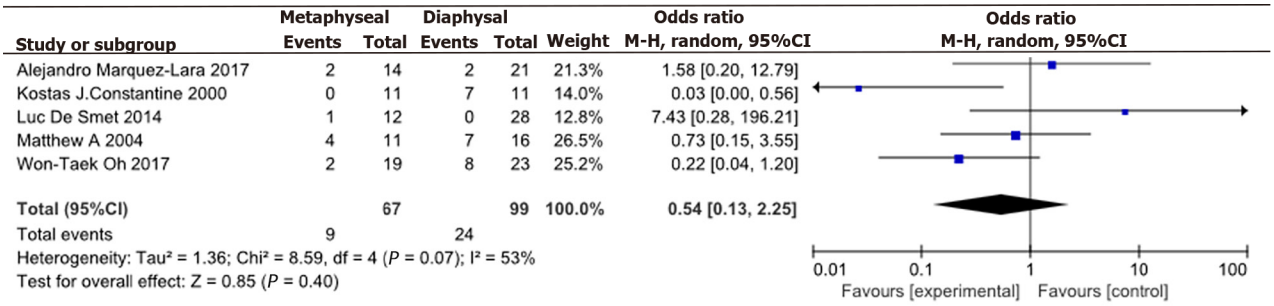

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Figure 4 Complication rates.

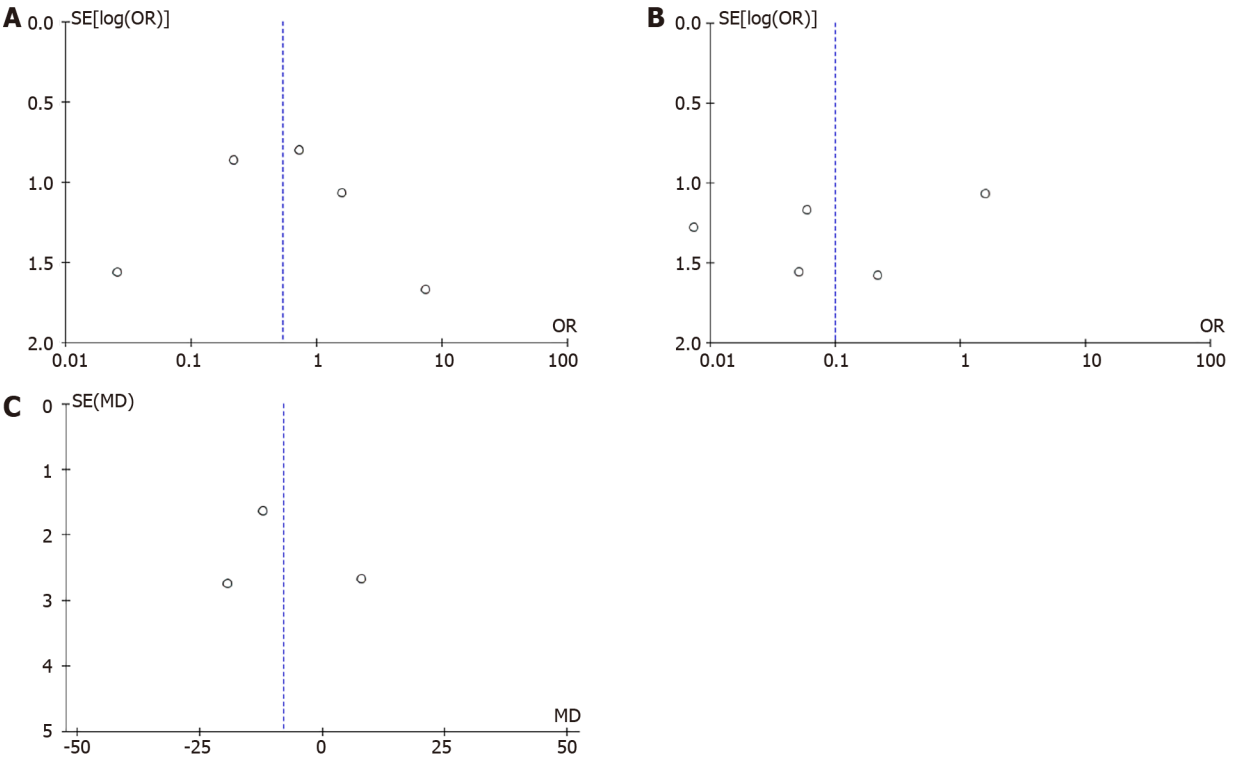

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Figure 5 Funnel plot. A: The incidence of complications; B: The secondary procedure rate; C: Pos-op DASH score.

groups. Specifically, grip strength improved by 32% and 28% in the MUSO group ($P < 0.05$) and DUSO group ($P < 0.05$), respectively. Linear regression analysis showed that the length of ulnar osteotomy was not significantly associated with grip strength improvement based on Bernstein *et al*[4] study (F = 0.194 $P > 0.05$)

DISCUSSION

To the best of our knowledge, this is the first meta-analysis comparing effectiveness of MUSO and DUSO in UIS treatment. The effects of MUSO and DUSO in UIS treatment are controversial. In this study, the incidence of complications, postoperative DASH scores, pain VAS results, and improved grip strength were similar between the DUSO and MUSO groups. However, the rate of secondary operation was lower after MUSO than after DUSO.

The improvement of grip strength should be evaluated as a percentage of contralateral wrist between groups based on the preoperative and postoperative grip strength. Nonetheless, some studies have reported postoperative grip strength as a percentage of the contralateral wrist. Herein, data from Bernstein *et al*[4] showed that the grip strength improvement was not significantly different between the 2.5-mm and 3.0-mm ulnar shortening lengths ($P = 0.336$). Quadlbauer *et al*[36] also is reported that positive ulnar variance caused by distal radius fracture is associated with decreased grip strength. These

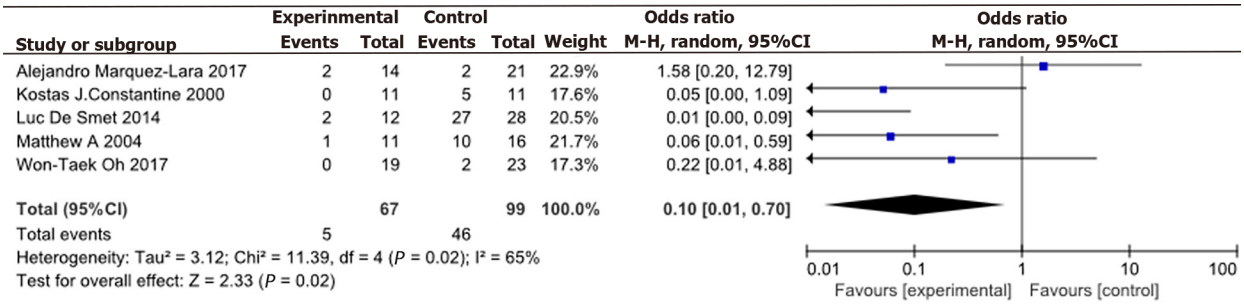

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Figure 6 Secondary procedure rate.

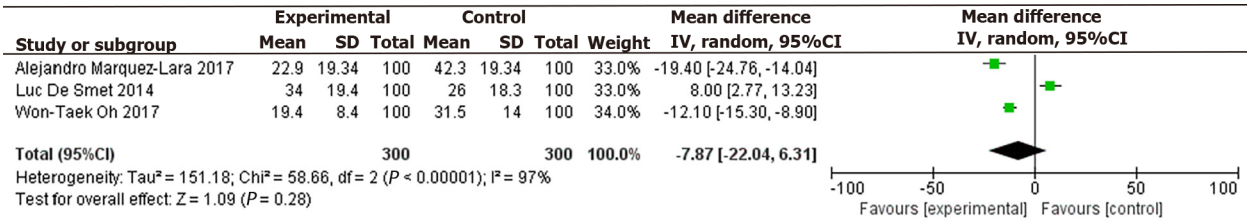

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Figure 7 Postoperative DASH score outcome.

studies showed that USO unloading ulnar-wrist hypertension can treat UIS[37]. Furthermore, results showed that preoperative or postoperative pain was not correlated with the degree of ulnar variance, indicating that preoperative ulnar variance should not be considered for procedural decision-making. Bernstein *et al*[4] suggested that the change of ulna should be reduced to -2.5mm after the operation. Furthermore, the improvement in grip strength was not significantly different between the MUSO group and the DUSO group. Moreover, preoperative and postoperative grip strength were significantly different between the two groups ($P < 0.05$). Bernstein *et al*[4] did not analyze the relationship between ulna shortening and grip strength improvement in different lengths. DUSO is associated with high nonunion rate. Schmidle *et al*[38] promoted bone healing at the osteotomy site using ulnar osteotomy locking plate. The surgical method improves the healing rate of DUSO mainly in the following aspects: (1) Oblique osteotomy expands the bone contact surface of osteotomy; (2) guide saw makes osteotomy more accurate than manual osteotomy; and (3) slide hole design plate can easily close the osteotomy gap and tension screw to compress the osteotomy surface. Meanwhile, Terzis *et al*[39] recently reported that USO can achieve a 100% healing rate using similar saw blade guide plates and slide hole design plates for the treatment of symptomatic UIS after distal radius fractures. The difference in complication rates between DUSO and MUSO for the treatment of ulnar impaction syndrome has gradually reduced due to the improvement of the instrument and the development of DUSO[37,40]. MUSO and DUSO for UIS treatment may depend on surgeon preference. Although many surgeons prefere DUSO, MUSO may be more suitable for UIS patients with osteoporosis, nonunion risk[23,24], and smoking history[33]. Besides, DUSO patients may be at risk of a second fracture at the osteotomy site after plate removal. Terzis *et al*[39] showed that excessive ulnar shortening is postoperative risk factor for distal radioulnar joint inconsistency, leading to the development of osteoarthritis. Nuñez *et al*[33] indicated that the amount of ulnar shortening is balanced with soft tissue. Besides, ulnar shortening should obtain ulnar variance from 0 to 2 mm, indicating that ulnar change larger than 4 mm is suitable for DUSO.

In this study, the pain relief was slightly better in the MUSO than in the DUSO group, inconsistent with Nuñez *et al*[33]'s study. Specifically, Nuñez *et al*[33] found that tobacco use and preoperative opioid consumption are risk factors for pain after osteotomy and thus can act as predictors of pain relief. Nuñez *et al*[33] performed MUSO at distal metaphyseal of ulna to repair the radius-ulnar level (negative variance of the ulna after MUSO; 1-2 mm). Finally, the ulnar osteotomy site at the metaphysis was completely closed, and osteotomy site was fixed with the distal ulnar hook plate[33]. Diaphyseal osteotomy is an extra-articular operation where the pressure of the distal ulnar wrist joint is removed without affecting the distal ulnar wrist joint pressure and radioulnar joint (DRUJ) function. However, diaphysis osteotomy can damage the distal interosseous membrane and cause postoperative tendinitis because of the diaphysis plate. Metaphyseal osteotomy is suitable for the reconstruction of the TFCC fovea attachment and the shortening of the ulna, indicating that MUSO may be more minimally invasive. Wrist arthroscopy-assisted MUSO should start at the tip of the ulnar styloid process, followed by a longitudinal incision of 6-8 cm to the proximal end for the treatment of TFCC injury with ulnar

impaction because TFCC attachment avulsion is usually combined with UIS[33]. Compared with wrist arthroscopy-assisted DUSO, minimally invasive method is significantly effective for the treatment of ulnar impaction with TFCC injury. The incision of wrist arthroscopy-assisted DUSO may be larger than 12 cm. Although DUSO and MUSO are both extra-articular surgeries, they may lead to radiologically visible degenerative changes in DRUJ[34]. Cha *et al*[34] indicated that surgeons should inform patients with type III DRUJ before surgery and the potential risk of changes in DRUJ arthritis. Nonetheless, the relationship between radiological degeneration of DRUJ and USO of UIS is unclear. The removal of the ulnar head is usually performed at the dome of the ulnar head or near the metaphyseal bone. Arthroscopic discectomy involves the removal of the dome of the ulnar head or moving ulnar head, mechanically decompressing the ulnocapal joint load[41], thus avoiding DRUJ damage. Postoperative wrist pain may be caused by pressure tension of ulnocarpal interosseous ligament due to excessive osteotomy. The tensioned ulnocapal ligament, especially at DRUJ, increases the risk of arthritis in DRUJ. Arthroscopic wafer resection has an advantage at the intra-articular ulnar head, making it superior to DUSO or MUSO since it reduces the risk of arthritis changes in DRUJ[4,9,11,41].

CONCLUSION

DUSO is associated with a higher secondary procedure rate[4,9,11,41], especially the removal of the plate. DUSO is also associated with a risk of a second fracture at the osteotomy site after plate removal. Although DUSO and MUSO have similar effect for UIS treatment, MUSO is associated with a lower secondary procedure rate, slightly lower postoperative DASH score, and slightly better pain relief, and thus is suitable for UIS treatment.

ARTICLE HIGHLIGHTS

Research background

Although metaphyseal ulnar shortening osteotomy (MUSO) is safer for the treatment of ulnar impaction syndrome (UIS) than diaphyseal ulnar shortening osteotomy (DUSO), DUSO is widely used for UIS treatment.

Research motivation

It is unknown whether any factor should be considered when choosing DUSO or MUSO for UIS treatment or whether it should be based on surgeon's decision only. This study tries to give some references to the surgeons.

Research objectives

This meta-analysis aimed to evaluate the effectiveness of DUSO and MUSO for UIS treatment and determine the factors that should be considered when choosing surgical treatment for UIS.

Research methods

Cochrane Library, MEDLINE (Ovid), PubMed, and EMBASE databases were searched. A manual search was also conducted on the relevant research to ensure that no research was omitted.

Research results

Two sample *t*-test showed that the postoperative grip strength of the unaffected extremity was not significantly different between the two groups. Two sample t-test was also applied to compare postoperative grip strength outcomes between two common lengths of ulnar shortening osteotomy. The postoperative grip strength outcomes were not significantly different between the 2.5-mm and 3.0-mm groups. However, the pre- and postoperative percentages of grip strength of the contralateral wrist were significantly different between the two groups. Specifically, grip strength improved by 32% and 28% in the MUSO group and DUSO group, respectively.

Research conclusions

Although DUSO and MUSO have similar effect for UIS treatment, MUSO is associated with a lower secondary procedure rate, slightly lower postoperative DASH score, and slightly better pain relief, and thus is suitable for UIS treatment.

Research perspectives

Although MUSO can be used for UIS treatment, it has not been verified in many patients. A large-scale and appropriate research requires long-term outcomes to distinguish and describe the benefits of one technology over another. Besides, previous retrospective studies had inherent selection biases using

different surgical techniques and equipment. Most included studies did not consider or report the etiology of UIS. Therefore, large sample size, multicenter prospective studies are needed to verify the above results. Besides, these studies should use unified surgical techniques and equipment for clearer conclusions. Surgical interventions were not randomly allocated because of ethical reasons. This meta-analysis summarized the bias risk of the included studies, pooled the selected outcomes, and compared the different outcomes between MUSO and DUSO for UIS treatment.

FOOTNOTES

Author contributions: Deng HL and Zhao JM concepted the study; Deng HL, Lu ML and Mao QL collected the data; Deng HL, Lu ML, Tang ZM and Zhao JM contributed to the formal analysis; Deng HL and Zhao JM contributed to the investigation; Deng HL, Zhao JM and Lu ML contributed to the methodology; Deng HL, Zhao JM, Tang ZM and Lu ML supervised the study; Zhao JM validated the study; Deng HL and Lu ML contributed to the visualization of the study; Deng HL and Lu ML originally drafted the manuscript; Deng HL, Zhao JM, Tang ZM and Mao QL reviewed and edited the manuscript.

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META-ANALYSIS

Relationship between body mass index and short-term postoperative prognosis in patients undergoing colorectal cancer surgery

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Abstract

BACKGROUND

Obesity is a state in which excess heat is converted into excess fat, which accumulates in the body and may cause damage to multiple organs of the circulatory, endocrine, and digestive systems. Studies have shown that the accumulation of abdominal fat and mesenteric fat hypertrophy in patients with obesity makes laparoscopic surgery highly difficult, which is not conducive to operation and affects patient prognosis. However, there is still controversy regarding these conclusions.

AIM

To explore the relationship between body mass index (BMI) and short-term prognosis after surgery for colorectal cancer.

METHODS

PubMed, Embase, Ovid, Web of Science, CNKI, and China Biology Medicine Disc databases were searched to obtain relevant articles on this topic. After the articles were screened according to the inclusion and exclusion criteria and the risk of literature bias was assessed using the Newcastle-Ottawa Scale, the prognostic indicators were combined and analyzed.

RESULTS

A total of 16 articles were included for quantitative analysis, and 15588 patients undergoing colorectal cancer surgery were included in the study, including 3775 patients with obesity and 11813 patients without obesity. Among them, 12 articles used BMI ≥ 30 kg/m^2 and 4 articles used BMI ≥ 25 kg/m^2 for the definition of obesity. Four patients underwent robotic colorectal surgery, whereas 12 underwent conventional laparoscopic colorectal resection. The quality of the literature was good. Meta-combined analysis showed that the overall complica-

tion rate of patients with obesity after surgery was higher than that of patients without obesity [OR = 1.35, 95%CI: 1.23-1.48, Z = 6.25, P < 0.0001]. The incidence of anastomotic leak after surgery in patients with obesity was not significantly different from that in patients without obesity [OR = 0.99, 95%CI: 0.70-1.41), Z = -0.06, P = 0.956]. The incidence of surgical site infection (SSI) after surgery in patients with obesity was higher than that in patients without obesity [OR = 1.43, 95%CI: 1.16-1.78, Z = 3.31, P < 0.001]. The incidence of reoperation in patients with obesity after surgery was higher than that in patients without obesity; however, the difference was not statistically significant [OR = 1.15, 95%CI: 0.92-1.45, Z = 1.23, P = 0.23]; Patients with obesity had lower mortality after surgery than patients without obesity; however, the difference was not statistically significant [OR = 0.61, 95%CI: 0.35-1.06, Z = -1.75, P = 0.08]. Subgroup analysis revealed that the geographical location of the institute was one of the sources of heterogeneity. Robot-assisted surgery was not significantly different from traditional laparoscopic resection in terms of the incidence of complications.

CONCLUSION

Obesity increases the overall complication and SSI rates of patients undergoing colorectal cancer surgery but has no influence on the incidence of anastomotic leak, reoperation rate, and short-term mortality rate.

Key Words: Coloretal rectum cancer; Body mass index; Short-term prognosis; Cancer surgery

Core Tip: Colorectal rectal cancer (CRC) is a common malignant tumor in gastroenterology, ranking the third in the global incidence rate of malignant tumors, second only to lung cancer and breast cancer, with a mortality rate of about 8% of all malignant tumors. Like other malignant tumors, the etiology of CRC is still unclear. It may occur in the colon or anywhere in the rectum, but it is most common in the rectum and sigmoid colon, and the rest are in the cecum, ascending colon, descending colon and transverse colon in turn. So far, the radical treatment of CRC is still surgical treatment. The definition of radical cancer resection is to remove tumors visible to the naked eye, including primary and drainage lymph nodes. Although lesions can be removed during surgery, complete removal is still not easy for patients with extensive local diseases. For patients with advanced CRC, the tumor size is relatively large, there are many vascular variations, the field of vision of laparotomy is poor, and the operation is difficult.

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INTRODUCTION

Colorectal rectal cancer (CRC) is a common malignant tumor and ranks third in the incidence of malignant tumors worldwide; it is second only to lung and breast cancers, with a mortality rate of approximately 8%[1] of all malignant tumors. Similar to other malignancies, the cause of CRC remains unclear and can occur anywhere in the colon or rectum; however, it is most common in the rectum and sigmoid colon, whereas the remainder is found sequentially in the cecum, ascending, descending, and transverse colon[2]. Surgical treatment still remains the radical treatment of CRC, and radical resection of intestinal cancer is defined as the removal of macroscopic tumors, including primary and draining lymph nodes. Although the lesion can be removed during surgery, complete removal is still difficult in patients with extensive local disease[3]. For patients with advanced CRC, the tumor size is relatively large, with high vascular variation, and the visual field of laparotomy is poor, making the surgery difficult. In recent years, laparoscopy has emerged as an auxiliary operation with the advantages of a small surgical wound, an open operation field, and rapid postoperative recovery. It has been gradually applied to radical resection of CRC and has achieved an ideal clinical effect[4]. Obesity is a state in which excess heat in the human body is converted into excess fat, which accumulates in the body and may cause damage to the circulatory, endocrine, and digestive systems[5]. Studies have suggested that abdominal fat accumulation and mesenteric fat hypertrophy in patients with obesity make laparoscopic surgery very difficult, which is not conducive to the operation and affects patient prognosis[6]. However, other studies have also shown that obesity is not associated with a short-term prognosis after

surgery[7]. The controversial findings may be related to the sample size in the study, individual differences between patients and tumors, or time to evaluate body mass index (BMI). We conducted a meta-analysis to explore the relationship between BMI and short-term prognosis after surgery for CRC.

MATERIALS AND METHODS

Database

In January 2023, we retrieved the PubMed, Embase, Ovid, Web of Science, CNKI, and China Biology Medicine disc databases in the keyword-free search mode. Key words included: "*obesity*" or "*obese*" or "*BMI*" or "*laparoscopic colorectal resection*."

Literature inclusion criteria

(1) Study type: All studies were observational cohort studies (either retrospective or prospective); (2) Research participants: The primary disease of all the research participants was CRC, including all malignant tumors occurring in the colon or rectum. It was clarified in the study that the patients were treated by surgical resection, and the resection operations included but was not limited to the following common laparoscopic operations: Right hemicolectomy, expanded right hemicolectomy, ileocolic resection, and left hemicolectomy; (3) Grouping or cohort division: There must be two or more definite cohorts in the study. The cohorts were grouped such that patients were divided into obese and non-obese groups according to BMI ≥ 30 kg/m^2 or BMI ≥ 25 kg/m^2[8]; and (4) Outcome indicators: Short-term prognosis indicators of the two groups, such as complication rate, mortality after surgery, reoperation rate, and hospital stay, must be provided in the study.

Literature exclusion criteria

(1) Patients with non-primary CRC; (2) Patients who did not provide the grouping criteria for obesity or for whom cohort data of obese and non-obese were not available; the patient type was visceral obesity; (3) The study type was a non-observational cohort study, such as a case study; and (4) Studies with missing outcome indicators and for which data were not available, such as studies with only long-term prognostic survival analysis and no short-term prognostic survival indicators.

Literature screening

After literature retrieval, repetitive literature was excluded using software. The titles and abstracts were read by two researchers, and screening was conducted according to the inclusion and exclusion criteria. After the final literature was determined, the full text of the literature was obtained individually from the Internet. If the original text was not obtained, the author of the original text was contacted by phone or email to obtain the full text. The full texts of the articles were read for data extraction and further screening to remove articles with no data or incomplete indicators.

Literature quality and bias risk assessment

Literature quality and bias risk assessment were performed using the Newcastle-Ottawa Scale[9] for quality analysis of the included literature. The scale was used to evaluate the object selection, comparability, and outcome indicators in the literature. The maximum score was 9 points, and the quality was good, with a score of > 5 points. Higher scores indicated better literature quality and less bias, with a score of 5–7 indicating medium quality and 8–9 indicating high quality. Articles with scores < 5 were excluded.

Data extraction

Two researchers independently extracted literature data: Study type, date of publication, study location, age of the patient, tumor type, tumor stage, BMI, intraoperative indicators, postoperative indicators, and prognosis indicators. After the two researchers completed data extraction, they cross-examined each other's results and discussed and finalized the differences generated.

Statistical methods

(1) The discrete variables were reported as effect quantity with OR and 95%CI; (2) Statistical comparisons were described using forest plot; (3) Literature heterogeneity was analyzed using I^2 method and Q-test, and I^2 > 50% or P < 0.1 indicated the heterogeneity of the results; (4) In case of no heterogeneity between the articles, the fixed-effects model (Mantel–Haenszel) was used; in case of heterogeneity between the articles, the Dersimonian–Laird method was used; (5) Survey of heterogeneity: Subgroup analysis was used to investigate heterogeneity; (6) Meta-regression analysis was used to investigate factors that were significant for effect size; (7) Sensitivity analysis: Diagnostic tests were used to analyze studies that might have influenced the pooled results; literature was culled one by one and the combined effects of the remaining articles were calculated to identify the articles that most affected the results; and (8) Publication bias was detected using the Egger's test and results of

publication bias were presented using a trim-filled plot.

RESULTS

Literature screening results

As shown in Figure 1, which is a flow chart of the literature selection process, 873 articles were initially retrieved. After initial deduplication and screening, 18 articles[6,10-26] were included in the final screening. However, articles[16] lacking a short-term prognosis indicator and articles[19] whose data could not be obtained were excluded; finally, 16 articles were included. A total of 15588 patients (3775 with obesity and 11813 without obesity) were included in the study. Among them, 12 articles used BMI ≥ 30 kg/m^2 and 4 articles used BMI ≥ 25 kg/m^2 for the definition of obesity. Four patients underwent robotic colorectal surgery and 12 underwent conventional laparoscopic resection. The basic characteristics, grouping information, and outcome indicator lists of all articles and patients are listed in Table 1.

Literature quality and bias assessment

Among the 16 included articles, 10[6,10-15,17,18,26] had a quality score of 8–9, with little bias and high quality. A total of six articles[20-25] were scored 6–7, with a small amount of bias and medium quality. The overall quality was good (Table 2).

Meta-analysis results

Total complication rate after surgery for CRC (Obese *vs* Non-obese): All articles[6,10-15,17,18,20-26] reported the total complication rates of patients with obesity and those without obesity after surgery. There was no statistical heterogeneity between the articles (I^2 = 41%, P = 0.05). According to the fixed-effects model and meta-analysis, the complication rate of patients with obesity after surgery was higher than that of patients without obesity [OR = 1.35, 95%CI: 1.23-1.48, Z = 6.25, P < 0.0001] (Figure 2).

Incidence of postoperative anastomotic leak in patients with CRC (Obese vs Non-obese): Twelve articles[10-15,17,20-23,26] reported the incidence of anastomotic leak in patients with obesity and those without obesity after surgery. There was no statistical heterogeneity between the articles (I^2 = 0%, P = 0.63). A fixed-effects model was used. The incidence of anastomotic leak in patients with obesity after surgery was not statistically different from that in patients without obesity according to the meta-analysis [OR = 0.99, 95%CI: 0.70-1.41, Z = -0.06, P = 0.956] (Figure 3).

Incidence of SSI in patients with CRC after surgery (Obese vs Non-obese): The incidence of surgical site infection (SSI) between patients with obesity and those with obesity after surgery was reported in 13 articles[6,10-15,17,20-23,26]. There was no statistical heterogeneity between the articles (I^2 = 11%, P = 0.33). According to the fixed-effects model and meta-analysis, the incidence of SSI in patients with obesity after surgery was higher than that in patients without obesity [OR = 1.43, 95%CI: 1.16-1.78, Z = 3.31, P < 0.001] (Figure 4).

Reoperation rate after surgery for CRC (Obese vs Non-obese): Nine articles[6,10,11,13,14,17,24-26] reported the postoperative reoperation rates of patients with obesity and those without obesity. There was no statistical heterogeneity between the articles (I^2 = 1%, P = 0.43). According to the fixed-effects model and meta-analysis, the reoperation rate of patients with obesity after surgery was higher than that of patients without obesity, but the difference was not statistically significant [OR = 1.15, 95%CI: 0.92-1.45, Z = 1.23, P = 0.23] (Figure 5).

Postoperative mortality of patients undergoing CRC surgery (Obese vs Non-obese): Eleven articles[6,10,11,13,14,17,18,20,22,24,25] reported the short-term mortality rates of patients with obesity and those without obesity after surgery. There was no statistical heterogeneity between the articles (I^2 = 0%, P = 0.46). Using a fixed-effects model and meta-analysis, it was found that the mortality rate of patients with obesity after surgery was lower than that of patients without obesity. However, the differences were not statistically significant [OR = 0.61, 95%CI: 0.35-1.06, Z = -1.75, P = 0.08], as shown in Figure 6.

Source survey of heterogeneity

Although there was no statistical heterogeneity between the articles in the analysis of the overall complication incidence index after surgery (I^2 = 41%, P = 0.05), there was still some heterogeneity. We conducted subgroup analysis according to the "*geographical location*", "*surgery approach*," and "*obese BMI* " and found that after the articles were grouped according to the study site and "*geographical location*," the inter-group heterogeneity test between subgroups was P < 0.05, indicating that the "*geographical location*" of the study site was one of the sources of heterogeneity in this study, as shown in Table 3.

Meta-regression analysis

In the analysis of the overall complication incidence index after surgery, to understand the factors that

Table 1 Basic characteristics, patient characteristics, grouping information, surgical measures, and prognosis indicators of included articles

Ref.	Country	Patient's age (years)	Obesity definition	Overall number of people	Grouping number (O/N)	Surgical measures	Outcome indicators
Hannan *et al*[10], 2022	Ireland	67	BMI: 30 kg/m^2	107	34/73	Robotic colorectal surgery	a, b, c, d, e
Lagares-Garcia *et al* [11], 2016	United States	59.9 ± 13.8	BMI: 30 kg/m^2	67	34/33	Robotic colorectal surgery	a, b, c, d
Akiyoshi *et al*[12], 2011	Japan	63.9 (23–91)	BMI: 25 kg/m^2	1,169	243/926	Laparoscopic colorectal resection	a, b, e
Merkow *et al*[13], 2009	United States	68.02 ± 6.18	BMI: 30 kg/m^2	1,679	607/1072	Laparoscopic colorectal resection	a, c, d, e
Choi *et al*[14], 2017	Korea	66.7 ± 11.2	BMI: 25 kg/m^2	313	80/233	Laparoscopic colorectal resection	a, b, c, d, e
Zhang *et al*[15], 2021	China	55 (36–78)	BMI: 30 kg/m^2	356	48/308	Laparoscopic colorectal resection	a, b, c, d, e
Yamashita *et al*[16], 2021	Japan	70 (24–96)	BMI: 25 kg/m^2	1,648	313/1335	Laparoscopic colorectal resection	a, b, e
Bège *et al*[18], 2009	France	62 ± 10.7	BMI: 30 kg/m^2	210	24/186	Laparoscopic colorectal resection	a, b, c, d, e
Hede *et al*[19], 2015	Sweden	72.7 ± 13.1	BMI: 30 kg/m^2	6,675	1528/5147	Laparoscopic colorectal resection	a, d
Makino *et al*[21], 2014	United States	67.5 ± 11.7	BMI: 30 kg/m^2	152	76/76	Laparoscopic colorectal resection	a, b, d, e
Bamboat *et al*[22], 2012	United States	65	BMI: 30 kg/m^2	245	68/177	Laparoscopic colorectal resection	a, b, e
Miyamoto *et al*[23], 2014	Japan	65.9 ± 9.6	BMI: 25 kg/m^2	561	140/421	Laparoscopic colorectal resection	a, b, d, e
Bayraktar *et al*[24], 2018	Turkey	60 ± 11	BMI: 30 kg/m^2	101	30/71	Robotic colorectal surgery	a, b, e
Poulsen *et al*[25], 2012	Denmark	69 (37–97)	BMI: 30 kg/m^2	425	93/332	Laparoscopic colorectal resection	a, c, d
Bell *et al*[26], 2018	Australia	71.6	BMI: 30 kg/m^2	1464	299/1165	Laparoscopic colorectal resection	a, c, d
Peacock *et al*[27], 2020	United States	54.1 ± 12.5	BMI: 30 kg/m^2	533	161/372	Robotic colorectal surgery	a, b, c, e

O/N: Obese/Non-obese; SSI: Surgical site infection; a: Postoperative complication rate; b: Anastomotic leak rate; c: 30-d reoperation rate; d: 30-d mortality rate; e: SSI rate.

may affect the results of Pooled ES, we used the "*year of publication*," "*sample size*," and "*patient's age*" to regression pooled ES, and found that none of the three factors had a statistically significant effect on the results ($P > 0.05$), which indicates that none of the three factors was able to affect the results Figure 7.

Sensitivity analysis

The results of the analysis of the postoperative complication rate indicators were verified using sensitivity diagnosis, and it was found that the literature significantly affected the results, which might be related to the fact that the sample size of the literature was much larger than that of other studies [18]. After literature[18] was excluded, the remaining 15 studies were excluded individually, and no significant deviations were found, indicating that the final pool result was stable, as shown in Figure 8.

Analysis of publication bias

In the analysis of the incidence indicators of postoperative complications, publication bias was detected using Egger's *t*-test, with $t = 0.43$ and $P = 0.20$, indicating no significant left-right asymmetry in the funnel plot, as shown in Figure 9.

Table 2 Quality Assessment Based on New Castle–Ottawa Scale

Ref.	Case selection (/4)	Comparability (/2)	Outcome indicators (/3)	Total score (/9)
Hannan *et al*[10], 2022	4	2	3	9
Lagares-Garcia *et al*[11], 2016	4	2	2	8
Akiyoshi *et al*[12], 2011	4	2	2	8
Merkow *et al*[13], 2009	4	2	3	9
Choi *et al*[14], 2017	4	2	2	8
Zhang *et al*[15], 2021	4	2	2	8
Yamashita *et al*[16], 2021	4	2	3	9
Bège *et al*[18], 2009	4	2	2	8
Hede *et al*[19], 2015	4	2	3	9
Makino *et al*[21], 2014	3	2	2	7
Bamboat *et al*[22], 2012	3	2	2	7
Miyamoto *et al*[23], 2014	2	2	2	6
Bayraktar *et al*[24], 2018	2	2	2	6
Poulsen *et al*[25], 2012	3	2	2	7
Bell *et al*[26], 2018	2	2	2	6
Peacock *et al*[27], 2020	4	2	2	8

Table 3 Subgroup analysis of indicators of overall complication incidence after surgery

Grouping number	Subgroup grouping method	Subgroup	Number of articles	Effect size	Heterogeneity	
					I^2 (%)	tau^2
1	Geographical location	Europe	6	OR = 1.59, (1.40, 1.80)	0	0
		North America	5	OR = 1.14, (0.94, 1.37)	0	0
		Asia	5	OR = 1.13, (0.84, 1.52)	35.4	0.04
2	Surgery approach	Robotic colorectal surgery	4	OR = 1.18, (0.85, 1.64)	0	0
		Laparoscopic colorectal resection	12	OR = 1.28, (1.08, 1.51)	53.3	0
3	Obese body mass index	30 kg/m^2	12	OR = 1.34, (1.14, 1.57)	21.8	0.02
		25 kg/m^2	4	OR = 1.14, (0.81, 1.58)	51.3	0.06

DISCUSSION

Over the past few years, overweight and obesity have gradually become widespread epidemics. Obesity is related to the occurrence of several diseases. In addition to cardiovascular and cerebrovascular diseases, obesity is closely related to the occurrence of many cancers, including colorectal, endometrial, and breast cancers[27,28]. However, studies on obesity and surgical prognosis of these tumors are rare and controversial.

To explore the impact of being overweight on the short-term prognosis of CRC surgery, 16 observational cohort studies with 15588 participants were included in this meta-analysis. The results showed that being overweight can increase the overall incidence of complications after CRC surgery and the incidence of SSI. However, the impact on the incidence of anastomotic leak, reoperation rate, and mortality was not obvious. In recent years, laparoscopic colorectal cancer resection has been widely used in clinical colorectal cancer radical surgery because of its small wound, open operation field, few complications, rapid postoperative recovery, and other advantages, and its short-term and long-term efficacy has been widely recognized worldwide[29]. However, for some patients with CRC, the tumor size is relatively large and the visual field during laparotomy is poor. As the operation involves the anatomy and root treatment of multiple important blood vessels, such as ileocolic and colonic vessels, the difficulty of completing the operation under laparoscopy is greatly increased. In addition, with changes in the dietary habits of people, an increasing number of people are becoming obese. Obesity is

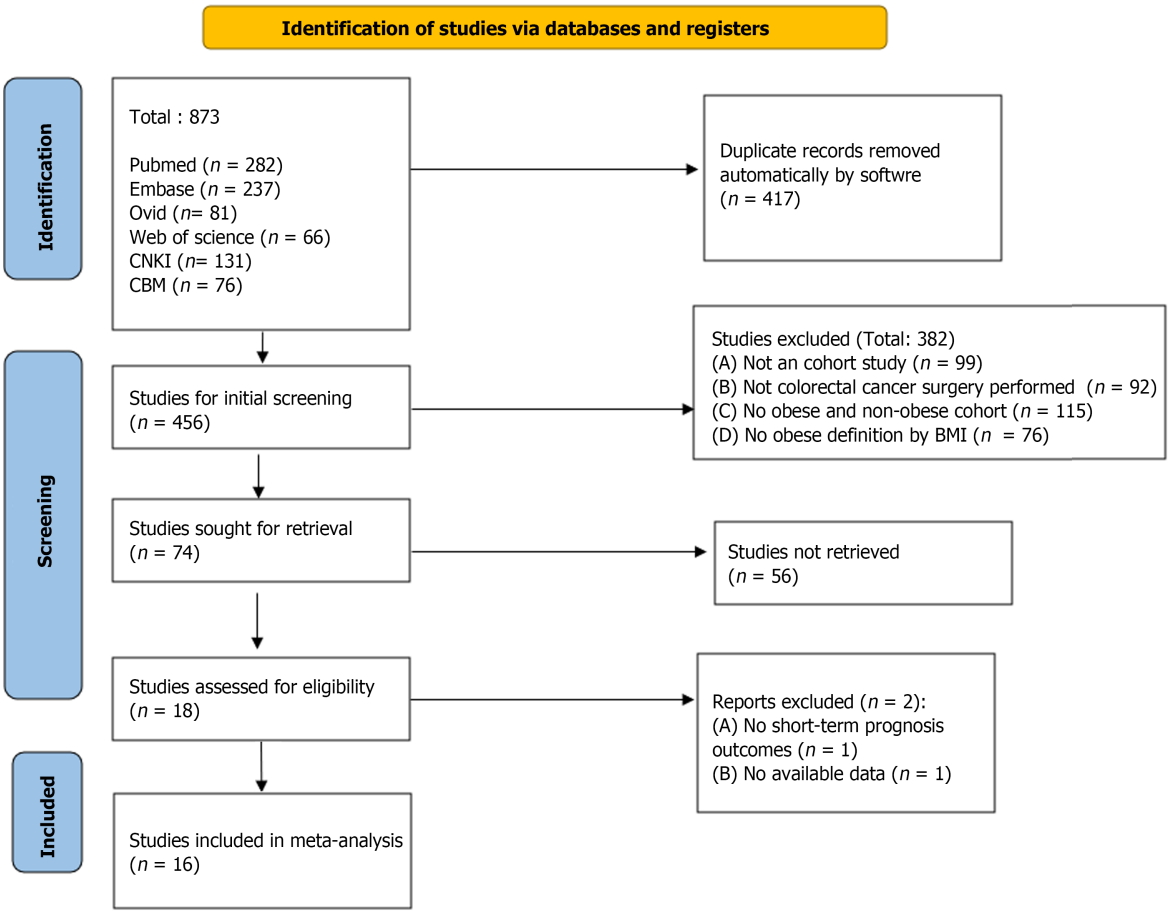

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Figure 1 Literature selection flow chart.

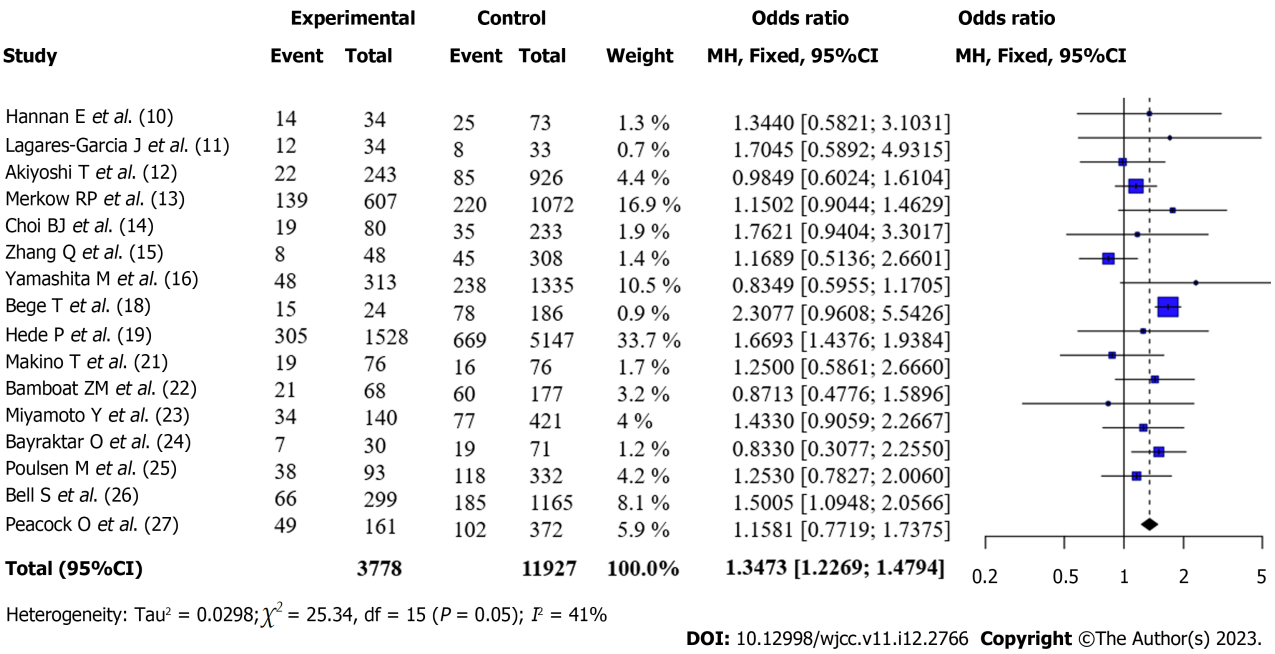

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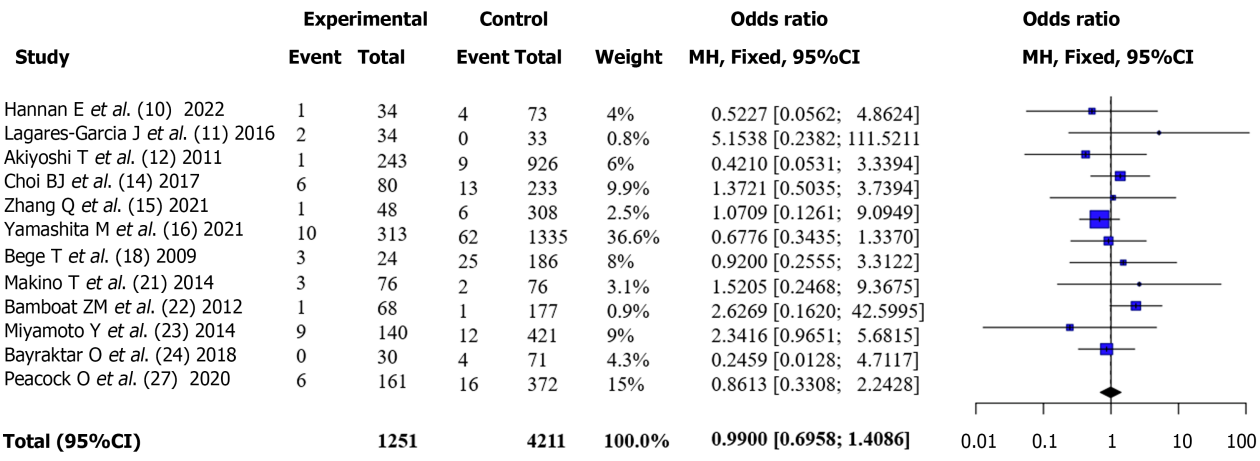
Figure 2 Comparison of total complication rates after surgery in patients with colorectal rectal cancer (Obese VS Non-obese).

not only an induction factor for multiple internal medicine diseases but also has many negative effects on surgery[30]. Patients with obesity and CRC are very likely to suffer from severe vascular injury during surgery due to abdominal fat accumulation, mesenteric fat hypertrophy, and narrow space in the abdominal cavity, which makes laparoscopic radical resection difficult. Obesity may also result in



Heterogeneity: Tau² = 0.0493; χ^2 = 8.87, df = 11 (*P* = 0.63); I^2 = 0%

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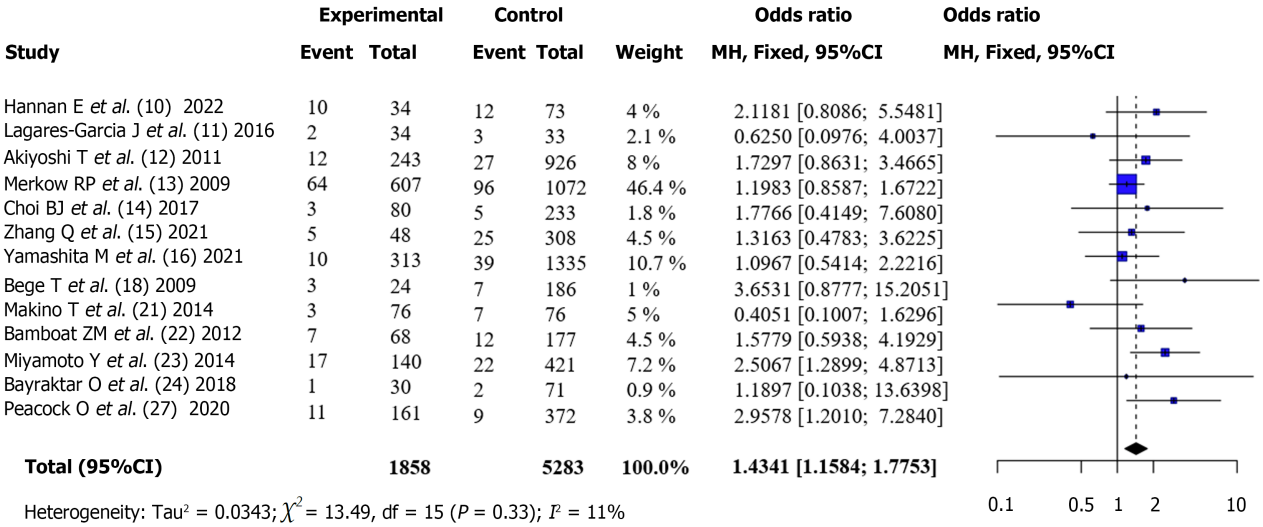
Figure 3 Comparison of the incidence of anastomotic leak after surgery in patients with colorectal rectal cancer (Obese VS Non-obese).



Heterogeneity: Tau² = 0.0343; χ^2 = 13.49, df = 15 (*P* = 0.33); I^2 = 11%

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Figure 4 Comparison of surgical site infection incidence in patients with colorectal rectal cancer after surgery (Obese VS Non-obese).

reduced oxygen circulation in wounds, insufficient collagen synthesis, insufficient antibiotic concentration, and impaired immune function, which make patients vulnerable to infection, causing complications, such as incision infection, intestinal obstruction, and anastomotic leak, which prolong the hospitalization time of patients and increase reoperation and mortality rates[4].

In this study, we conducted a regression analysis of the three factors that may affect the results of the meta-analysis, including "*year of publication*," "*sample size*," and "*patient's age*" and found that none of the three factors could affect the results of the meta-analysis. In the stability analysis, we removed the large sample literature that may have affected the results and found that the results were not fundamentally reversed. Publication bias analysis showed that there was no statistically significant asymmetry on either side of the funnel, which indicated that the results of this study were stable and reliable, and the evidence was sufficient.

In this study, we adopted a subgroup analysis approach to explore the sources of heterogeneity in the meta-analysis. As some included studies adopted BMI ≥ 30 kg/m² as the definition of obesity, while others adopted BMI ≥ 25 kg/m² as the definition of obesity, it is very likely that the different BMI definitions of obesity increased the heterogeneity between the articles. The World Health Organization defines grade I obesity as BMI of 30 kg/m² and above, grade II obesity as BMI 35.00–39.99 kg/m², and grade III obesity as BMI ≥ 40.00 kg/m². However, due to the prevalence of obesity among different populations and different understandings of obesity, it is also common to adopt BMI ≥ 25 kg/m² as the definition of obesity in regions (such as some countries in East Asia)[31]. However, in this subgroup analysis, it was found that the heterogeneity between the two standard groups was not statistically significant, which indicates that regardless of which definition standard was adopted, it had little

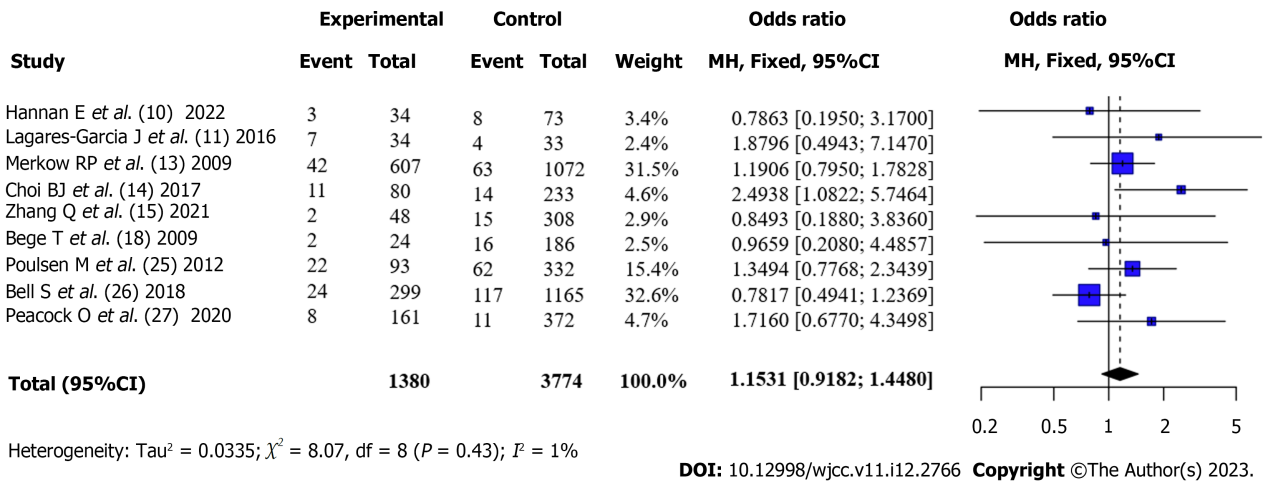

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Figure 5 Comparison of the incidence of reoperation after operation in patients with colorectal rectal cancer (Obese VS Non-obese).

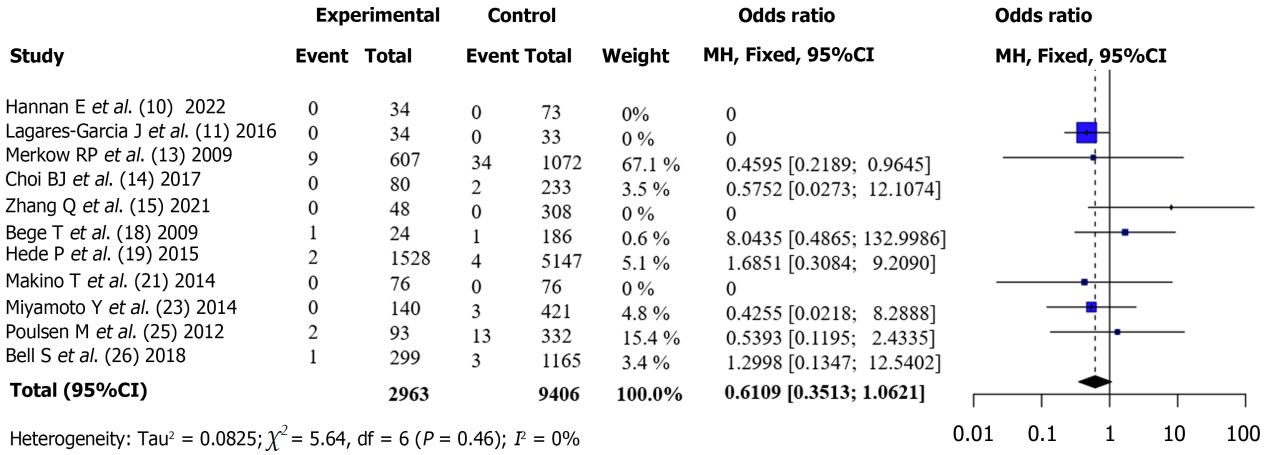

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Figure 6 Comparison of mortality rates after surgery in patients with colorectal rectal cancer (Obese VS Non-obese).

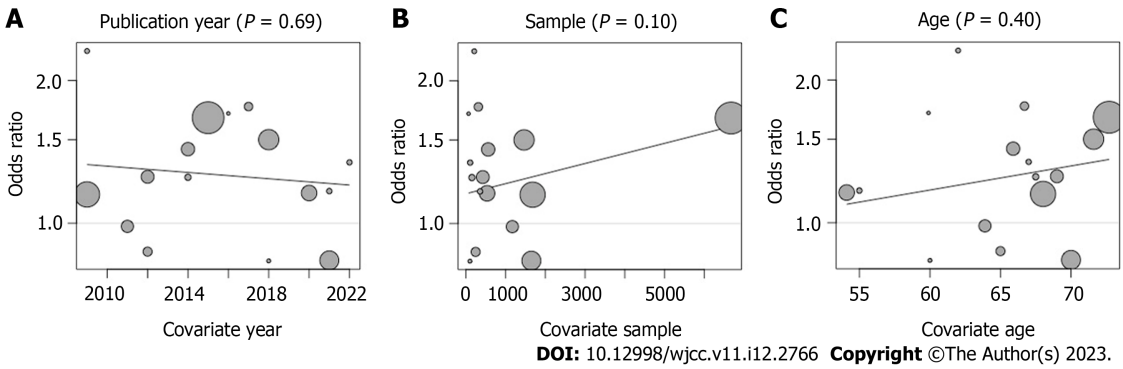

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Figure 7 Meta-regression analysis of indicators of postoperative complication rate: Publication year (*P* = 0.69), sample size (*P* = 0.10), and patient age factors (*P* = 0.40).

impact on the results.

We further divided the 16 articles into three regions, namely Europe, America, and Asia, according to the regions where the research was conducted. The subgroup analysis found that the heterogeneity among the groups in the three regions was statistically significant and that the ethnic groups in the three regions had significant effects on the results of the meta-analysis. Studies have suggested that East Asian populations are highly vulnerable to obesity and cardiovascular diseases, which may be related to the surgical prognosis of CRC. However, the specific mechanisms require further investigation.

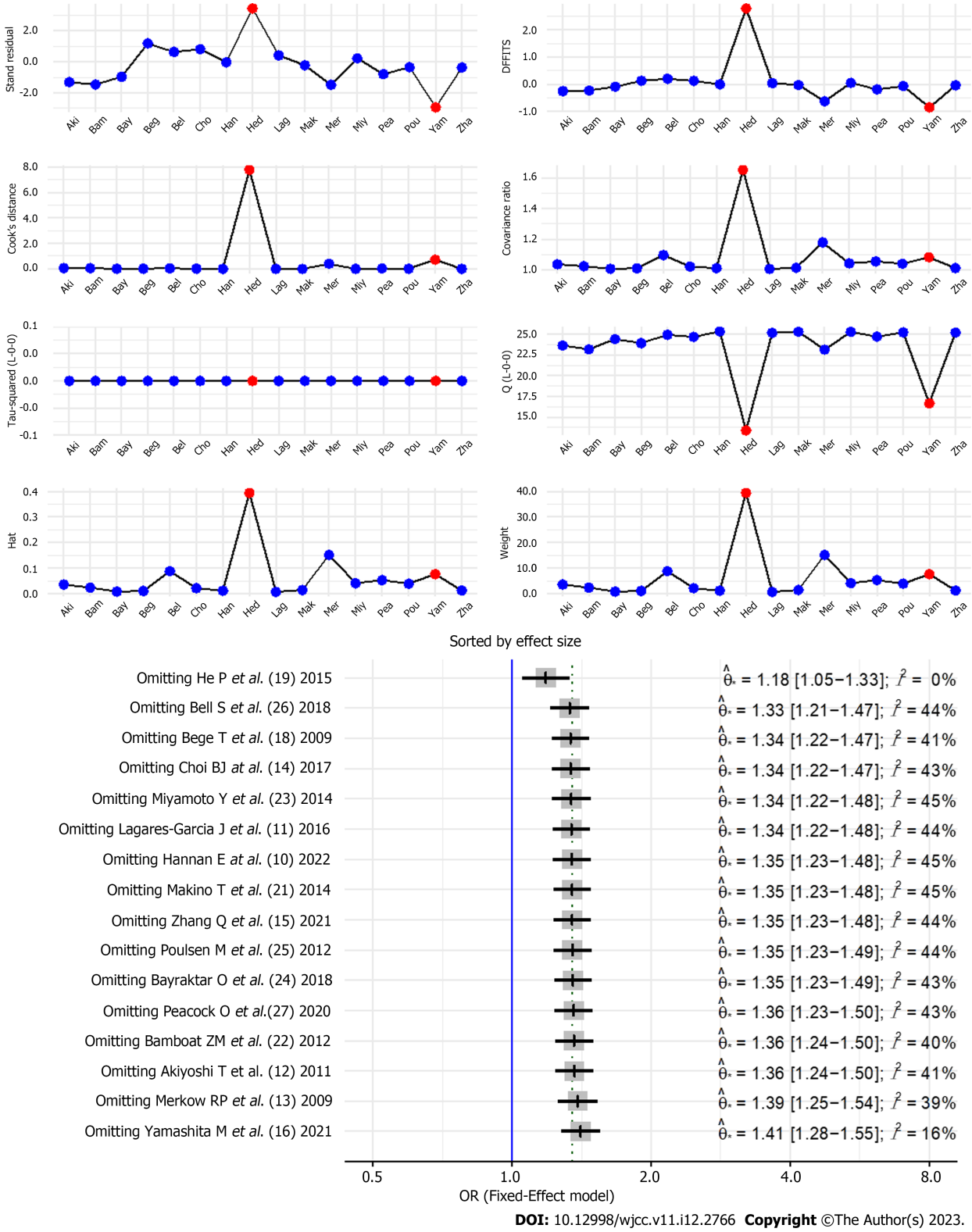

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Figure 8 Sensitivity analysis of postoperative complication incidence index.

In recent years, great progress has been made in the robot-assisted radical resection of CRC. Panteleimonitis *et al*[32] in their research compared it with conventional laparoscopic surgery and found that for patients with obesity, robot-assisted colorectal cancer surgery compared with laparoscopic surgery had a shorter hospital stay and a lower readmission rate of 30 d; however, the operation time was longer. This suggests that robot-assisted colorectal cancer surgery may have a better prognosis than laparoscopic surgery for patients with obesity; however, the heterogeneity between the two surgeries was not statistically significant in this subgroup analysis, and there was no significant difference between the total complication rates of the two surgeries. Therefore, the advantages of robot-assisted colorectal surgery require further studies and validation using different research indicators.

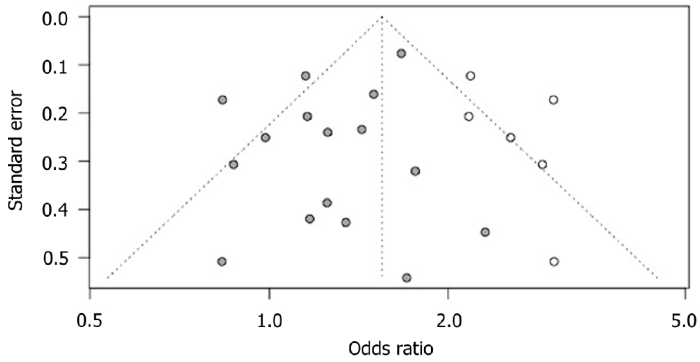

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Figure 9 Trim-filled funnel plot of complication incidence after surgery.

Although the sample size included in this study was sufficient and the results of the sensitivity analysis were stable, there were still some limitations. First, the prognostic indicators were not complete enough, and there were no informative indicators, such as the patient's hospital stay, postoperative urinary tract infection, and acute renal failure; Second, the included studies were observational cohort studies, and process control for the studies was insufficient. Some patients who switched to laparotomy when laparoscopic surgery was ineffective were considered to have undergone laparoscopic surgery; and Third, some patients with benign tumors in some studies were included in this meta-analysis, and there may be some bias. Thus, further research on this topic is warranted.

CONCLUSION

Obesity (excessive BMI) can increase the overall complication and SSI rates of patients with CRC after radical surgery but has no significant effect on the incidence of anastomotic leak, reoperation rate of patients, and short-term mortality rate.

ARTICLE HIGHLIGHTS

Research background

Obesity is a state in which excess heat is converted into excess fat, which accumulates in the body and may cause damage to multiple organs of the circulatory, endocrine, and digestive systems. Studies have shown that the accumulation of abdominal fat and mesenteric fat hypertrophy in patients with obesity makes laparoscopic surgery highly difficult, which is not conducive to operation and affects patient prognosis. However, there is still controversy regarding these conclusions.

Research motivation

Research on the state of obese patients converting excess heat into excess fat, which can accumulate in the body and cause damage to multiple organs of the circulatory, endocrine, and digestive systems. Abdominal fat accumulation and mesenteric fat in obese patients make laparoscopic surgery difficult, detrimental to surgery, and affecting patient prognosis.

Research objectives

To explore the relationship between body mass index (BMI) and short-term prognosis after surgery for colorectal cancer.

Research methods

PubMed, Embase, Ovid, Web of Science, CNKI, and China Biology Medicine Disc databases were searched to obtain relevant articles on this topic. After the articles were screened according to the inclusion and exclusion criteria and the risk of literature bias was assessed using the Newcastle-Ottawa Scale, the prognostic indicators were combined and analyzed.

Research results

A total of 16 articles were included for quantitative analysis, and 15588 patients undergoing colorectal cancer surgery were included in the study, including 3775 patients with obesity and 11813 patients without obesity. Among them, 12 articles used BMI ≥ 30 kg/m^2 and 4 articles used BMI ≥ 25 kg/m^2 for

the definition of obesity. Four patients underwent robotic colorectal surgery, whereas 12 underwent conventional laparoscopic colorectal resection. The quality of the literature was good. Meta-combined analysis showed that the overall complication rate of patients with obesity after surgery was higher than that of patients without obesity [OR = 1.35, 95%CI: 1.23-1.48, Z = 6.25, P < 0.0001]. The incidence of anastomotic leak after surgery in patients with obesity was not significantly different from that in patients without obesity [OR = 0.99, 95%CI: 0.70-1.41), Z = -0.06, P = 0.956]. The incidence of surgical site infection (SSI) after surgery in patients with obesity was higher than that in patients without obesity [OR = 1.43, 95%CI: 1.16-1.78, Z = 3.31, P < 0.001]. The incidence of reoperation in patients with obesity after surgery was higher than that in patients without obesity; however, the difference was not statistically significant [OR = 1.15, 95%CI: 0.92-1.45, Z = 1.23, P = 0.23]; Patients with obesity had lower mortality after surgery than patients without obesity; however, the difference was not statistically significant [OR = 0.61, 95%CI: 0.35-1.06, Z = -1.75, P = 0.08]. Subgroup analysis revealed that the geographical location of the institute was one of the sources of heterogeneity. Robot-assisted surgery was not significantly different from traditional laparoscopic resection in terms of the incidence of complications.

Research conclusions

Obesity increases the overall complication and SSI rates of patients undergoing colorectal cancer surgery but has no influence on the incidence of anastomotic leak, reoperation rate, and short-term mortality rate.

Research perspectives

Colorectal rectal cancer (CRC) is a common malignant tumor and ranks third in the incidence of malignant tumors worldwide; it is second only to lung and breast cancers, with a mortality rate of approximately 8% of all malignant tumors. Similar to other malignancies, the cause of CRC remains unclear and can occur anywhere in the colon or rectum; however, it is most common in the rectum and sigmoid colon, whereas the remainder is found sequentially in the cecum, ascending, descending, and transverse colon. Surgical treatment still remains the radical treatment of CRC, and radical resection of intestinal cancer is defined as the removal of macroscopic tumors, including primary and draining lymph nodes. Although the lesion can be removed during surgery, complete removal is still difficult in patients with extensive local disease. For patients with advanced CRC, the tumor size is relatively large, with high vascular variation, and the visual field of laparotomy is poor, making the surgery difficult. In recent years, laparoscopy has emerged as an auxiliary operation with the advantages of a small surgical wound, an open operation field, and rapid postoperative recovery. It has been gradually applied to radical resection of CRC and has achieved an ideal clinical effect.

FOOTNOTES

Author contributions: Li Y conceptualized and designed the study, and collected and compiled the data; Jiang J provided administrative support; Li Y provided the research materials and patients; Deng JJ and Jun Jiang analyzed and interpreted the data; and all authors wrote and approved the final version of the manuscript.

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CASE REPORT

Cardiac amyloidosis presenting as pulmonary arterial hypertension: A case report

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Abstract

BACKGROUND

Pulmonary hypertension is a rare cardiopulmonary disease, with an insidious onset that usually worsens rapidly. Amyloid light chain (AL) amyloidosis is a rare systemic disease caused by extracellular deposition of pathologic, insoluble, and proteinaceous fibrils in organs and tissues; however, it is difficult to diagnose given its varied and nonspecific symptoms. To date, rare cases of amyloidosis with pulmonary hypertension have been reported. Of note, the optimal treatments for cardiac amyloidosis complicated with pulmonary hypertension remain unclear.

CASE SUMMARY

We report a case of a 51-year-old woman who presented with progressively worsening dyspnea. Transthoracic echocardiography indicated severe pulmonary hypertension. Twenty-seven months after first admission, the patient returned with symptoms of progressive heart failure. A myocardial tissue sample stained with Congo red was positive, and the patient was ultimately diagnosed with AL amyloidosis with cardiac involvement.

CONCLUSION

Although pulmonary hypertension may be idiopathic, it is frequently associated with other conditions. In rare cases, pulmonary hypertension can be a complication of AL amyloidosis, which should be seriously considered in any adult presenting with nonspecific signs or symptoms of cardiac distress.

Key Words: Cardiac amyloidosis; Heart involvement; Pulmonary hypertension; Case report

Core Tip: Symptomatic pulmonary hypertension is only rarely described and, when present, is typically associated with progressive disease, such as elevated filling pressures secondary to cardiac amyloid. In this case, the patient initially presented with pulmonary hypertension, she was found, 2 years later, to have amyloid light chain (AL) amyloidosis with cardiac involvement. We highlight the diagnostic difficulties presented by pulmonary hypertension in a patient with AL amyloidosis, and illustrate the complicated progression of the disease, as well as the poor efficacy of current palliative medicine.

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INTRODUCTION

Pulmonary hypertension is a rare cardiopulmonary disease with an insidious onset that usually worsens rapidly, and, if left untreated, has a median survival of 2–3 years[1]. Although pulmonary hypertension may be idiopathic, it is frequently associated with other conditions. The most common clinical disorders that cause pulmonary hypertension include primary cardiac abnormalities, chronic pulmonary embolism, pulmonary parenchymal problems, obstructive sleep apnea, connective tissue disorders, cirrhosis with portal hypertension, and use of appetite suppressants[2]. Amyloid light chain (AL) amyloidosis is a rare systemic disease caused by extracellular deposition of pathologic, insoluble, and proteinaceous fibrils in organs and tissues[3]. Group I pulmonary hypertension is a rare complication of AL amyloidosis[4]. In addition to AL amyloidosis, transthyretin-related amyloidosis is considered a disease in the field of cardiology. Cardiac amyloidosis is confirmed by endomyocardial biopsy, with Congo red staining, nuclear scintigraphy and immunohistochemistry to determine the amyloid type[5]. To date, only a few, rare cases of amyloidosis with pulmonary hypertension have been reported. We present the following article in accordance with the CARE reporting checklist.

In this report, we highlight the diagnostic difficulties presented by pulmonary hypertension in a patient with AL amyloidosis, and illustrate the complicated progression of the disease, as well as the poor efficacy of current treatment strategies.

CASE PRESENTATION

Chief complaints

A 51-year-old woman was admitted to hospital due to dyspnea, occurring over a 1-mo period.

Physical examination

Physical examination revealed blood pressure of 101/55 mmHg, heart rate of 65 beats/min.

Laboratory examinations

Plasma N-terminal brain natriuretic peptide (NT-proBNP) was elevated to 3780 pg/mL (normal range 0-125 pg/mL).

Imaging examinations

Electrocardiography (ECG) demonstrated a sinus rhythm with a heart rate of 65 bpm, a left anterior fascicular block, poor R-wave progression in leads V1-V3, and a non-specific T wave and ST-segment (Figure 1A). A 2-dimensional transthoracic echocardiogram revealed right ventricular enlargement, with a chamber diameter of 27 mm, a left ventricular cavity of normal diameter, an end diastolic chamber size of 42 mm and preserved systolic function, as well as an ejection fraction of 64%. The left atrium (42 mm) and right atrium (48 mm × 48 mm) were both enlarged. Transmitral Doppler flow was consistent with restrictive physiology. The left ventricle was revealed to have impaired diastolic dysfunction (mitral E wave velocity = 0.99 m/s, A wave (1.28 m/s, medial E/e' > 15). Transthoracic echocardiography indicated severe pulmonary hypertension on the basis of the estimated right ventricular systolic pressures (the pulmonary arterial pressure was 51 mmHg). Pulmonary arterial hypertension is defined as pulmonary capillary wedge pressure < 15 mmHg and pulmonary vascular resistance > 3 Wood Units as assessed by right heart catheterization[6]. The criterion for clinically significant pulmonary hypertension when detected by Doppler echocardiography is not precisely defined. Commonly used definitions of pulmonary hypertension are a pulmonary artery systolic pressure > 35 mmHg or mean > 25 mmHg at rest or mean > 30 mmHg when exercising[7]. Color

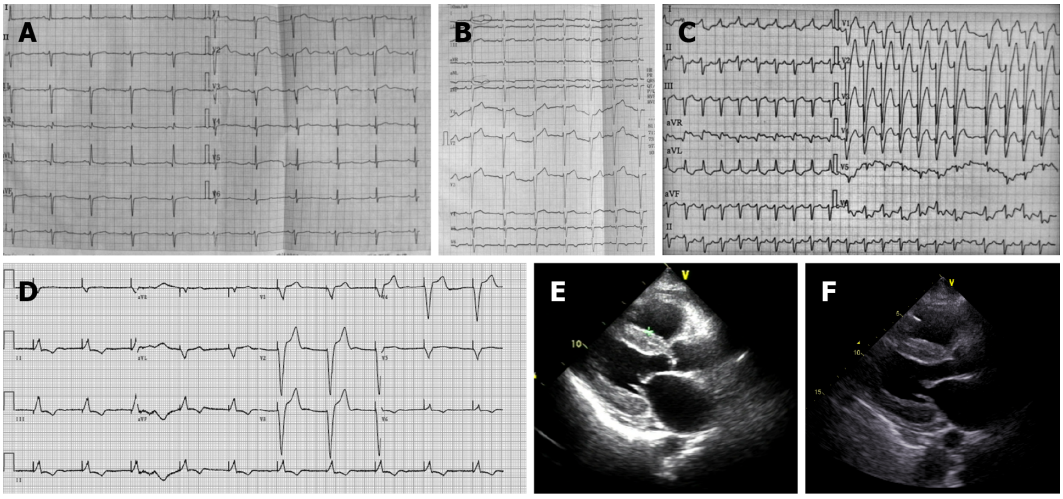

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Figure 1 Serial changes on electrocardiography and echocardiography. A: Electrocardiography (ECG) demonstrated a left anterior fascicular block, poor R-wave progression in leads V1-V3, and a non-specific T wave and ST-segment; B: 11 mo later, ECG demonstrated a new left bundle branch block, ST-segment depression in leads I and augmented unipolar limb lead (AVL) and T wave inversion in leads I, AVL, and V4-V6; C: 21 mo later, ECG demonstrated atrial fibrillation, left bundle branch block with wider QRS wave group, ST segment elevation in leads V1-V3, and T wave inversion in leads I, AVL and V4-V6; D: Echocardiography revealed characteristic sparkling and a granular texture in the ventricle wall; E: Pacing ECG was showed; F: Echocardiography revealed atrial enlargements and worsening systolic dysfunction (ejection fraction 48%).

Doppler showed mild regurgitation at the mitral and pulmonary valves. Furthermore, moderate tricuspid valve regurgitation was observed (the tricuspid regurgitation area was 7.8 cm^2).

When pulmonary hypertension was identified, the patient was further evaluated for an underlying etiology. A high resolution computed tomography angiogram of the chest did not show evidence of pulmonary embolism or signs of interstitial or other lung disease. The patient had negative findings upon spirometry, and denied a family history of pulmonary hypertension, sleep apnea, and premature death. No laboratory markers or clinical symptoms that suggested collagen vascular disease were detected in the patient. Furthermore, a Doppler ultrasound of the portal vein and liver scan did not show signs of portal hypertension. The patient also showed serologic test results that were negative for human immunodeficiency virus, and the patient refused right heart catheterization.

FINAL DIAGNOSIS

The patient was diagnosed with pulmonary hypertension based on echocardiographic finding. Pulmonary hypertension in heart failure with preserved ejection fraction represents the most complex situation. We cannot make a clear distinction between idiopathic pulmonary arterial hypertension (group 1 pulmonary hypertension) and pulmonary hypertension secondary to left heart disease (group 2 pulmonary hypertension) without right heart catheterization, Idiopathic pulmonary arterial hypertension was considered in our case who had an early indication of left ventricle diastolic dysfunction (E/e' > 15 and enlarged left atria), but severe pulmonary hypertension.

TREATMENT

The patient was treated with a phosphodiesterase 5 inhibitor (sildenafil, 20 mg, three times a day) and diuretics (furosemide, 20 mg, twice a day and spironolactone, 20 mg, three times a day), and showed subsequent improvement in signs and symptoms of right heart failure, in addition to a slight lowering of pulmonary hypertension.

OUTCOME AND FOLLOW-UP

However, the patient returned 11 mo after her first admission and presented with worsening dyspnea, paroxysmal nocturnal dyspnea, and complaints of an inability to lie flat on her back. Echocardiography showed newly-presenting left ventricular hypertrophy (the septal and left posterior wall thicknesses were 12 mm and 12 mm, respectively). NT-proBNP was elevated from 3780 pg/mL to 7910 pg/mL

(normal range 0-125 pg/mL). ECG demonstrated a left anterior fascicular block, a new left bundle branch block, ST-segment depression in leads I and augmented unipolar limb lead (AVL) and T wave inversion in leads I, AVL, and V4-V6 (Figure 1B).

Ten months later (21 mo after first admission), the patient's respiratory condition continued to deteriorate. The patient was admitted due to new appearance of orthopnea and worsening edema in the lower extremities. NT-proBNP was again elevated at 11600 pg/mL. Transthoracic echocardiography showed worsening systolic dysfunction, and echocardiography revealed progressive left ventricular hypertrophy (the septal and left posterior wall thicknesses were 14 mm and 13 mm, respectively). Furthermore, severe tricuspid regurgitation (13.2 cm^2) and higher pulmonary artery pressure (58 mmHg) were also observed. ECG demonstrated atrial fibrillation, left bundle branch block with wider QRS wave group, ST segment elevation in leads V1-V3, and T wave inversion in leads I, AVL and V4-V6.

Six month later (27 mo after first admission), the patient returned again with symptoms of New York Heart Association class III heart failure. ECG showed atrial fibrillation with rapid ventricular response, left bundle branch block (Figure 1C), first degree atrioventricular block, Mobitz type I second-degree Atrioventricular block, and premature ventricular contraction on 24-h dynamic electrocardiography. Echocardiography revealed progressive atrial enlargement (the left atrial diameter was 51 mm, and the right atrial diameter was 52 mm × 62 mm). The patient also had worsening systolic dysfunction (ejection fraction 48%). The ventricle wall had a characteristic sparkling apperance, with a granular texture (Figure 1D). Immunohistochemistry of amyloid deposits was used to distinguish transthyretin from other proteins that may cause amyloidosis. Immunoglobulin light chain was associated with AL amyloidosis. Serum free light-chain analysis showed lambda light-chain was increased at 378 mg/L (normal range 8.3-27 mg/L), with an altered kappa/Lambda of 22/378. The lambda and kappa light-chain were not detected in the urine. Cardiac magnetic resonance imaging showed suspected delayed subendocardial gadolinium enhancement. The patient underwent endomyocardial biopsy at another hospital. Amyloid deposits were detected by Congo red staining. Myocardial tissue sample was positive, but periumbilical fat aspirates, as well as samples from the tongue, gums and bone marrow were all negative. The patient was ultimately diagnosed with stage III AL amyloidosis with cardiac involvement, per the Mayo 2012 staging system. In this patient, the most likely cause of pulmonary hypertension was deposition of amyloid in the pulmonary vasculature.

The patient's therapeutic plan was to receive three cycles of therapy consisting of cyclophosphamide/bortezomib/dexamethasone (CyBorD). Bortezomib (1.3 mg/sqm/day) and cyclophosphamide (300 mg/day) were administered on the 1st, 5th, 15th, and 22nd day of each 35-d course, and dexamethasone (20 mg/day) was administered on days 1, 2, 8, 9, 15, 16, 21, and 22. Unfortunately, 1 d after the first cycle of therapy, the patient experienced an episode of cardiopulmonary arrest due to cardiac arrest, with a quick return of spontaneous circulation after a brief cardiopulmonary resuscitation. The next day, the patient experienced cardiac arrest 4 times, returning to spontaneous circulation after cardiopulmonary resuscitation in each case. A pacemaker was implanted to address the recurrent cardiac arrests and the pacing electrocardiogram is shown in Figure 1E. Echocardiography revealed atrial enlargements and worsening systolic dysfunction (ejection fraction 48%) (Figure 1F).

It was unclear whether there was a causal relationship between CyBorD and cardiac arrest. However, the patient refused CyBorD chemotherapy for cardiac amyloidosis. The patient died 5 years after the first admission and 3 years after the diagnosis of cardiac amyloidosis.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient.

DISCUSSION

Cardiac amyloidosis is a rare disease, and patients frequently experience significant delays between the onset of non-specific symptoms and a confirmed amyloidosis diagnosis. Symptomatic pulmonary hypertension is only rarely described and, when present, is typically associated with progressive disease, such as elevated filling pressures secondary to cardiac amyloidosis (Table 1)[4,8]. Although our patient initially presented with pulmonary hypertension, she was found, 2 years later, to have AL amyloidosis with cardiac involvement. This report further emphasizes the insidious nature of amyloidosis that makes it difficult to diagnose. Multiple underlying factors and a long term follow-up must be considered for patients with pulmonary hypertension in order to reduce the time to diagnosis.

Doppler echocardiography is a commonly used method for diagnosing pulmonary hypertension[9]. Echocardiography provides an estimate of the systolic pressure in the pulmonary artery. However, a definitive diagnosis of pulmonary hypertension requires a direct pulmonary arterial pressure measurement *via* right heart catheterization. Generally pressures obtained *via* echocardiography are similar to those obtained by catheterization, if they are in the lower pressure ranges. Based on criteria from the National Institutes of Health, a mean pulmonary artery pressure ≥ 25 mmHg at rest (> 30 mmHg with exercise) is the standard for the diagnosis of pulmonary hypertension[9].

Table 1 Previous reports of cases of pulmonary hypertension with amyloidosis

Case	Ref.	Age (year)/sex	Biopsy site	Type of amyloid	MPAP (mmHg)	MM	Treatment	Time to death (mo)
1	Chapman *et al* [19], 1999	91/F	Lung, heart	AL	NI	(-)	NI	NI
2	Cirulis *et al*[4], 2016	53/F	Lung, heart	IgGκ AL	46	(+)	Bortezomib-thalidomide-dexamethasone, sildenafil	Survival
3	D'Aloia *et al*[20], 2008	75/M	Fat, heart	AL	NI	(-)	NI	NI
4	Dingli *et al*[10], 2001	61/F	BM, fat	IgGκ AL	58	(+)	Diuretics, melphalan, prednisone, cyclophosphamide, vincristine doxorubicin, dexamethasone	1
5	Dingli *et al*[10], 2001	64/F	BM	IgGλ AL	NI	(+)	Diuretics, vincristine, BCNU, Melphalan, cyclophosphamide, prednisone	29
6	Dingli *et al*[10], 2001	82/M	BM	IgGλ AL	NI	(-)	Diuretics, digoxin, calcium channel blocker	32
7	Dingli *et al*[10], 2001	54/F	Lung	IgGκ AL	48	(-)	Diuretics, calcium channel blocker, aspirin	2
8	Dingli *et al*[10], 2001	48/F	Liver	Amyloid A AL	62	(-)	Calcium channel blocker, colchicine	2
9	Eder *et al*[8], 2007	73/F	BM	AL	90	(+)	Prednisone, chlorambucil, dexamethasone, cyclophosphamide	8
10	Hashimoto *et al* [21], 2015	85/F	BM	IgGκ AL	60	(+)	Melphalan-prednisolone, Lenalidomide-dexamethasone, bortezomib, cyclophosphamide, vincristine, and dacarbazine	29
11	Kruczak *et al* [22], 2013	67/F	Lung, colon mucosa	Transthyretin AL	95	(-)	Methylprednisolone, melphalan and cyclophosphamide	1
12	Lehtonen and Kettunen[23], 2007	48/M	BM, fat	AL	46	(+)	Sildenafil, melphalan, prednison	NI
13	Lutz *et al*[24], 1995	61/F	Heart, lung	β2M AL	75	(-)	Antihypertensive medication	12
14	Shiue and McNally[25], 1988	65/F	BM, lung, rectal	AL	39	(+)	Melphalan, prednisolone, diuretics	1
15	Sullivan and Schwarz[26], 1994	72/F	BM, lung	AL	56	(+)	NI	6
16	Krishnan *et al* [27], 2015	69/F	BM, heart, renal	AL	41	(+)	Sildenafil, bumetadine, warfarin, metoprolol succinate, ambrisentan	NI
17	Present case, 2019	51/F	BM, heart, fat	IgGλ AL	51	(-)	Sildenafil, cyclophosphamide, bortezomib, dexamethasone	60

F: Female; M: Male; BM: Bone morrow; MPAP: Mean pulmonary artery pressure; MM: Multiple Myeloma; AL: Light chain amyloid; NI: No information; β 2M: Beta-2 microglobulin.

Due to etiologic uncertainty and several possible contributing factors, further diagnostic evaluation was pursued in our patient. However, the underlying disease causing pulmonary hypertension was unclear at the time of the initial presentation. Two years later, our patient was finally diagnosed with amyloidosis following progressively worsening symptoms and echocardiographic evidence indicating characteristic sparkling and granular texture of the ventricle wall.

In patients with AL amyloidosis, the most common etiologies of pulmonary hypertension are left-side restrictive cardiomyopathy from amyloid deposition or diffuse lung disease[8,10]. Pulmonary amyloidosis rarely causes symptoms despite the fact that it is commonly found in bronchoscopic lung biopsy[11]. The main patterns of pulmonary involvement are tracheobronchial or parenchymal, the latter being further classified radiographically, either as solitary/multiple nodular parenchymal, or as a diffuse alveolar septal pattern[12]. A tracheobronchial pattern is a common form of respiratory amyloidosis, in which amyloid is found in the subepithelial interstitial tissue and often surrounds tracheobronchial ducts and acini. Nodular parenchymal amyloidosis is rare and amyloid is often

present only in the alveolar interstitium at nodule peripheries. A diffuse parenchymal pattern is the least common form of respiratory amyloidosis, in which amyloid is present in the media of small blood vessels and in the parenchymal interstitium. In all reported cases, vascular obstructions due to amyloid deposits are considered the cause of increased pulmonary vascular resistance[13]. Amyloid deposition in blood vessel walls can result in endothelial dysfunction. The abnormal endothelial cells express lower levels of nitric oxide synthase and cyclooxygenase, as well as increased levels of endothelia, and promote the onset of vasoconstriction and smooth muscle proliferation. It is possible that similar mechanisms operate in the pulmonary condition, lead to vasoconstriction and pulmonary hypertension, even in the absence of severe intra-vascular amyloid deposits. An increase in pulmonary vascular resistance requires a higher pulmonary arterial pressure to maintain the same right ventricular output, which eventually leads to pulmonary arterial hypertension.

Treating pulmonary hypertension in patients with amyloidosis can be a challenging. Despite a paucity of data, diuretics and vasodilators, with calcium channel blockers, are often appropriate therapies used to treat patients with pulmonary hypertension[14]. However, patients with amyloidosis often have orthostatic hypotension and cannot tolerate the high doses required for successful treatment. The pulmonary hypertension-specific drugs that have emerged over the past 2 decades have largely focused on targeting the underlying complex etiology *via* the endothelial, prostacyclin, and nitric oxide pathways. Phosphodiesterase type 5 inhibitors, such as Sildenafil, are a class of drugs used to prolong the physiological effects of Nitric oxide–cyclic guanosine monophosphate (NO/cGMP) signaling by inhibiting cGMP degradation[15]. Sildenafil is approved for treatment of pulmonary hypertension as a class I indication in World Health Organization-Functional Class (WHO-FC) II and III, and as a class IIa indication in WHO-FC IV patients[16]. However, pulmonary hypertension-specific drugs are not recommended treatments for patients with pulmonary hypertension related to left heart disease[17]. Since 2013, several randomized controlled trials have been completed in patients with pulmonary hypertension related to left heart disease, and no effect was observed on the primary end-point of mean pulmonary artery pressure. The principle of the treatment applied is always related to the underlying disease. Our patient was first treated with sildenafil; however, her symptoms continued to gradually progress which is in accordance with those in previous studies. However, it was difficult to determine whether the clinical deterioration was related to the use of sildenafil in our patient. Such an event, underscores the importance of a treatment strategy that addresses the underlying etiology in order to effectively improve pulmonary hypertension. Therapeutic interventions for AL amyloidosis are controversial. Definitive management involves stopping production of the paraprotein responsible for amyloid formation. The combination of CyBorD, as a first-line treatment, has shown signs of early promise, with high rates of hematologic responses in many patients[18]. Unfortunately, our patient suffered cardiac arrests during CyBorD chemotherapy. Therefore, the patient declined further CyBorD treatment and we did not observed any changes in pulmonary hypertension following treatment of the underlying process driving amyloid deposition.

CONCLUSION

Although pulmonary hypertension may be idiopathic, it is frequently associated with other conditions. Pulmonary hypertension is a rare complication of AL amyloidosis, which is associated with a poor prognosis and significant mortality. Further studies are required to develop targeted therapies to effectively improve outcomes among patients with pulmonary hypertension, and in those with other comorbidities due to AL amyloidosis.

FOOTNOTES

Author contributions: Gao M completed the clinical data collection and the manuscript draft; Chen LP and Yang N improved later revision of the article; Zhang WH and Tong Q participated in the treatment decisions; Zhang ZG, Zhang WH and Tong Q revised the manuscript critically to ensure the authenticity and practicability; All authors read and approved the final manuscript.

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CASE REPORT

Short-term outcome of total knee replacement in a patient with hemophilia: A case report and review of literature

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Abstract

BACKGROUND

Hemophilia A is a rare inherited bleeding disorder caused by mutations in the factor VIII gene. This clotting factor plays an intrinsic role in the blood coagulation pathway. Patients with hemophilia may develop orthopedic manifestations such as hemarthrosis, but multiple malunion of fractures over the knee is rare and difficult to treat.

CASE SUMMARY

We report a patient with hemophilia A who developed severe knee osteoarthritis along with fracture malunion and nonunion. Total knee replacement was performed using a custom-made modular hinged knee prosthesis (cemented) equipped with extended distal and proximal stems. At 3 years' follow-up, the patient exhibited excellent clinical function and remained satisfied with the surgical outcome. Surgical intervention was accompanied by rigorous coagulation factor replacement.

CONCLUSION

This case highlights various unique scenarios specific to individuals with hemophilia and fracture deformity.

Key Words: Total knee replacement; Hemophilia; Multiple malunion of fractures; Hemophiliac arthropathy; Coagulation factor replacement; Case report

Core Tip: This patient had hemophilia for many years, with hematopathic arthritis of both knees. An old fracture of the left lower extremity had healed, a distal femur fracture had recurred, and he had malunion of fractures of the proximal tibia and fibula. We resolved the left knee hematopathic arthritis, distal femur fracture nonunion, and proximal tibia fracture malunion with a single operation of total knee replacement with custom prosthesis.

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INTRODUCTION

Hemophilia A is a rare inherited bleeding disorder caused by mutations in the factor VIII gene. This clotting factor plays an intrinsic role in the blood coagulation pathway[1]. This disorder is known to be X-linked recessive and, is thus, more commonly encountered in males[2].

Hemophilia can be mild, moderate or severe, depending on the plasma factor levels of 6%–40%, 1%–5%, or < 1%, respectively[3]. Patients with hemophilia may develop orthopedic manifestations-hemarthrosis. Hemarthrosis is repeated bleeding into the joints, such as: Ankle, elbow and knee, leading to cartilage damage and degenerative articular changes, potentially resulting in severe osteoarthritis.

The third decade of life is the peak occurrence of the disease, and nearly 90% of patients with hemophilia have hemophiliac arthropathy[4]. The knee is the most involved joint in hemophilia, and some feasible treatment methods have been applied, and radiological and arthroscopic synovectomy is effective, in addition to arthrodesis, and most importantly, total knee replacement (TKR)[5-7]. The major surgical procedures can be safely performed in hemophilia patients with chronic arthropathy using available clotting factor concentrates, and TKR is considered the gold standard[8,9]. An increasing number of studies have reported TKR in patients with hemophilia[6,10-12], although this procedure is challenging due to the high risk of bleeding and periprosthetic joint infection[1,13,14].

However, cases involving patients with hemophiliac arthropathy and multiple malunion of fractures over the knee are rarely reported. Here, we report a patient with hemophilia and nonunion of a femoral fracture and malunion fractures of the tibia and fibula. The outcome of this patient has, to date, been satisfactory > 2 years after surgery. The patient exhibited excellent clinical function and has remained satisfied with the surgical outcome.

The patient was informed that anonymized data regarding the case would be submitted for publication, and he provided consent.

CASE PRESENTATION

Chief complaints

A 55-year-old man was diagnosed with moderate hemophilia A.

History of present illness

The patient sustained many fractures to his left thigh, in addition to tibia, fibula, and a femoral fracture in 2013. Due to economic reasons and the unique treatment difficulties in patients with hemophilia, all fractures had been treated nonsurgically with plaster fixation. Before and after the fractures in 2013, factor VIII was infused intermittently. However, medical hemostasis management was not standardized. Fortunately, all of the above fractures successfully healed in 2016, although deformity resulted (Figure 1A-C). He was unable to ambulate by himself. He sustained a fracture to his left thigh again in 2018, and the left knee had bony ankylosis (Figure 1D). Along with severe knee osteoarthritis, this prompted him to undergo surgery for his left thigh (Figure 2A and B). He consulted the authors due to severe pain and a severely dysfunctional left leg, although his right leg was also affected by hemophiliac arthritis (Figure 2C). At that time, the total range of motion (ROM) in his left knee joint was 0° and he had no mobility, with a Hospital for Special Surgery Knee Scale score (HSSKS)[15] of 30 (Tables 1 and 2). Panoramic X-ray of the lower limbs revealed that the left thigh was nearly 8 cm shorter than the right femur (Figures 2C-E).

Table 1 Range of motion of the left knee during treatment

Variable	Preoperatively	Postoperatively	
		3 d	16 mo
Flexion	0	30	80
Extension	0	10	5
Range of motion	0	20	75

Data presented as degrees.

Table 2 Hospital for special surgery knee-rating scale scores for the left knee during treatment

Variable	Preoperatively	Postoperatively	
		3 d	16 mo
Pain	0	10	25
Function	2	6	15
Range of motion	0	3	11
Muscle strength	0	4	8
Flexion deformity	5	5	8
Instability	0	5	8
Subtraction	-4	-3	-2
Total score	3	30	73

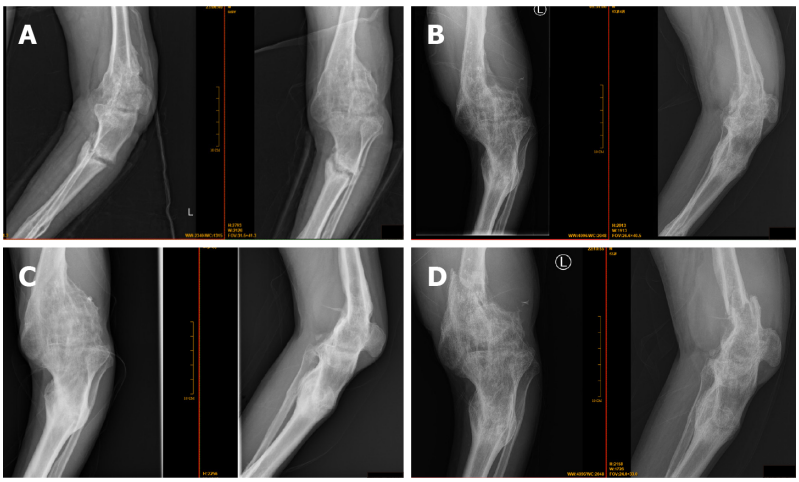

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Figure 1 Typical radiographs of the patient from 2013 when he first come to our clinic. A: Preoperative left knee anteroposterior and lateral radiographs in 2013, showed hemophiliac knee arthritis, old tibia and fibula fractures, and deformity of the distal femur fracture; B: In 2016, radiographs showed aggravated hemophiliac knee arthritis with knee fusion, deformity of the distal femur fracture, and deformity of the tibia and fibula fractures; C: On November 30, 2018, radiographs showed exacerbation of hemophiliac knee arthritis with knee fusion, deformity of the distal femur fracture, and deformity of the tibia and fibula fractures as before; D: On December 14, 2018, radiographs showed hemophiliac knee arthritis with knee fusion, deformity of the tibia and fibula fractures, and recurrent fresh fracture of the distal femur on the top of the original deformity.

History of past illness

The patient had moderate hemophilia A.

Physical examination

The left thigh was nearly 8 cm shorter than the right thigh. The patient had left lower extremity dysfunction with tenderness at the distal femur and bone abrasion.

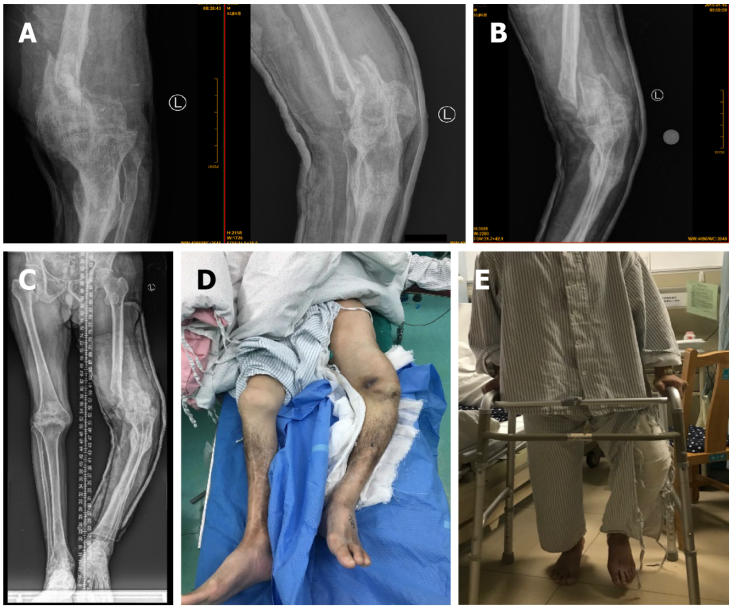

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Figure 2 Preoperative radiographs of the left thigh of the patient with hemophilia. A: On January 8, 2019, left knee anteroposterior and lateral radiographs showed hemophiliac knee arthritis with knee fusion, and recurrent fresh fracture of the distal femur was fixed with a cast; B: On January 16, 2019, left knee anteroposterior radiographs showed further displacement of the distal femoral fracture with a cast; C: Panoramic radiographs of lower limbs showed that the left thigh was nearly 8 cm shorter than the right thigh. D and E: Preoperative images of the left leg.

Laboratory examinations

At the first examination, the patient's serum factor VIII level was 5% and inhibitor of factor VIII was absent, and he was negative for hepatitis C and human immunodeficiency virus.

Imaging examinations

(1) Preoperative left knee anteroposterior and lateral radiographs in 2013, showed hemophiliac knee arthritis, old tibia and fibula fractures, and deformity of the distal femur fracture; (2) In 2016, radiographs showed aggravated hemophiliac knee arthritis with knee fusion, deformity of the distal femur fracture, and deformity of the tibia and fibula fractures; (3) On November 30, 2018, radiographs showed exacerbation of hemophiliac knee arthritis with knee fusion, deformity of the distal femur fracture, and deformity of the tibia and fibula fractures as before; and (4) On December 14, 2018, radiographs showed hemophiliac knee arthritis with knee fusion, deformity of the tibia and fibula fractures, and recurrent fresh fracture of the distal femur on the top of the original deformity.

FINAL DIAGNOSIS

Hemophiliac arthropathy of both knees; hemophiliac knee arthritis with left knee fusion; fracture of distal femur; deformity of the tibia and fibula; and hemophilia A.

TREATMENT

To relieve joint dysfunction and pain in the left leg, TKR was scheduled. The other knee joint also appeared to require arthroplasty; however, this procedure was difficult for the patient to accept due to many factors, especially economic. The procedure was performed under the guidance of the expert consensus in China and a previous review[8,16]. Coagulation factors should be supplemented to 110% before the procedure, tranexamic acid should be used to prevent intraoperative bleeding[17], and should be supplemented according to operating duration, with a blood salvage system used during surgery. Blood loss during surgery in the present case was 900 mL, and the duration of the procedure was 4 h. The implants were cemented, and were a custom-made modular hinged knee prosthesis equipped with extended distal and proximal stems (Beijing Chunlizhengda Medical Instruments Co. Ltd., China) because it was necessary to treat both the femoral shaft fractures and the proximal tibial deformity fracture (Figure 3).

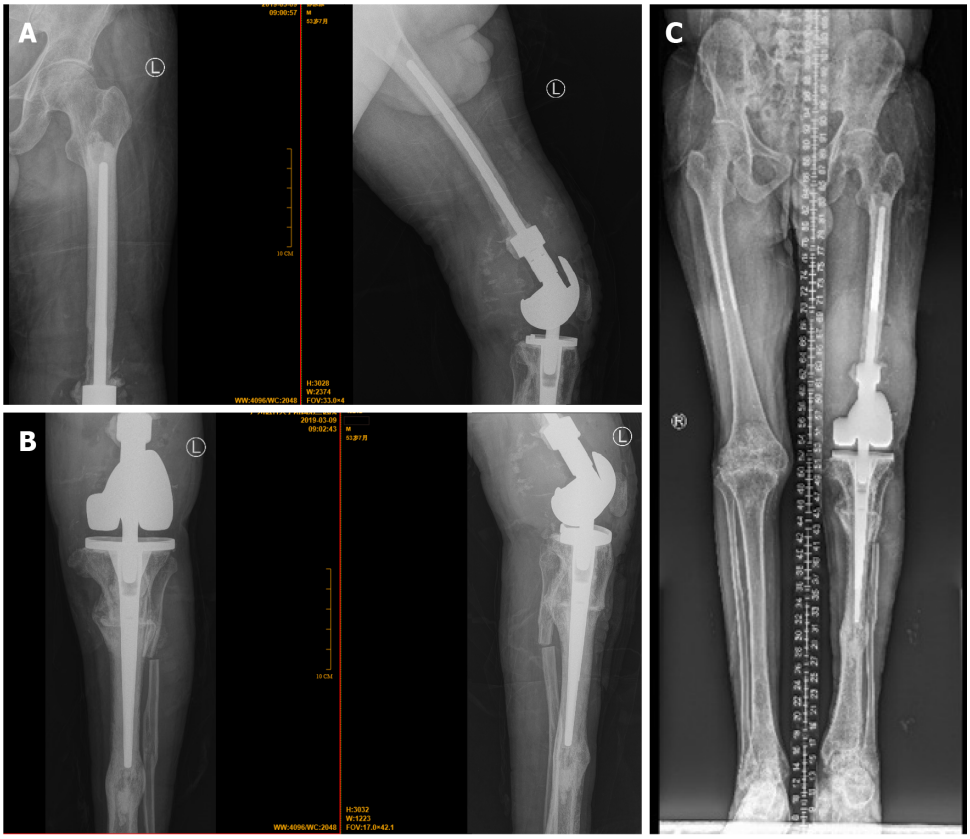

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Figure 3 Postoperative radiographs of the patient with hemophilia. A: Femur anteroposterior and lateral; B: Left knee anteroposterior and lateral; C: Panoramic view of lower limbs. The prosthesis was in the correct position with no radiographic evidence of hardware complications. The lower extremity line of strength was good, short contraction of the left lower extremity was improved, and fracture deformity of the left lower limb was corrected.

OUTCOME AND FOLLOW-UP

The plan for supplementation of clotting factors before, during and after surgery is summarized in Table 3. Rehabilitation exercise started on postoperative day 2 with partial weight bearing (Figure 4A and B). From previous investigators combined with patient characteristics, the patient received physical therapy from day 2 after the operative. Therapy sessions were carefully coordinated with factor replacement, also need to avoid exacerbation of pain or wound condition/hemostasis[18-20]. Furthermore, a continuous passive motion machine was used to restore total ROM of the knee joint, with flexion exercises starting at 45°. After 16 mo' postoperative follow-up, the patient exhibited an ROM of 75° (5°–80°), with an HSSKS score of 73 (Table 2; Figure 4C-E and Video 1). At 3 years' postoperative follow-up, the patient was satisfied with the left thigh outcome.

DISCUSSION

Hemophilia is among the most common bleeding disorders come across in orthopedic surgery. It is an X-linked recessive condition affecting 1 in 5000 males[3,7]. Factor deficiency leads to recurrent spontaneous hemarthroses, which then lead to contractures and early degenerative joint disease. The knee joint is the most common affected by hemophiliac arthropathy[7]. In a recent meta-analysis, the prevalence of hemophilia among males was estimated to be 5.5/100000 in Mainland China[21]. There were 16083 patients with hemophilia A and 2447 with hemophilia B registered in Mainland China in 2019[22]. The hemophilia care level in China lags behind that in developed countries[23]. Sun *et al*[24] found that hemophilia patients in China received less prophylaxis, these patients faced greater difficulty in obtaining replacement factor products, and were vulnerable to more annual bleeds. Currently, TKR is considered to be the gold standard for patients with hemophilia who develop severe arthropathy[6,25]. Several previous studies have reported satisfactory outcomes[25-28].

TKR in patients with hemophilia is a viable alternative to conventional methods of treatment for chronic arthropathy, and expectations for pain relief and functional gain can be high[10]. With continuous advances and developments in surgical treatment in recent years, and the emergence of recombinant clotting factors, the success ratio of surgical treatment for hemophilia has gradually

Table 3 Perioperative clotting factor replacement regimen

Time of day	At surgery	72 h	1st week	2nd week
Morning	110	100	80	> 50
Evening	110	100	80	> 50

Data presented as %.

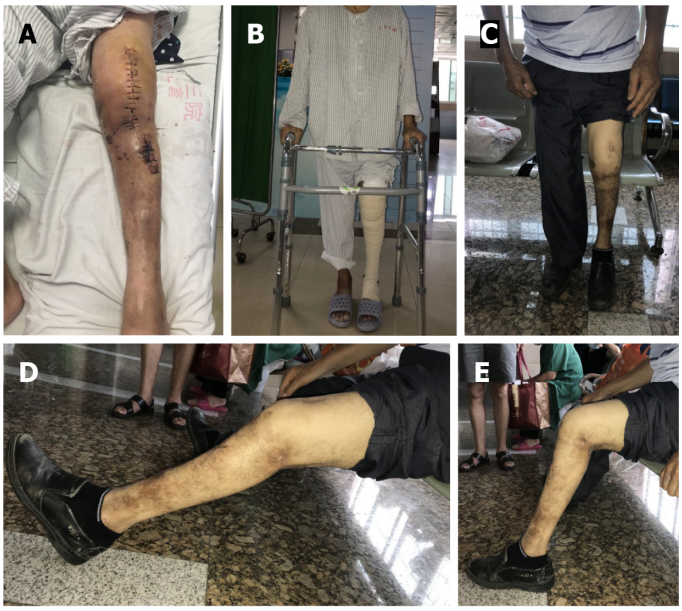

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Figure 4 Post-operative and follow-up images of the patient with hemophilia. A and B: Postoperative images of the left leg; C-E: Postoperative images demonstrated the range of motion of the left leg 16 mo after surgery. The deformity of the left leg was corrected after surgery, the length was restored, and normal function was basically restored at 16 mo after surgery.

increased[26]. In our case, we maintained a high level of clotting factor replacement throughout the first 2 wk postoperatively. Moreover, the level was higher than currently recommended by international guidelines. According to previous research, this can reduce the rate of infection[13]. Due to the complexity of orthopedic procedures, such as TKR and osteotomy, the duration of surgery is longer than normal, which increases the risk for intraoperative bleeding and infection. Postoperatively, the patient described in this report was treated with elastic bandages to prevent deep venous thrombosis. On postoperative days 2 and 7, intra-articular hemorrhage occurred twice, for which 150 and 300 mL of accumulated blood, respectively, was drawn from the knee joint under sterile conditions. Rehabilitation was effective. Safe rehabilitation exercises were prescribed after surgery and the patient used a walking cane the day after surgery[29] (Figure 4B). Physical therapy typically included isometric exercise for the quadriceps, hamstrings and gluteal muscles, knee ROM exercises include active and passive, and progressive resistive lower extremity exercises when the patient progressed[19]. We also prescribed rehabilitation to restore ROM of the knee joint by starting with continuous passive motion for functional exercises from postoperative day 2. All rehabilitation exercises followed daily supplementation of coagulation factors.

TKR is an effective procedure for improving ROM and decreasing functional deficits resulting from hemophiliac arthropathy. Knee score information show that TKR improves overall function[5]. TKR provides significant improvement in pain and better function in patients with end-stage hemophiliac arthropathy of the knee jiont. Peri- and postoperative care tends to be more complicated than in patients without hemophilia undergoing TKR and requires a multidisciplinary team approach[30]. With our patient, preoperative preparation included supplementation of clotting factors, an adjustment plan for supplementation, preparation of the prosthesis, and rehearsal of the surgical process. Postoperatively, we prevented possible complications such as hemorrhage, infection and venous thromboembolism. Our patient experienced intra-articular hemorrhage twice, with 150 and 300 mL of blood drained. However, under strict postoperative management and supplementation of coagulation factors, there was no postoperative infection and further bleeding. After careful postoperative rehabilitation, the patient achieved satisfactory recovery. Ideally, any patient with severe hemophilia should be followed-up by a

specialist, with once or twice per year[20]. Our patient recover well during annual follow-up after discharge, with ambulatory function similar to healthy individuals.

CONCLUSION

Several important factors should be considered before considering surgery in patients with hemophilia. In particular, osteotomy orthopedic surgery should be performed at the same time. Osteotomy angle of the tibia, supplementation of clotting factors, customization of prostheses, and patient tolerance should all be considered. Postoperative rehabilitation exercise is also important to achieve good outcomes. Collectively, TKR using customized prostheses has been demonstrated to be a viable option for patients with hemophiliac arthropathy and fracture deformities.

FOOTNOTES

Author contributions: Yin DL and Zeng MD analyzed and interpreted the patient data; Lin JM assistance make plan for supplementation of clotting factors; Chen P performed the following up and collected the image data; Yin DL and Lin JM were a major contributor in writing the manuscript; Zeng MD, Li YH and Yin DL participated in the operation; all authors have read and approve the final manuscript.

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CASE REPORT

Modified inferior oblique anterior transposition for dissociated vertical deviation combined with superior oblique palsy: A case report

Yao Zong, Ze Wang, Wen-Lan Jiang, Xian Yang

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Abstract

BACKGROUND

Inferior oblique anterior transposition (IOAT) has emerged as an effective surgery in the management of dissociated vertical deviation (DVD) combined with superior oblique palsy (SOP). Traditional IOAT usually provides satisfactory primary position alignment and simultaneously restricts the superior floating phenomenon. However, it also increases the risk of the anti-elevation syndrome and narrowing of the palpebral fissure in straight-ahead gaze, especially after the unilateral operation.

CASE SUMMARY

We report the outcomes of the modified unilateral IOAT in two patients with unilateral DVD combined with SOP. The anterior-nasal fibers of the inferior oblique muscle were attached at 9 mm posterior to the corneal limbus along the temporal board of the inferior rectus muscle, the other fibers were attached a further 5 mm temporal to the anterior-nasal fibers. Postoperatively, both hypertropia and floating were improved, and no obvious complications occurred.

CONCLUSION

In these cases, the modified unilateral IOAT was an effective and safe surgical method for treating DVD with SOP.

Key Words: Anterior transposition; Inferior oblique muscles; Dissociated vertical deviation; Superior oblique palsy; Anti-elevation syndrome; Case report

Core Tip: Inferior oblique anterior transposition (IOAT) is effective for dissociated vertical deviation combined with superior oblique palsy; however, unilateral IOAT also increases the risk of the anti-elevation syndrome. This modified unilateral IOAT involves a more backward new insertion and the new insertion line perpendicular to the inferior rectus muscle axis, which provides satisfactory primary position alignment and restricts the superior floating phenomenon without obvious postoperative complications.

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INTRODUCTION

The clinical features of dissociated vertical deviation (DVD) with superior oblique palsy (SOP) are variable and include unstable vertical strabismus after covering in the primary position due to significant DVD; spontaneous upward drifting of one or both eyes when binocularity is blocked after neutralizing the hypertropia; and superior oblique muscle (SO) paralysis[1,2]. The goals of surgery are improvement of primary position hypertropia and reduction of upward floating. Inferior oblique anterior transposition (IOAT) has been recognized as the standard surgical procedure[1,2]. The complications after this procedure remain a difficult problem, such as the anti-elevation syndrome (AES)[3] and eyelid fission narrowing in straight-ahead gaze[4], especially after unilateral surgery. We here report the results of a modified unilateral IOAT in two patients with DVD and SOP.

IOAT was first proposed by Gobin[5] in 1964 and used in the treatment of esotropia with V sign, the inferior oblique muscle (IO) was transposed to the equatorial sclera (about 14 mm from the corneal limbus) and approximately 50% of patients were orthotropic after the procedure. The application of IOAT in the treatment of inferior oblique overaction (IOOA) and DVD was first proposed by Elliott and Nankin[6] in 1981. IOAT is a more effective treatment for IOOA and DVD than simple IO recession, with the anterior fibers of the IO fixed temporally at the inferior rectus (IR) insertion (Elliott's point). It was reported that 67% (14/21) of patients' hypertropia was corrected, but it was easily overcorrected, resulting in restricted elevation in 24% of the patients.

This novel unilateral IOAT method involves a more backward reinsertion line perpendicular to the IR axis with J-deformity. The anterior-nasal fibers of the IO were attached at 9 mm posterior to the corneal limbus along the temporal board of the IR, and the posterior fibers were attached a further 5 mm temporal to the first suture.

This procedure was performed by a single surgeon (YX) for DVD with SOP in the two patients between June and August 2020. One day after surgery, they were orthotropic in primary gaze without diplopia and remained orthotropic one year after the procedure without obvious AES. This approach ensured surgical effectiveness and prevented the onset of AES, especially after unilateral surgery.

This study was approved by the Medical Ethics Committee of Qingdao University. This report complies with all local laws and the principles of the Declaration of Helsinki.

CASE PRESENTATION

Chief complaints

Case 1: An 11-year-old Chinese girl presented with persistent exotropia after a strabismus procedure five years earlier.

Case 2: A 17-year-old Chinese girl presented with intermittent exotropia of the left eye. She had been tilting her head to the left since infancy.

History of present illness

Case 1: The patient had been tilting her head to the right since infancy and, in 2015, was diagnosed with constant exotropia. She underwent lateral rectus recession (6 mm) with medial rectus resection (5 mm) in her right eye, but residual exotropia and abnormal head position persisted postoperatively through to the current presentation.

Case 2: The patient presented with intermittent exotropia of the left eye. She had been tilting her head to the right since infancy without any prior treatment.

History of past illness
The patients had no previous medical history.

Personal and family history
Case 1: The patient's parents and sister are healthy and have no family history of similar disease.

Case 2: The patient's parents, sister and brother are healthy and have no family history of similar disease.

Physical examination
Case 1: The patient's temperature was 36.3 °C, heart rate was 92 bpm, respiratory rate was 23 breaths/min, and blood pressure was 94/54 mmHg.

Case 2: The patient's temperature was 36.5 °C, heart rate was 98 bpm, respiratory rate was 20 breaths/min, and blood pressure was 104/67 mmHg.

Laboratory examinations
Routine blood and biochemical tests were normal in both cases.

Imaging examinations
Ultrasonography did not indicate intraocular disease in both cases.

Ophthalmological examination
Case 1: On examination, the patient's best-corrected visual acuity (BCVA) was 1.0 in both eyes. She had primary position exotropia of 40Δ at both distance and near, and a hypertropia of 10Δ in the left eye by alternate prism cover test. DVD was observed in both eyes, although more pronounced in the left, and only appearing when covering one eye. There was bilateral IOOA (+3) and a significant V-pattern. A positive Bielschowsky tilt test was found in both sides[7] (Figure 1A).

Case 2: The patient's BCVA was 1.0 in both eyes, with refractions of −3.00 for the right and +3.00 +0.25 × 65° for the left eye. Exodeviation and hypertropia were highly variable due to significant dissociated horizontal deviation[8] in the left eye and DVD in the right. Exotropia of 10-20Δ and right hypertropia of 15-30Δ were observed on alternate prism cover test in the primary position at distance and near. She had latent nystagmus in both eyes and an anomalous head posture. There was unilateral superior oblique underaction (−2) along with IOOA (+2) in the right eye, and a positive Bielschowsky tilt test on the right-hand side (Figure 2A).

FINAL DIAGNOSIS
The final diagnosis for both cases were DVD with SOP.

TREATMENT
Case 1
Levofloxacin eye drops were applied to prevent infection in both eyes 2 d before the surgery. With the patient and her mother's consent, she underwent the modified unilateral IOAT with lateral rectus recession (5 mm) and medial rectus resection (4 mm) in her left eye under general anesthesia.

The anterior-nasal fibers of the left IO were attached at 9 mm posterior to the corneal limbus along the temporal board of the left IR, and the posterior fibers were attached a further 5 mm temporal to the first suture using an absorbable 6/0 suture. The left lateral rectus (LR) was backward to 5 mm from the original insertion site and the left medial rectus was resected about 4 mm and re-sutured to the original insertion site using an absorbable 6/0 sutures. At the end of the surgery, the surgeon applied tobramycin dexamethasone ointment to the left eye, bandaged it and waited for the patient to wake up before sending the patient back to the ward. After the surgery, the patient was instructed to apply levofloxacin eye drops and tobramycin dexamethasone drops to the left eye.

Case 2
Levofloxacin eye drops were applied to prevent infection in both eyes 2 d before the surgery. With the patient and her mother's consent, she underwent the modified unilateral IOAT in her right eye with lateral rectus recession 7 mm in her left eye under general anesthesia.

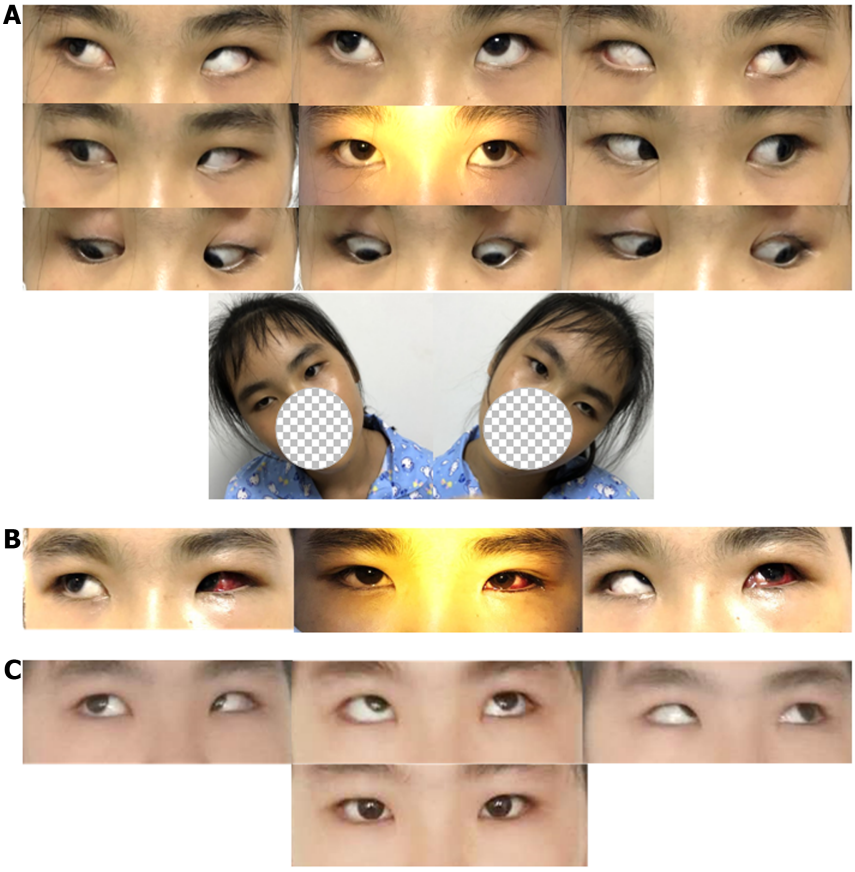

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Figure 1 Clinical photographs of Case 1. A: Preoperative images showing primary position exotropia and hypertropia in the left eye, and positive Bielschowsky tilt tests demonstrating superior oblique palsy in both eyes; B and C: Postoperative images showing primary position orthophoria without obvious anti-elevation syndrome in the left eye at the 1-d and 12-mo follow-up.

The anterior-nasal fibers of the right IO were attached at 9 mm posterior to the corneal limbus along the temporal board of the right IR, and the posterior fibers were attached a further 5 mm temporal to the first suture using an absorbable 6/0 suture. The left LR was backward to 7 mm from the original insertion site using an absorbable 6/0 suture. At the end of the surgery, the surgeon applied tobramycin dexamethasone ointment to both eyes, bandaged them and waited for the patient to wake up before sending the patient back to the ward. After the surgery, the patient was instructed to apply antibiotic eye drops to the both eyes.

OUTCOME AND FOLLOW-UP

Case 1

One day after surgery, primary gaze orthophoria was achieved, without head turn or diplopia (Figure 1B), and one year after surgery, she remained orthophoric in primary gaze and without obvious AES and eyelid fission narrowing (Figure 1C).

Case 2

One day after surgery she achieved orthophoria in primary gaze, without head turn and diplopia (Figure 2B). Twelve months after surgery, she remained orthophoric in primary gaze without limitation of elevation in both eyes (Figure 2C).

DISCUSSION

SOP is the most common paralysis of single cyclovertical muscle and is the fourth cranial nerve (trochlear nerve) palsy, which involves the SO[9]. The incidence of SOP is approximately 12.9 (95% confidence interval 9.0–16.9) per 100000 adolescents younger than 19 years of age[10] and 54.1 (95% confidence interval 50.2–58.0) per 100000 adults[11]. In SOP, there is hypertropia of the paralytic eye

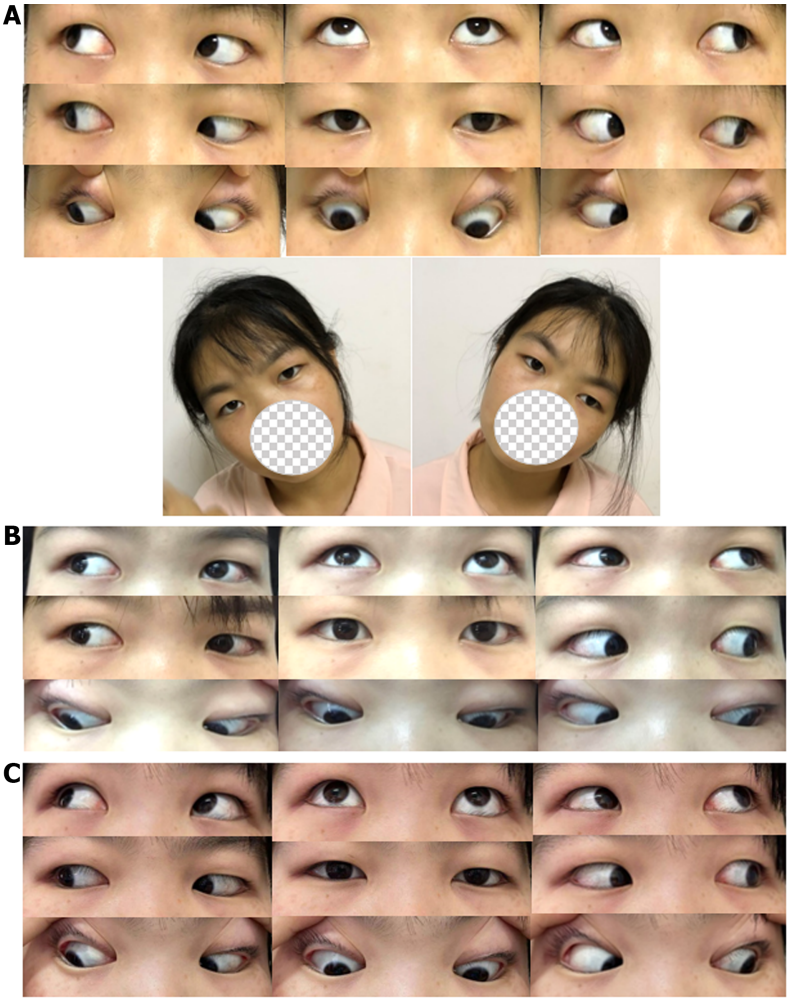

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Figure 2 Clinical photographs of Case 2. A: Preoperative images showing primary position exotropia and hypertropia in the right eye, and a positive Bielschowsky tilt test demonstrating superior oblique palsy in the right eye; B and C: Postoperative images showing primary position orthophoria without obvious anti-elevation syndrome in the right eye at the 2-wk and 12-mo follow-up.

with abnormal head position. Examination of version shows underaction of the SO and overaction of the antagonist IO. The main surgical methods are to weaken the antagonist muscle of the paralytic muscle; to weaken the yoke muscle of the another eye; to strengthen the paralytic muscle; and to weaken the superior rectus (SR) of the paralytic eye[9]. DVD is an innervation disorder which occurs in more than 50% of infantile strabismus[12]. The main clinical feature is either eye slowly drifting upward and outward with extortion when occluded. Traditional surgical treatment for DVD focuses on the SR recession, and for patients with IOOA, IOAT is also considered[13].

By displacing the IO insertion to anterior to the temporal insertion site of the IR (Elliott point) in a crossed-swords manner, IOAT was more effective improvement of IOOA and DVD compared with the standard recession of IO[6]. This IOAT has been widely employed; however, the risks of overaction and AES were high, especially in unilateral IOAT (more than half). AES is an elevation restriction in abduction, that might be contributed by both suturing the IO anterior to the IR insertion, and spreading the posterior lateral corner of the IO out temporally[14].

Stager[15,16] established that the neurovascular bundle of the IO was an ancillary origin of the posterior-temporal fibers of the IO following IOAT for limiting eye upturn, and the neurofibrovascular bundle attaches to the IO 2 mm temporal to the IR, 12 mm from the insertion of the IO. Based on the autopsy results from cadaveric eyes by Apt L[17], the temporal length of the IO was about 14 mm, so the Elliott point might increase the risk of excessive muscle tension of temporal IO fibers. Kushner[18] suggested that AES might be an "innervational restriction," as opposed to a mechanical restriction and appears to be caused by tautness of the lateral fibers of the transposed IO. Therefore, they sutured the anterior nasal corner of the IO to the temporal corner of the IR insertion and let the posterior temporal corner hang back. This approach is better for preventing AES, but less powerful for reducing DVD.

To avoid AES, some have suggested that the insertion line should be oriented parallel to the IR axis, the anterior IO nasal fibers should be at or just (≤ 2 mm) anterior to the temporal IR insertion in a "crossed-swords" manner, and the posterior temporal fibers should be folded and buried under the

fixed anterior IO nasal fibers[19]. This transposition has been seen to weaken mild to moderate IOOA and correct small primary position hypertropia. Guemes and Wright[20] suggested that the bilateral graded IOAT was effective in normalizing versions and correcting vertical deviations in primary position, and the new insertion (the temporal insertion site of the IR or 1-2 mm behind) line perpendicular to the IR axis with a "J" deformity for the IOOA combined with DVD (6 to 15 PD), without long-term observation of complications.

Thus, the reattachment points and attachment line directions are the key factors affecting operative outcomes and complications. Based on the above study, we chose a new anterior transposition to 9 mm posterior to the corneal limbus along the temporal board of the IR to reduce the risk of AES, with the wider insertion (about 5 mm) perpendicular to the IR axis to enhance the orthotic effects on vertical strabismus and spontaneous upward drifting.

The basic idea of IO transposition surgery according to the degree of IOOA is gradually moving the insertion of the IO anteriorly; if 1-mm anterior IR insertion still does not sufficiently improve the vertical strabismus and spontaneous upward drifting, a new line of attachment perpendicular to the IR insertion will be used. This surgical approach chose the new insertion line perpendicular to the IR axis to decline the upward drift of the DVD and vertical strabismus, weakening the effect of the anterior transposition of the new insertion of the IOAT, thus preventing the onset of AES. This approach ensured surgical effectiveness and prevented the onset of AES, especially after unilateral surgery.

Other advantages to this version of the IOAT procedure is that using the limbus as a reference point is more accurate and reasonable than the IR, and nasal transposition is not necessarily required which reduces operating difficulty.

CONCLUSION

In the cases presented here, the modified unilateral IOAT improved the patients' primary position hypertropia and superior floating phenomenon, with no obvious postoperative anti-elevation syndrome and no significant effect on lower lid configuration and function for 1 year. Therefore, this procedure is an effective and safe surgical methodfor t reating DVD with SOP. Certainly, more data are required to corroborate these findings and a controlled comparative study is necessary to draw definitive conclusions. In addition, a cohort study is in progress to better assess the procedure.

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FOOTNOTES

Author contributions: Zong Y and Yang X were the patient's surgeons; Zong Y contributed to the conception, manuscript writing, revision, and final approval of the manuscript; Jiang WL contributed to the provision of study materials; Yang X and Wang Z contributed to the design, manuscript writing and revision; all authors have read and approved the final manuscript.

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CASE REPORT

Treatment of talipes equinovarus after triceps surae intramuscular hemangioma surgery by Ilizarov technology in adults: A case report

Zhang-Xin Chen, Meng-Yuan Wang, Cong Zhang, Zhen-Qi Ding, Wei Chen

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Abstract

BACKGROUND

Postoperative complications of triceps surae intramuscular hemangioma surgery with talipes equinovarus have rarely been described, and the evidence for treatment is limited. The purpose of this case study was to report the new application of the Ilizarov technique, which successfully treated talipes equinovarus in adults after triceps surae intramuscular hemangioma.

CASE SUMMARY

A 29-year-old woman treated with the Ilizarov technique for talipes equinovarus in the right leg after triceps surae intramuscular hemangioma surgery. The equinus deformity was roughly corrected after 2 years of follow-up, without significant secondary sequelae.

CONCLUSION

Talipes equinovarus caused by postoperative sequelae of intramuscular hemangioma was successfully corrected by the Ilizarov technique. The Ilizarov technique may be used for treating talipes equinovarus caused by various causes.

Key Words: Triceps surae intramuscular hemangioma; Ilizarov technique; Talipes equinovarus; Treatment; Case report

Core Tip: The purpose of this case study was to report the new application of the Ilizarov technique, which successfully treated talipes equinovarus in adults after triceps surae intramuscular hemangioma. The Ilizarov technique may be a surgical method for treating postoperative deformity of limbs, even in adult patients. Physicians should be aware of new uses for this type of treatment.

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INTRODUCTION

Conditions such as cerebral palsy[1], trauma[2], diabetes mellitus[3], muscular dystrophy[4], maldevelopment, or idiopathic[5] all have the potential to cause spasticity or contractures of the Achilles tendons, leading to clubfoot deformity[6]. Several genetic factors also have the potential to cause clubfoot deformity[3]. Clinical cases of Triceps surae intramuscular hemangioma resulting in ankle Achilles tendon contracture with equinus deformity and toe walking are rare[7-12]. Several surgical approaches have been described for treating the deformity, including serial casting of the ankle and knee[13], primary soft tissue release[14], the Ponseti method[15], Z-plasty, total talus resection, and tibioclavicular fusion with Achilles tendon lengthening[16]. Among them, the serial casting of the ankle and knee for surgical extension, which, like primary soft tissue release, requires surgical release and predisposes to bleeding from damaged vessels and makes full correction difficult in patients with more severe contractures[13,14]. The Ponseti method has good results mainly for congenital idiopathic clubfoot, but there is still a recurrence rate of one in three for clubfoot deformities after angioma surgery[17].

No clinical evidence can be reported at this time. Z-plasty, total talus resection, and tibioclavicular fusion with Achilles tendon lengthening all appear to provoke limb incongruence, bone loss, and other conditions with some probability of recurrence due to some disruption of the original ankle structure [18]. For patients after sural angioma surgery, there are no cases of Achilles tendon contracture treated with the sequelae of sural angioma surgery using the Ilizarov technique. This case report describes the Ilizarov technique to treat postoperative Achilles tendon contractures resulting from triceps surae hemangioma.

CASE PRESENTATION

Chief complaints

A 29-year-old Chinese woman presented to the orthopedics clinic with the inability to walk for 11 years due to talipes equinovarus.

History of present illness

Symptoms started 11 years before presentation with talipes equinovarus walk after intramuscular hemangioma surgery.

History of past illness

The patient was admitted with a high arch deformity of her right foot. At the age of 11 years, a right lower leg tumor was detected, which was not given special attention. The patient was found to have an increased mass in the right leg at the age of 27 years and attended hospital for magnetic resonance imaging, which indicated abnormal signals in the right thigh. Hemangioma was considered and confirmed as intramuscular hemangioma (Figure 1). After surgery, the patient gradually developed a high arch deformity of the right foot, and could not walk normally. She sought treatment in many hospitals, and most of them suggested amputation of stump and installation of a prosthetic limb, which was rejected by the patient.

Personal and family history

The patient denied any family history of malignant tumors.

Physical examination

A marked 15-cm surgical scar was noted on the right lower leg, which was markedly thin and reduced by 6 cm compared with the contralateral circumference, a high arched right equinus foot, broken skin

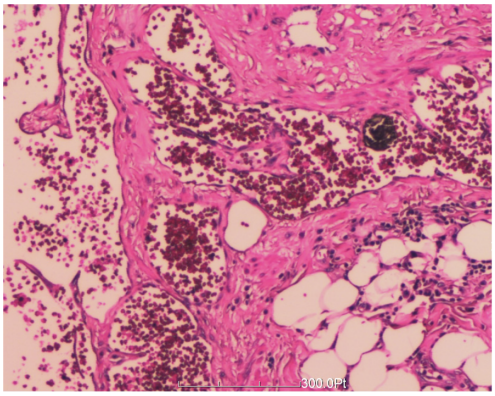

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Figure 1 Immunohistochemical results (hemangioma).

on the right foot, flexor plantar deformity of the right ankle, limited dorsiflexor activity, regular movement of the right knee, and normal sensation (Figure 2).

Laboratory examinations

Hemangioma was considered and confirmed as intramuscular hemangioma.

Imaging examinations

Preoperative X-ray showed corrected foot drop deformity, and no signs of fracture, and other bone abnormalities in the ankle joints. Preoperative tibial tuberosity advancement (TTA) was 164° (Figure 3A). The TTA reflects the degree of talus inclination in the sagittal plane and is an indicator of the correction of pronation deformity, which is important for the stability of the entire hindfoot. TTA was measured between the tibial anatomical axis and the axis of the talus[19]. Postoperative X-ray re-examination showed that the right ankle was in a functional position, and an external fixator was in position (Figure 3B). A 1-mo review by postoperative X-ray showed that the right ankle was in a functional position, the ankle joint space was narrowed, and an external fixator was in position (Figure 3C). A 4-mo postoperative review (removal of the external fixator) showed that the right ankle joint had a normal relationship; there were no signs of fracture or other bony abnormalities in the constituted bones (Figure 3D-F). The patient's postoperative changes were consistent with the preoperative assessment and the expected surgical outcome. The surrounding soft tissues were slightly swollen (TTA 113°).

FINAL DIAGNOSIS

Combined with the patient's medical history, the final diagnosis was talipes equinovarus after triceps surae intramuscular hemangioma surgery.

TREATMENT

Preoperative preparation

A routine preoperative examination was performed. According to the length, circumferential diameter, and degree of deformity of the affected limb, the Ilizarov annular external fixator with a three-dimensional orthopedic function was assembled. The orthopedic device was equipped with two full rings in the lower leg, one U-shaped ring, and one-half ring in the foot, which could correct the foot dropping horseshoe high arch deformity.

Surgical procedure

Under anesthesia, the patient was lied in supine position, and a tourniquet was placed on the middle and upper third of the right thigh (pressure 55 KPa). After routine disinfection, a sterile cavity towel was placed. After making a 6-cm long incision along the medial side of the calf, the subcutaneous fascia was separated to expose the tendon. The tendon was extended by about 4 cm in a "Z" incision. When overlapping sutures of the Achilles tendon, the ankle ring holder was put on, the external ring fixator was adjusted with the axis in line with the middle course of the affected limb, and two and two half whole stitches were passed through the calf segment, respectively. One full needle was inserted in the

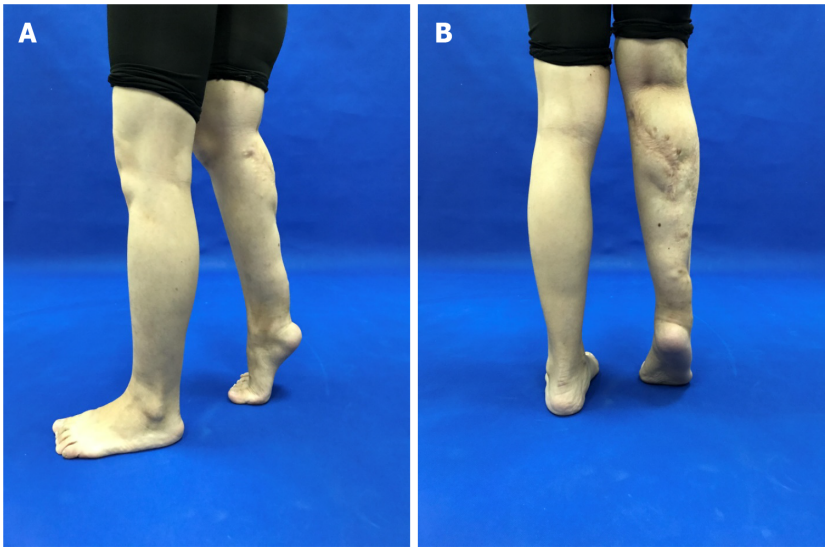

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Figure 2 Preoperative photo. A: Profile; B: Back.

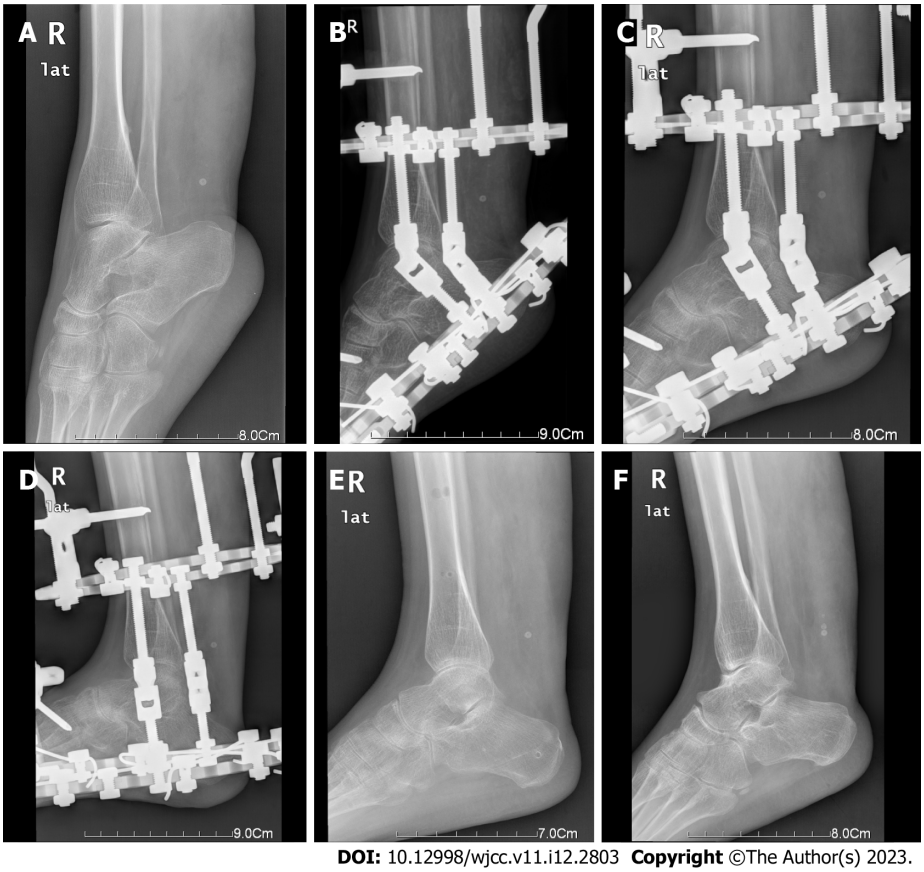

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Figure 3 X-ray. A: Preoperative X-ray (TTA 164°); B: Postoperation X-ray (1 d); C: Postoperation X-ray (1 mo); D: Postoperation X-ray (2 mo); E: Postoperation X-ray (4 mo); F: Postoperation X-ray (1 yr).

forefoot, one-half needle in the heel, and two full needles across the heel. The medial and lateral hinges were located at the medial and lateral malleolus (*i.e.*, the rotation centerline of the ankle joint). The front and rear tie rods and adjusting areas were installed to stabilize the annular fixator in the appropriate position of the right foot to avoid the high skin tension caused by surgical incision (Figure 4).

Postoperative treatment

After surgery, the wound was kept dry until routine healing, and on the 7th postoperative day, the

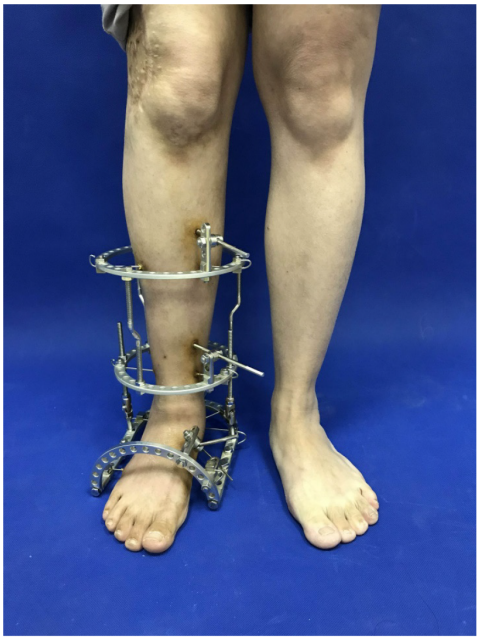

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Figure 4 Ilizarov technique external fixation used the patient view from front.

anterior and posterior bars were adjusted to correct the deformed stump. The stump could be turned and walk with the protection of the external fixation frame and the help of the orthopedic insole. Four weeks after the operation, the foot drop was corrected roughly, the ankle movement was expected, after which the external fixator was continued to perform the flexion-extension exercise. There was no pain and discomfort in the ankle joint, and at 4 mo after surgery, after removal of the external frame, the abduction was discarded and the patient walked on her own, with normal ankle movement and no dysmorphic activity (Figure 5).

OUTCOME AND FOLLOW-UP

TTA 164° was measured by preoperative radiography. Two physicians performed grading according to the American Orthopedic Foot and Ankle Society Ankle Hindfoot Scale (AOFAS-AHFS)[19], which yielded a mean score of 22.5, illustrating that the patient had poor ankle movement preoperatively, and 4 mo after corrective surgery, TTA was 113°. After return to normal angulation, the average AOFAS-AHFS score was 90.0, the ankle function returned to normal, the dorsiflexion activity was significantly improved, and there was adequate ankle activity at 2 year's follow-up, with no other complications.

DISCUSSION

Most intramuscular tumors with fatty rings are benign, and peripheral nerve sheath tumor is the most common tumor type[20,21]. Two major categories of lesions emerged from the study of Mulliken and Glowacki[22] in 1982: Hemangioma and vascular malformation. For hemangioma treatment, percutaneous sclerotherapy is often used, which may cause equinus[23]. When sclerotherapy fails, the embedded hemangioma is usually treated by resection. Most muscle tissue needs to be removed simultaneously with tumor resection. This may lead to patients without average muscle mass, muscle strength reduction, and stress contracture of the Achilles tendon, leading to the limitation of the ankle joint activity and appearance of equinus[24].

Equinus correction using the Ilizarov technique provides the benefits of early weight bearing. The unique advantage is to promote regeneration of soft tissue around the bone, including skin, muscle, and neurovascular structures. Its versatility allows correction of the foot position by adjusting the frame postoperatively[25]. The Ilizarov technique can enhance the direct total load capacity and promote osteogenesis because of its unique biomechanical principles[26]. Applying the Ilizarov technique in postoperative adjustment and tissue regeneration under slow drafting after surgery does not cause paralysis of nerves and blood vessels and skin necrosis, thus avoiding scar formation. The Ilizarov technique can be used for all causes of Achilles tendon contracture. Our patient had a rare case of muscle fibrosis and scarring due to surgical excision following invasion of the muscle by a hemangioma.

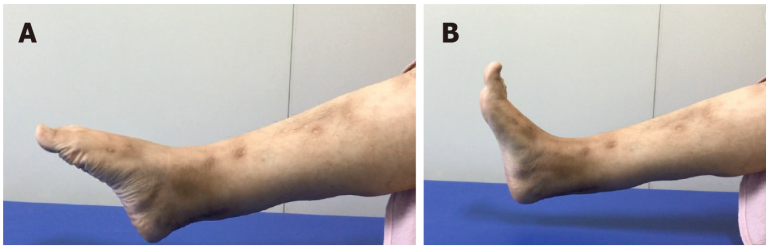

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Figure 5 Postoperative ankle joint. A: Postoperative straight; B: Postoperative back stretch.

The Ilizarov technique may provide a new solution for foot drop due to muscle scarring from various causes or muscle necrosis due to osteofascial syndrome.

In this study, the Achilles tendon can be extended acutely during the operation due to the Z-shaped incision. However, the length of skin, blood vessels, and neuroanatomy[19] are limited, and their elasticity is finite, so they cannot be extended acutely during the operation. Skin, blood vessels, and neuroanatomy can only develop slowly after the procedure, ensuring that the hinges are correctly positioned during surgery. When adjusting the external fixator postoperatively, it is important to adjust the distance between the anterior and posterior bars after opening the joint gap. At the same time, postoperative lengthening can adjust it in accordance with the patient's tolerance. In this process, in protecting the outer frame hinge, we advocate postoperative ankle flexion and extension exercise to prevent joint stiffness, ensure the stability of the ankle joint, and restore the function of the ankle. Follow-up with regular postoperative radiography can prevent traumatic arthritis due to anterior ankle impingement.

CONCLUSION

We report a case of postoperative sequelae of triceps surae hemangioma that caused Achilles tendon contracture, which was successfully corrected by the Ilizarov technique. The tolerance of skin, nerve, and blood vessels should be considered when acute lengthening of the Achilles tendon is performed interactively. The patient's postoperative orthopedic exercises were performed interactively. Meanwhile, foot and ankle flexion and extension exercises were performed under the protection of the hinge, guaranteeing foot and ankle functional recovery. In this case, good outcomes were achieved, with the range of motion of the ankle roughly restored and ability to walk normally with no toe-walking. This case may advise physicians to correct talipes equinovarus by the Ilizarov technique.

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FOOTNOTES

Author contributions: Chen ZX drafted the manuscript and collected clinical data; Wang MY and Zhang C edited the manuscript; Chen W and Ding ZQ were the surgeons of the patient, evaluated the study and participated in manuscript revision; all authors participated in manuscript preparation and approved the final version.

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CASE REPORT

Open surgery: Still a great option to treat patients with post-traumatic arteriovenous fistulas: A case report

Roman Kalinin, Igor Suchkov, Nina Mzhavanadze, Yulia Borisova, Ilya Panin

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Abstract

BACKGROUND

In the modern era of endovascular surgery percutaneous interventions are being widely used to treat a number of vascular disorders including arteriovenous fistulas (AVF). Still, patients with hostile anatomy or complicated cases such as large post-traumatic AVFs may be successfully treated using conventional vascular surgery.

CASE SUMMARY

This paper presents state-of-the-art treatment options in subjects with post-traumatic AVFs and a case-report of a successful open surgical approach in a patient with a 25 year old history of a post-traumatic AVF between the common femoral artery and common femoral vein.

CONCLUSION

Open surgery is still a great option to treat patients with post-traumatic arteriovenous fistulas with hostile anatomy or in complicated cases. Concomitant conditions and complications should be addressed promptly.

Key Words: Arterio-venous fistula; Femoro-femoral AVF; Open vascular surgery; Case report

Core Tip: Conventional open vascular surgery is a great option in treatment of post-traumatic arterio-venous fistulas involving femoral vessels in patients with hostile anatomy or complicated cases leading to aneurysm formation and limb ischemia.

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INTRODUCTION

Stab, gunshot wounds or other traumas to the groin may lead to the discrete injury to the femoral vessels and nerve with delayed complications. Exact rates of post-traumatic arterio-venous fistulas (AVF) of the lower extremity arteries are not known. When not diagnosed in a timely manner, certain AVF complications may develop. Among them are lower leg edema, heart failure[1], vein dilation and chronic venous insufficiency[2], lower leg ischemia, trophic ulcers.

Percutaneous interventions are being widely used to treat a number of vascular disorders including AVF[3,4]. Still, patients with hostile anatomy or complicated cases such as large post-traumatic AVFs may be successfully treated using conventional vascular surgery.

We present a case of a male patient with a 25 year old history of a post-traumatic AVF between the common femoral artery and common femoral vein.

CASE PRESENTATION

Chief complaints

Non-healing left leg ulcers and a pulsatile mass in the left groin.

History of present illness

A 62 - year old male was admitted to the vascular surgery department with complaints on the lower limb trophic ulcers (Figure 1) and a pulsatile mass in the left groin. The patient had a history of a single stab wound to his left groin 25 years prior to admission. The subject recalled undergoing a surgical exploration of the left groin back in 1997, and had not contacted any medical professionals ever since.

History of past illness

No apparent history of past illnesses.

Personal and family history

No history of cardiovascular disease in the family.

Physical examination

A physical examination at admission showed that the patient was in a stable condition. Blood pressure was 130/80 mmHg, pulse rate 75 beats per minute, regular, respiratory rate 16, temperature 36.5°C. There were a large pulsatile mass in the left inguinal area, signs of lower leg ischemia, varicose veins and post-thrombotic syndrome, lower leg trophic ulcers, peripheral neuropathy.

Laboratory examinations

Laboratory tests were within normal values.

Imaging examinations

Duplex ultrasonography (DUS) revealed a communication and turbulent blood flow between the left common femoral artery and left common femoral vein (Figure 2), an aneurysm of the left common femoral vein with calcification of posterior and medial walls (Figure 3), occlusion of the femoral and deep femoral vein distal to their confluence with common femoral vein, and multiple varicose veins on the left thigh.

Contrast enhanced computed tomography angiography (CT-angiography) performed at admission revealed an arteriovenous fistula between the left common femoral artery and left common femoral vein with an aneurysm of the latter, aneurysms of the proximal parts of the left deep femoral vein, femoral vein with further venous occlusion; CT-angiography also revealed dilated left iliac arteries (Figure 4).

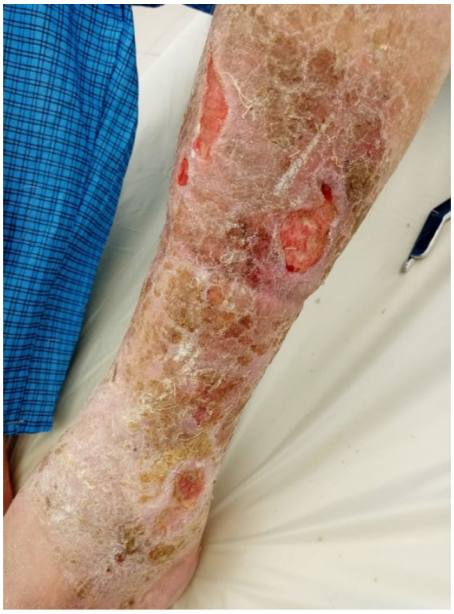

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Figure 1 A photograph depicting trophic ulcers of the left lower leg.

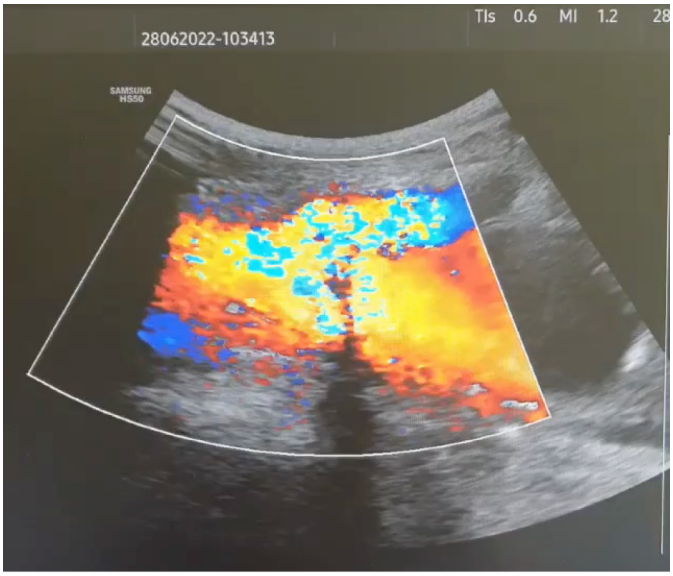

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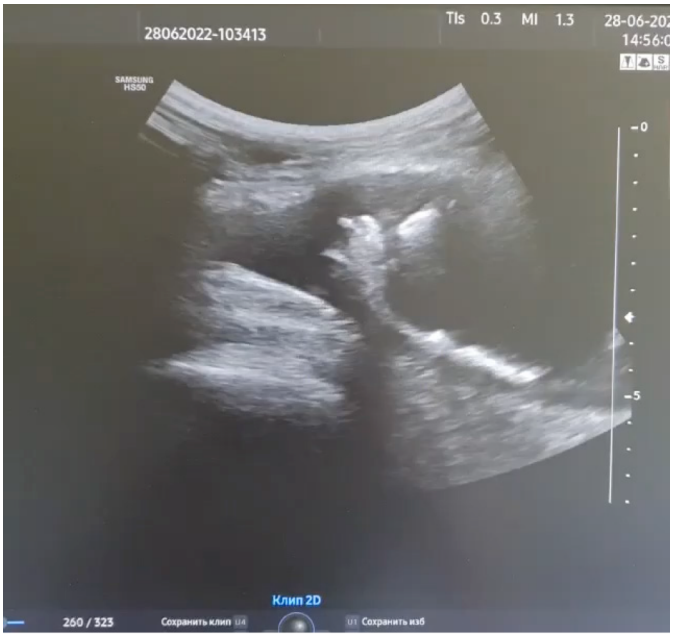
Figure 2 A sonogram of the left groin showing a communication and turbulent blood flow between the left common femoral artery (on top) and the left common femoral vein (on bottom).

Echocardiography was also performed and showed a normal ejection fraction, insignificant right and left atrial enlargement, mild left ventricular hypertrophy.

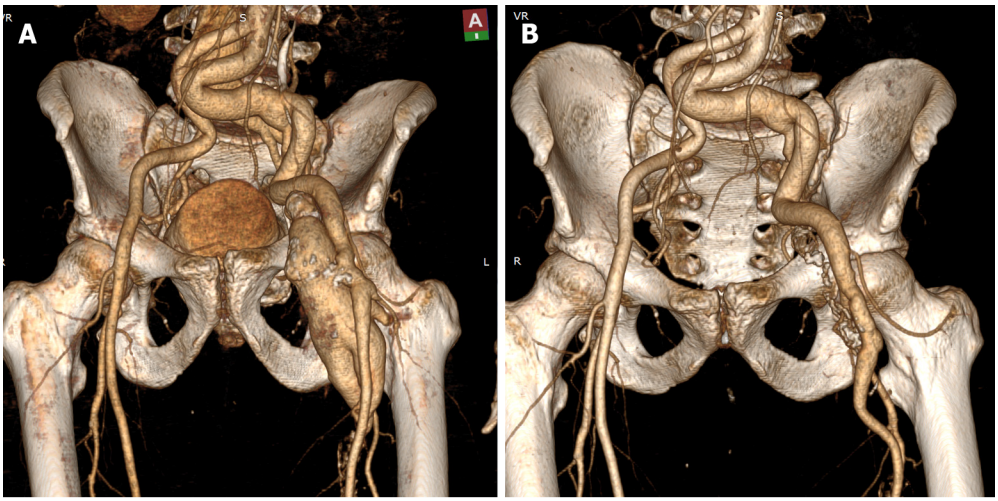
FINAL DIAGNOSIS

Post-traumatic arteriovenous fistula between left common femoral artery and left common femoral vein (after a single stab wound to the groin 25 years prior to admission). Aneurysm of the left common femoral vein. Post-thrombotic disease. Secondary varicose veins. Chronic lower limb ischemia. Trophic ulcers of the lower leg. Peripheral neuropathy.



DOI: 10.12998/wjcc.v11.i12.2811

Figure 3 A sonogram of the left groin showing the aneurysm of the left common femoral vein with calcification of posterior and medial walls.

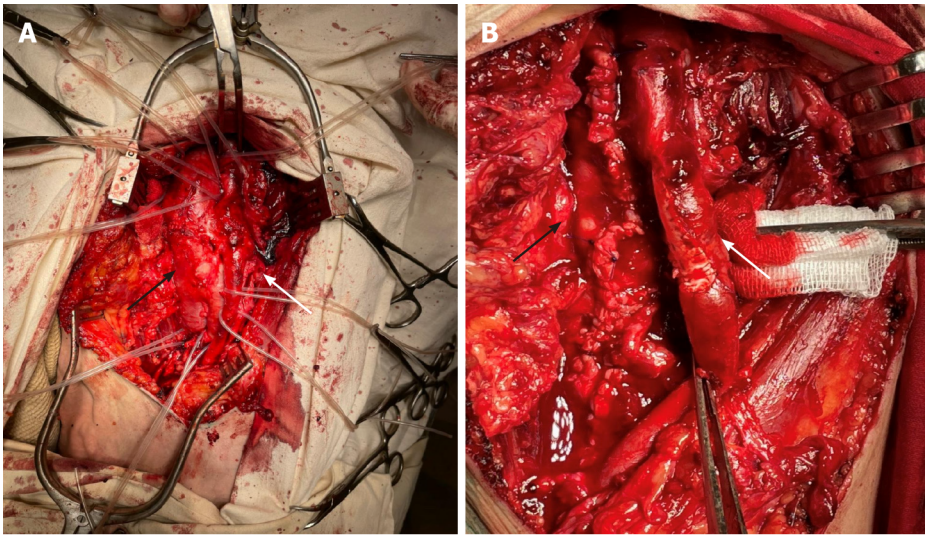


DOI: 10.12998/wjcc.v11.i12.2811

Figure 4 Computed tomography scan. A: Computed tomography (CT) -scan with contrast enhancement at admission (before treatment) demonstrating arteriovenous fistula between the left common femoral artery and left common femoral vein with an aneurysm of the latter, aneurysms of the proximal parts of the left deep femoral vein, femoral vein with further venous occlusion; CT-scans also shows dilated left iliac arteries; B: CT-scan with contrast enhancement before discharge (after treatment) demonstrating the absence of arteriovenous fistula between the left common femoral artery and left common femoral vein with preserved flow through both femoral and deep femoral arteries.

TREATMENT

We performed an open procedure. An open access to the femoral vessels in the left infrainguinal area (Figure 5A) with some technical difficulties due to extended fibrotic lesions at the sight of the AVF and left common femoral vein aneurysm, closure of the AVF with a synthetic PTFE patch, aneurysmorrhaphy of the left common femoral vein (Figure 5B). We decided to keep the dilated iliac arteries intact in order to avoid the use of extended synthetic grafts in the settings of multiple trophic ulcers. Intraoperative blood loss was 250 mL. The patient was started on aspirin 75 mg QD, atorvastatin 20mg QD, heparin 1000 units per hour IV for 24 h followed by enoxaparin 40 mg SC QD, famotidine 40 mg QD, amoxicillin/clavulanic acid 875 mg/125 mg IV BID, thioctic acid 600 mg IV QD.



DOI: 10.12998/wjcc.v11.i12.2811

Figure 5 We performed an open procedure. A: A photograph depicting the arteriovenous fistula between the left common femoral artery and left common femoral vein (white arrow), and the aneurysm of the left common femoral vein (black arrow); B: A photograph depicting a patch closure to the medial aspect of the common femoral artery (white arrow) and the common femoral vein following aneurysmorrhaphy (black arrow).

Endovascular treatment was avoided in this case due to the following reasons: placement of a stent graft into the common femoral artery would have put the patient at the potential risk of stent fracture related to hip joint flexion; blood flow to the deep femoral artery would have been compromised, too.

OUTCOME AND FOLLOW-UP

Post-operative period was uneventful. On the 7th day following the procedure we performed a repeat CT-scanning with contrast enhancement, which revealed the absence of arteriovenous fistula between the left common femoral artery and left common femoral vein with successfully preserved flow through both femoral and deep femoral arteries. Trophic ulcers healed within 2 mo following the procedure.

DISCUSSION

Endovascular surgery has been a leading trend in vascular surgery for the past decades. Arterio-venous fistulas of different nature and localization can be successfully treated using transcutaneous techniques such as endovascular coiling, embolization or placement of a stent-graft depending on the clinical settings[5-7].

As the AVF was located directly across the orifice of the deep femoral artery and was accompanied by a large aneurysm of the left common femoral vein, we decided to perform an open procedure as the placement of an endovascular stent graft might have caused diminished flow through the deep femoral artery and led to the possibility of a thrombus formation in a dilated common femoral vein with subsequent risks of pulmonary embolism.

Stab, gunshot wounds or other traumas to the groin should be carefully evaluated to exclude injury to the femoral vessels and nerve, which eventually may lead to the formation of arteriovenous fistulas and vascular aneurysms. A misdiagnosis may occur due to simple wound exploration with no prior or further DUS, CT-angiography, or digital subtraction angiography, which are necessary in order to avoid delayed complications[8].

CONCLUSION

In the era of endovascular procedures, conventional open vascular surgery is still a great option in treatment of post-traumatic arteriovenous fistulas involving femoral vessels in patients with complicated cases leading to aneurysm formation and lower limb ischemia. Possible concomitant conditions or complications such as heart failure or peripheral neuropathy should be addressed promptly.

FOOTNOTES

Author contributions: Kalinin RE and Suchkov IA designed the report; Mzhavanadze ND treated the patient and collected the patient's clinical data; Borisova YuO and Panin IV performed diagnostic procedures; Suchkov IA, Mzhavanadze ND, Borisova YuO and Panin IV analyzed the data and wrote the paper.

Informed consent statement: The patient was not required to give informed consent to this case report because the analysis used completely anonymous data; the consent was obtained before performing any medical investigation or start of treatment as required.

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CASE REPORT

Recovery from Bell's palsy after treatment using uncultured umbilical cord-derived mesenchymal stem cells: A case report

Hyunjun Ahn, Won-Ju Jung, Sang Yeon Lee, Kye-Ho Lee

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Peer-review model: Single blind

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Abstract

BACKGROUND

Bell's palsy is an idiopathic facial palsy with an unknown cause, and 75% of patients heal spontaneously. However, the other 25% of patients continue experiencing mild or severe disabilities, resulting in a reduced quality of life. Currently, various treatment methods have been developed to treat this disease. However, there is controversy regarding their effectiveness, and new alternative treatments are needed.

CASE SUMMARY

The patient suffered from left-sided facial paralysis due to Bell's palsy for 7 years. The patient received an uncultured umbilical cord-derived mesenchymal stem cell transplant eight times for treatment. After follow-up for 32 mo, the paralysis was cured, and there was no recurrence.

CONCLUSION

Uncultured umbilical cord-derived mesenchymal stem cell transplantation may be a potential treatment for patients with Bell's palsy who do not spontaneously recover.

Key Words: Bell's palsy; Facial palsy; Umbilical cord-mesenchymal stem cells; Allogenic; Case report

Core Tip: The effectiveness of the current treatment methods for Bell's palsy is debated. Therefore, alternative treatments are needed. In this study, we treated a patient with Bell's palsy classified as moderately severe dysfunction using uncultured umbilical cord-derived mesenchymal stem cells. After follow-up for 32 mo, the paralysis was cured, and there was no recurrence. This method could be a new treatment option to replace existing treatments for Bell's palsy.

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INTRODUCTION

Facial paralysis is a disease in which one side of the facial muscles become suddenly or gradually paralyzed. While facial paralysis can be caused by a number of factors, Bell's palsy-defined idiopathic facial paralysis is the cause of 60%-75% of all cases[1], and the cause of Bell's palsy is unknown. Although approximately 75% of the patients will heal spontaneously, it can lead to severe temporary oral insufficiency and potentially cause permanent eye damage because the eyelid on the affected side is unable to close[2,3]. Moderate to severe facial asymmetry persists in approximately 25% of patients with Bell's palsy, often compromising the patient's quality of life[2,3]. This long-term side effect of Bell's palsy can be devastating for patients[2,3].

Although Bell's palsy is considered idiopathic, herpes virus-specific immune response and ischemic or hereditary factors are closely related to its etiology[1,4,5]. In the early stages of the disorder, steroid therapy or antiviral administration has been shown to improve symptoms[6-8]. Nevertheless, in patients with long-term facial muscle dysfunction, symptoms may improve with facial exercises, acupuncture, and occupational and speech therapy[1,9-11]. In severe cases, symptoms can be relieved by nerve decompression and plastic surgery procedures[1,12]. Various treatment methods for patients with insufficient recovery from Bell's palsy have been developed, but the effectiveness of these methods is debated. Despite receiving various treatments, some patients still have symptoms of paralysis. Therefore, alternative treatments for these patients are still needed[1,6,13].

Based on the results of previous studies, mesenchymal stem cell (MSC) transplantation treatment may be effective for treating Bell's palsy. MSCs play an effective role in suppressing the function of the herpes virus and eliminating inflammation[14-16]. In addition, MSCs secrete cytokines that protect and regenerate neuronal cells and have the potential to differentiate into neuronal cells, which aids the regeneration of the damaged lesion site[17,18]. Therefore, we hypothesized that MSCs may be an effective treatment for Bell's palsy in patients with insufficient recovery. In this study, we used uncultured umbilical cord-derived (UC)-MSCs to treat a patient with Bell's palsy who experienced insufficient recovery. The patient had suffered from Bell's palsy for 7 years. We report the treatment of this case using UC-MSCs as evidence that it may be a potential effective treatment of Bell's palsy.

CASE PRESENTATION

Chief complaints

On March 5, 2013, a 49-year-old female, who suffered from Bell's palsy, visited the 97.7 B&H Clinic. The patient had paralysis on the left side of the face.

History of present illness

The patient was diagnosed with Bell's palsy in 2006. At first, the patient experienced only pain on the face, but tremors and paralysis gradually appeared on the left side of her face. As inferred from the patient's comments, at the time of diagnosis, the patient had grade 4 (moderately severe dysfunction) facial paralysis according to the House-Brackmann facial nerve grading system (Table 1)[1]. She was treated with steroids when symptoms first appeared, but the treatment was ineffective. She was further treated with acupuncture, meridian massage, and herbal medicine, but the paralysis remained.

History of past illness

The patient had no specific diseases or disorders.

Personal and family history

The patient's father suffered from a brain hemorrhage. However, the patient had no history of brain

Table 1 House-Brackmann facial nerve grading system

Grade	Description	Characteristics
1	Normal	Normal facial function in all areas
2	Mild dysfunction	Slight weakness noticeable upon close inspection; may have very slight synkinesis
3	Moderate dysfunction	Obvious, but not disfiguring, difference between two sides; noticeable but not severe synkinesis, contracture, or hemifacial spasm; complete eye closure with effort
4	Moderately severe dysfunction	Obvious weakness or disfiguring asymmetry; normal symmetry and tone at rest; incomplete eye closure
5	Severe dysfunction	Barely perceptible motion; asymmetry at rest
6	Total paralysis	No movement

hemorrhage or other related diseases.

Physical examination

At the time of the first visit, the patient participated in a brief question-and-answer session to confirm the history of the present illness and symptoms. The patient had left-side facial paralysis with the following symptoms: muscle tremors, disfiguring asymmetry, and incomplete left eye closure. Based on the House-Brackmann facial nerve grading system, we classified the patient as a grade 4, moderately severe dysfunction (Table 1)[1].

Laboratory examinations

Bell's palsy does not require blood tests for diagnosis or treatment. However, a complete blood count, basic metabolic panel, comprehensive metabolic panel, lipid panel, thyroid panel, and cardiac biomarkers were performed to check the patient's health. Upon examination, everything was normal.

Imaging examinations

Imaging examinations were not performed.

FINAL DIAGNOSIS

The patient was diagnosed, in our clinic, with Bell's palsy with insufficient recovery. In addition, the House-Brackmann facial nerve grading system evaluation through question-and-answer with the patient determined that the patient's symptoms had not improved over the 7 years after the first diagnosis.

TREATMENT

UC procurement

UCs were donated by the Obstetrics and Gynecology Department at Lynn Woman's Hospital (Seoul, South Korea). The donors' mothers consented to the donation of the UCs. The safety of the donated UCs was confirmed through the mothers' medical histories and blood and urine tests.

Isolation and quality evaluation of UC-MSCs

UC-MSCs were isolated from the donated UCs as described previously[17,19,20]. The UC was first disinfected with 70% ethanol and then washed with 1 × phosphate-buffered saline. Then, three vessels and the amniotic membrane of the UC were removed, and the UC was cut into 2-3 cm pieces with surgical scissors. The cut tissues were placed in a 50-mL conical tube containing a mixture solution of collagenase and hyaluronidase, further minced with surgical scissors and ground with a disposable tissue grinder, and incubated in a 37 °C, 50 mL/L CO_2 incubator for 1 h. The mixture solution was filtered (100 μm) and then centrifuged to collect the flow-through containing the purified UC-MSCs. The UC-MSC samples were resuspended in CryoStor® CS10 (Stemcell Technologies, Cambridge, MA, United States), frozen at -80 °C for 1 d, and transferred to a liquid nitrogen tank for storage until clinical application.

The isolated UC-MSCs were suitable for treatment after confirmation of negative microbiological tests and of the expression level of MSC-specific proteins (CD73 ≥ 70%, CD90 ≥ 90%, and CD105 ≥ 90%) (data not shown). The expression level of MSC-specific proteins was measured using CyFlow® Cube 6 (Sysmex, Lincolnshire, IL, United States) and FCS Express 5 software (De Novo Software, Glendale, CA,

United States).

Preparation of injection solution

We prepared a stock 4 mL injection solution consisting of uncultured UC-MSCs and 0.9% sodium chloride, USP with a concentration of 1 × 10^6 cells/mL. Before injection, the prepared 4 mL injection solution was divided into four 1 mL Ultra-Fine™ II Insulin Syringes (BD Biosciences, Franklin Lakes, NJ, United States) containing 1 mL each.

Treatment

We injected the injection solution evenly over the left-side of the patient's face. Each site was injected with 0.25 mL at a depth of 0.4-0.6 cm (a total of 16 injections were performed). Each injection site is marked with an 'X' in Figure 1.

OUTCOME AND FOLLOW-UP

The patient received a total of eight treatments at 2-mo intervals for 14 mo, and was followed up 18 mo after the end of treatment. The Bell's palsy did not recur during this period.

After UC-MSC transplantation, the patient experienced rapid improvement in the closure of her left eye. Before UC-MSC transplantation, the patient could only close her left eye about 50%. Three months after the first treatment, the patient was able to achieve left eye closure to 70%. This symptom continued to improve, and by 22 mo after the first treatment, the patient was able to completely close her left eye (Figure 1). In addition, before treatment, the patient's left eyebrow was located lower than the right eyebrow. During the follow-up period, the muscles around the eyebrow normalized, and the eyebrows were even (Figure 2).

The patient also experienced relief of asymmetrical lips after UC-MSC transplantation. Before treatment, the patient had difficulty speaking because her lips were slightly tilted to the right. Three months after the first treatment, the patient reported that the muscles around the lips had softened, and her speech became easier. The patient's lips were gradually improved and normalized over 28 mo (Figure 3).

Report of side effects

Immediately after each treatment, the patient showed no specific local facial nor systemic abnormalities as reactions. Also, during the treatment and follow-up period, the patient did not report any experience of abnormalities nor of side effects.

DISCUSSION

The patient had suffered from Bell's palsy for 7 years and remained disabled despite various treatments (including steroid drug therapy, acupuncture, meridian massage, and herbal medicine). The patient lived with facial asymmetry and discomfort due to stiffness in the affected region; these problems caused the patient to have psychological stress due to loss of self-confidence and lack of sleep. Eventually, her quality of life was greatly reduced due to related social avoidance.

Bell's palsy is an idiopathic disease of unknown cause[1]. Researchers have hypothesized that Bell's palsy develops as a result of damage to the facial nerve system due to various factors, including an immune response, inflammation, ischemia, and hereditary factors[1,4,5]. Although 75% of patients with Bell's palsy recover spontaneously, the remaining 25% experience mild or severe disability, which reduces their quality of life[2,3]. To increase the cure rate of Bell's palsy, steroids or antiviral drugs are given in the early course of the disorder, but their effectiveness is debated[6,7,21]. Patients with Bell's palsy who experience insufficient recovery can receive various treatments such as meridian massage, acupuncture, exercise therapy, *etc*. In severe cases, nerve decompression and plastic surgery procedures can be performed[1,9-11]. Even though new treatments have been developed for patients with Bell's palsy experiencing insufficient recovery, they are controversial, and new alternatives are needed. As mentioned in the previous section, the cause of Bell's palsy is not clearly known, but there are several suspected causes, such as a viral infection or damage to the facial neuron by an assortment of proposed factors[1,4,5]. According to various recent studies, MSCs have antiviral, anti-inflammatory, neuronal protective, and regeneration functions[14,16-18]. Based on these findings, we hypothesized that MSC transplantation could treat patients with Bell's palsy experiencing insufficient recovery. Although the cause of Bell's palsy is unknown, transplantation of MSCs has the potential to overcome the presumed causes of Bell's palsy.

Based on these findings, we hypothesized that MSC transplantation could successfully treat patients with Bell's palsy experiencing insufficient recovery.

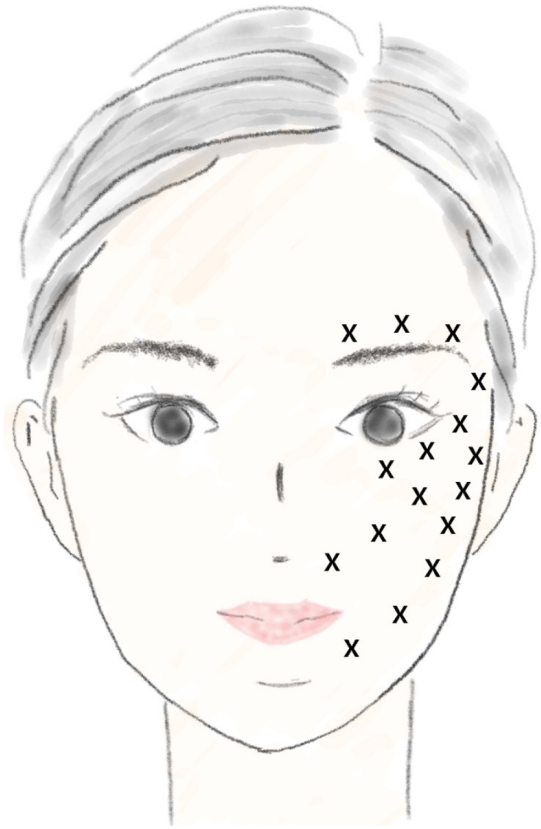

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Figure 1 Injection sites used for the transplantation of uncultured umbilical cord-mesenchymal stem cells. The patient was suffering from left-sided paralysis due to Bell's palsy. X: Injection sites.

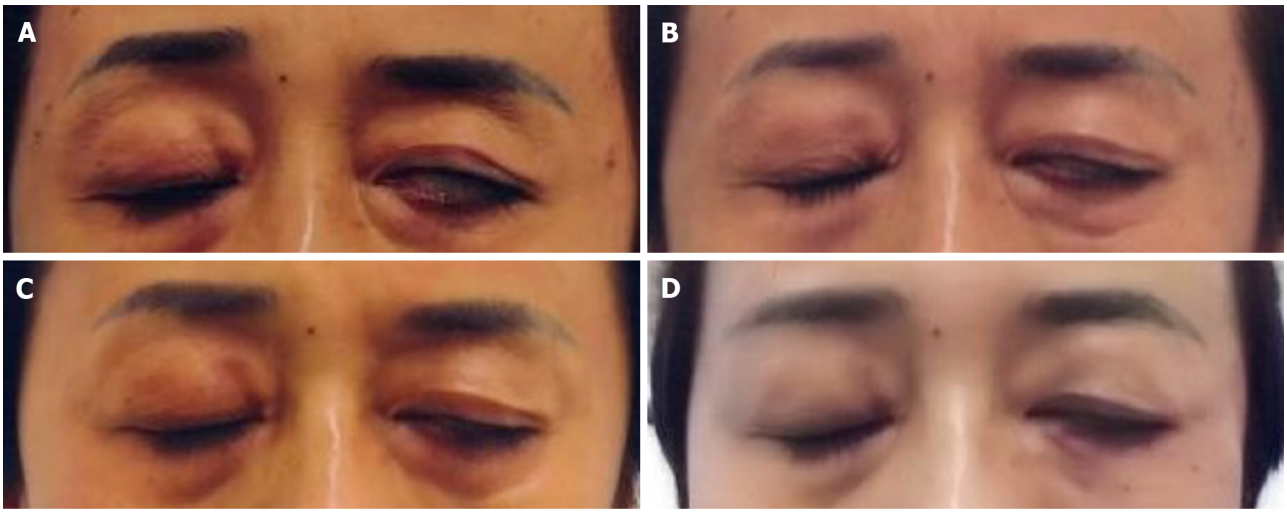

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Figure 2 Left eye closure and eyebrow location during the treatment and follow-up. A: The patient's eye closure and eyebrow location at 3 mo after the first treatment; B: Seven months after the first treatment; C: Twelve months after the first treatment; D: Twenty-two months after first treatment.

Although UC-MSCs are allogeneic cells, they are typically not rejected by the recipient and can be used universally[22]. In general, culturing is performed to obtain the number of MSCs required for treatment, but previous studies have indicated that MSCs undergo changes in their properties during culture, such as loss of their differentiation potential and change in their ability to secrete various cytokines and proteins due to the cell aging that occurs in the culturing period[23-25]. For these reasons, we used uncultured UC-MSCs, which are the youngest and most universally available, for treatment. Three months after the first treatment, the patient reported improvement in the closure of her left eye and stiff muscles around the lips. Over the 32-mo follow-up period, the patient reported that the

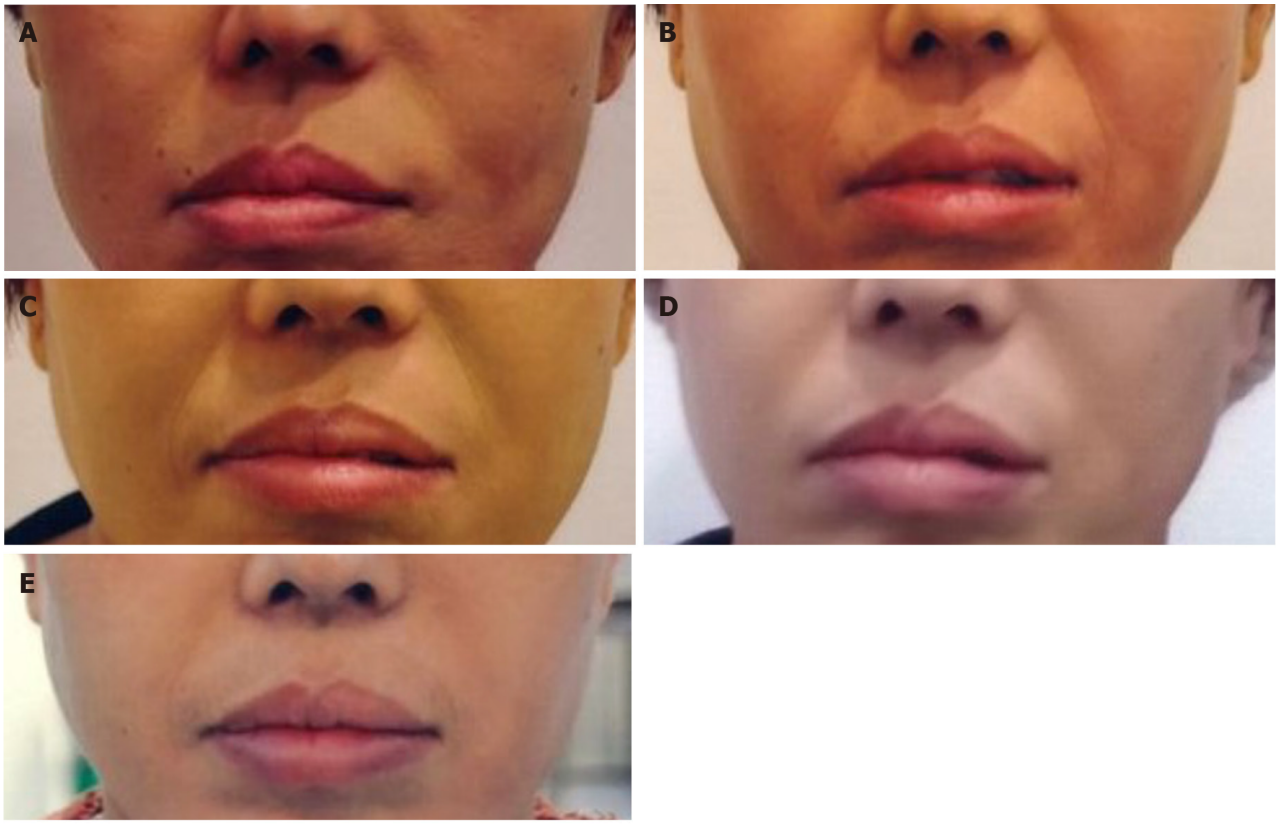

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Figure 3 Change in the patient's asymmetrical lips during the treatment and follow-up. A: The patient's asymmetrical lips at 3 mo after the first treatment; B: Ten months after the first treatment; C: Sixteen months after the first treatment; D: Twenty-two months after first treatment; E: Twenty-eight months after first treatment.

symptoms gradually improved and normalized. There was no recurrence of Bell's palsy symptoms during the follow-up.

A limitation of this report is the lack of pre-treatment images due to the refusal of the patient to have "before" images taken. However, 3 mo after treatment the patient consented to have images taken due to the improvement of symptoms. Although this is a case report of only 1 patient, we showed that uncultured UC-MSCs were effective in treating Bell's palsy. A well-controlled and large-scale clinical study is required to provide further evidence that uncultured UC-MSC transplantation is an effective treatment for Bell's palsy.

CONCLUSION

In this case study, a patient suffering from Bell's palsy for 7 years was treated with uncultured UC-MSC transplantation. Although this is a case report of 1 patient, we expect that a randomized controlled trial will provide evidence that using uncultured UC-MSC transplantation to treat patients with Bell's palsy with insufficient recovery is an effective new treatment.

FOOTNOTES

Author contributions: Ahn H, Jung WJ, Lee SY and Lee KH designed the report; Ahn H and Jung WJ collected the patient's clinical data; Ahn H and Jung WJ analyzed the data; Ahn H and Lee SY wrote the manuscript; Lee KH provided professional advice and revised the manuscript; all authors issued final approval for the version to be submitted.

Informed consent statement: The patient involved in this study gave her written informed consent authorizing disclosure of her protected health information.

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CASE REPORT

Pancreatic neuroendocrine tumor detected by technetium-99m methoxy-2-isobutylisonitrile single photon emission computed tomography/computed tomography: A case report

Chang-Jiang Liu, Hua-Jun Yang, Yan-Chun Peng, De-Yu Huang

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Abstract

BACKGROUND

Pancreatic neuroendocrine tumors (NETs) account for about 1%–2% of pancreatic tumors and about 8% of all NETs. Computed tomography (CT), magnetic resonance imaging, and endoscopic ultrasound are common imaging modalities for the diagnosis of pancreatic NETs. Furthermore, somatostatin receptor imaging is of great value for diagnosing pancreatic NETs. Herein, we report the efficacy of technetium-99m methoxy-2-isobutylisonitrile (^{99m}Tc-MIBI) single photon emission CT (SPECT)/CT for detecting pancreatic NETs.

CASE SUMMARY

A 57-year-old woman presented to our hospital with a 1-d history of persistent upper abdominal distending pain. The distending pain in the upper abdomen was aggravated after eating, with nausea and retching. Routine blood test results showed a high neutrophil percentage, low leukomonocyte and monocyte percentages, and low leukomonocyte and eosinophil counts. Amylase, liver and kidney function, and tumor markers alpha-fetoprotein, carcinoembryonic antigen, and cancer antigen (CA) 125, CA72-4, CA19-9, and CA153 were normal. Abdominal CT showed a mass, with multiple calcifications between the pancreas and the spleen. The boundary between the mass and the pancreas and spleen was poorly defined. Contrast-enhanced CT revealed that the upper abdominal mass

was unevenly and gradually enhanced. ^{99m}Tc-MIBI SPECT/CT revealed that a focal radioactive concentration, with mild radioactive concentration extending into the upper abdominal mass, was present at the pancreatic body and tail. The ^{99m}Tc-MIBI SPECT/CT manifestations were consistent with the final pathological diagnosis of pancreatic NET.

CONCLUSION

^{99m}Tc-MIBI SPECT/CT appears to be a valuable tool for detecting pancreatic NETs.

Key Words: Neuroendocrine tumors; Pancreas; Tc-99m-Methoxy-2-isobutylisonitrile; Single photon emission computed tomography; X-ray computed tomography; Case report

Core Tip: Neuroendocrine tumors (NETs) are rare. The gastroenteropancreatic tract is the most common site for NETs. Pancreatic NETs account for about 1%-2% of pancreatic tumors and about 8% of all NETs. Endoscopic ultrasound, computed tomography (CT), and magnetic resonance imaging are common imaging modalities for the diagnosis of pancreatic NETs. In addition, somatostatin receptor imaging is of great value for the diagnosis of pancreatic NETs. We experienced a case of pancreatic NET detected by technetium-99m methoxy-2-isobutylisonitrile (^{99m}Tc-MIBI) single-photon emission CT/CT, which was consistent with the final pathological diagnosis of pancreatic NET.

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INTRODUCTION

Neuroendocrine tumors (NETs) are relatively rare tumors arising from cells in the diffuse neuroendocrine system, occurring mainly in the gastroenteropancreatic (GEP) tract and lungs[1]. The GEP tract is the most common site for NETs[2]. Pancreatic NETs account for about 1%-2% of all pancreatic tumors [3] and about 8% of all NETs[4]. The diagnostic imaging modalities for pancreatic NETs include computed tomography (CT), magnetic resonance imaging, endoscopic ultrasound, and somatostatin receptor imaging[5]. However, the application of technetium-99m methoxy-2-isobutylisonitrile (^{99m}Tc-MIBI) single photon emission CT (SPECT)/CT for detecting pancreatic NET has not been reported.

CASE PRESENTATION

Chief complaints

A 57-year-old woman presented with upper abdominal distending pain lasting 1 d.

History of present illness

The patient had persistent pain that was aggravated after eating, accompanied by nausea and retching. Her abdominal CT findings revealed an upper abdominal tumor originating from the spleen or pancreas. Therefore, she was admitted to the hospital for further examination and treatment.

History of past illness

The patient underwent traumatic abdominal exploratory surgery more than 30 years ago.

Physical examination

An old surgical scar with a longitudinal length of about 6 cm was observed on the upper abdomen. A mass was palpable in the left-upper abdomen, which was hard, poor in mobility, and slightly tender.

Laboratory examinations

Routine blood test results showed a high neutrophil percentage, low lymphocyte and monocyte percentages, and a low eosinophil count. Routine urine and stool test results were normal. The levels of

electrolytes (sodium, chlorine, calcium, and magnesium) were normal. Amylase, liver and kidney function, and tumor markers alpha-fetoprotein, carcinoembryonic antigen, carbohydrate antigen (CA) 125, CA72-4, CA19-9, and CA153 were also normal.

Imaging examinations

CT and contrast-enhanced CT of the abdomen: Abdominal CT showed a mass with multiple calcifications between the pancreas and the spleen. The boundary between the mass and the pancreas and spleen was poorly defined (Figure 1). The maximum cross section of the mass was about 9.0 cm × 8.6 cm. Contrast-enhanced CT revealed that the upper abdominal mass was unevenly and gradually enhanced (Figure 2).

Abdominal ^{99m}Tc-MIBI SPECT/CT: ^{99m}Tc-MIBI SPECT/CT was performed 5 d after contrast-enhanced CT imaging. Scanning began 30 min after the injection of 740 MBq of ^{99m}Tc-MIBI. Abdominal ^{99m}Tc-MIBI SPECT/CT was performed using a PRECEDENCE SPECT/CT (Philips Medical Systems, Eindhoven, the Netherlands) system. CT scanning was performed in a spiral mode over the entire abdomen at 250 mAs per slice, 120 Kv, and with a slice thickness of 3.0 mm. Immediately after CT scanning, SPECT acquisition of the abdomen was performed. The SPECT system was equipped with low-energy, high-resolution parallel-hole collimators. The SPECT acquisition followed an elliptical orbit, with a step-and-shoot acquisition of 64 angles over 360° (180° per detector) and an acquisition time of 20 s per frame. The SPECT data were reconstructed with attenuation correction from CT acquisition and iterative reconstruction *via* AutoSPECT Pro software with astonish, four iterations, and 16 subsets. The ^{99m}Tc-MIBI SPECT/CT fused images were processed using Fusion Viewer (version 2.1) procedures. The SPECT slice thickness was the same as that of CT.

The ^{99m}Tc-MIBI SPECT/CT images showed the presence of a focal radioactive concentration, with mild radioactive concentration extending into the upper abdominal mass at the pancreatic body and tail (Figure 3).

FINAL DIAGNOSIS

The pathology of the pancreatic lesion indicated a well-differentiated pancreatic NET by hematoxylin and eosin staining (Figure 4A and B). The pathology of the spleen showed normal spleen cells by hematoxylin and eosin staining (Figure 4C). Immunohistochemical analysis showed that the tumor cells were positive for insulinoma-associated protein 1, synaptophysin, and cluster of differentiation 56 (Figure 5). The Ki-67 (marker of proliferation Ki-67) proliferative index was assessed at 10% (Figure 6).

TREATMENT

Two days after ^{99m}Tc-MIBI SPECT/CT, the pancreatic body and tail, the upper abdominal mass discovered by CT (the mass with multiple calcifications between the pancreas and the spleen), and the spleen were excised. During the operation, a pancreatic lesion was seen to expand outward and extend into the spleen. This was inconsistent with the abdominal CT findings.

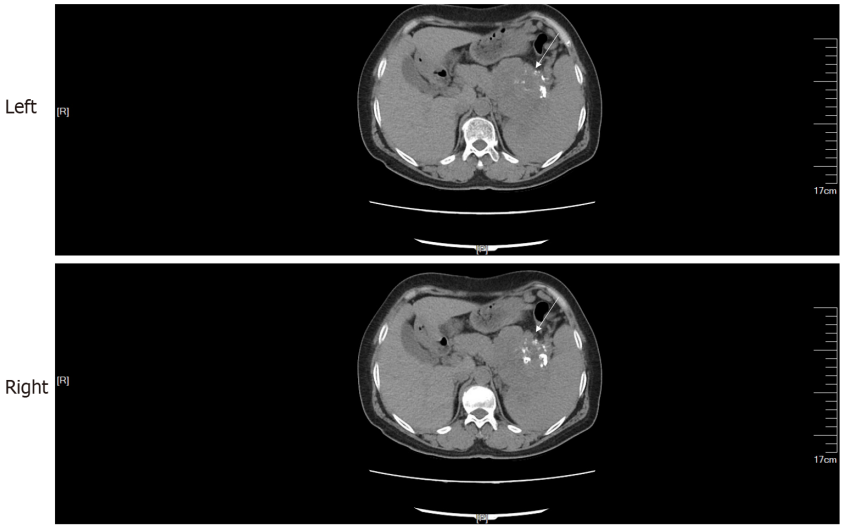
OUTCOME AND FOLLOW-UP

The patient was followed up 35 d after surgery. She complained of dull pain in her upper abdomen. Abdominal CT results showed encapsulated effusion in the surgical area (Figure 7), with no obvious abnormality in the remaining area. The patient's condition improved after ultrasound-guided closed abdominal drainage.

DISCUSSION

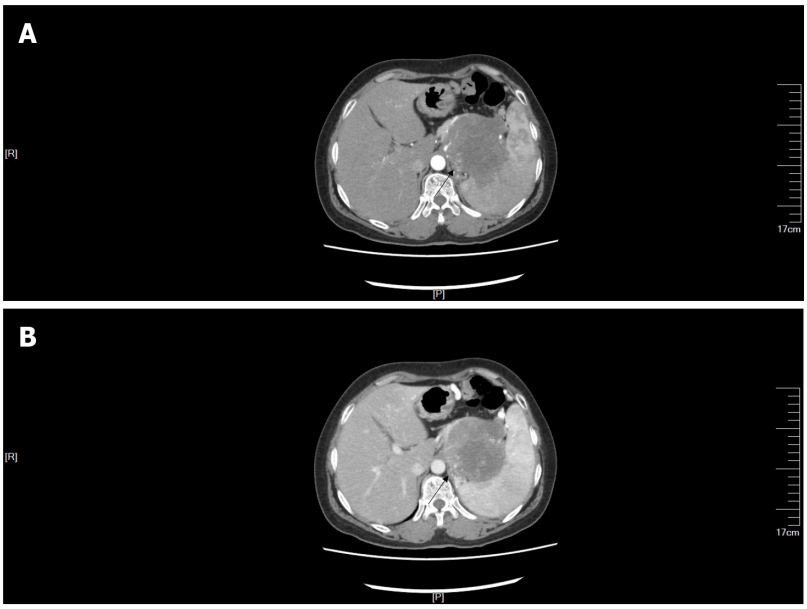
Pancreatic NETs are often divided into functional and nonfunctional pancreatic NETs. The majority of pancreatic NETs are nonfunctional[5]. The symptoms of a nonfunctional pancreatic NET include abdominal or back pain, nausea, vomiting, pancreatitis, and obstructive jaundice[5]. Patients with functional pancreatic NETs often present with symptoms caused by hormone production of the tumor, leading to an early diagnosis[6].

Endoscopic ultrasound, CT, and magnetic resonance imaging are common imaging modalities for the diagnosis of pancreatic NETs. In addition, somatostatin receptor imaging is of great value for the diagnosis of pancreatic NETs[7], but the method is not easily available in our hospital.



DOI: 10.12998/wjcc.v11.i12.2825

Figure 1 Abdominal computed tomography. A mass (arrow) with multiple calcifications between the pancreas and the spleen was observed. The boundary between the mass and the pancreas and spleen was poorly defined.



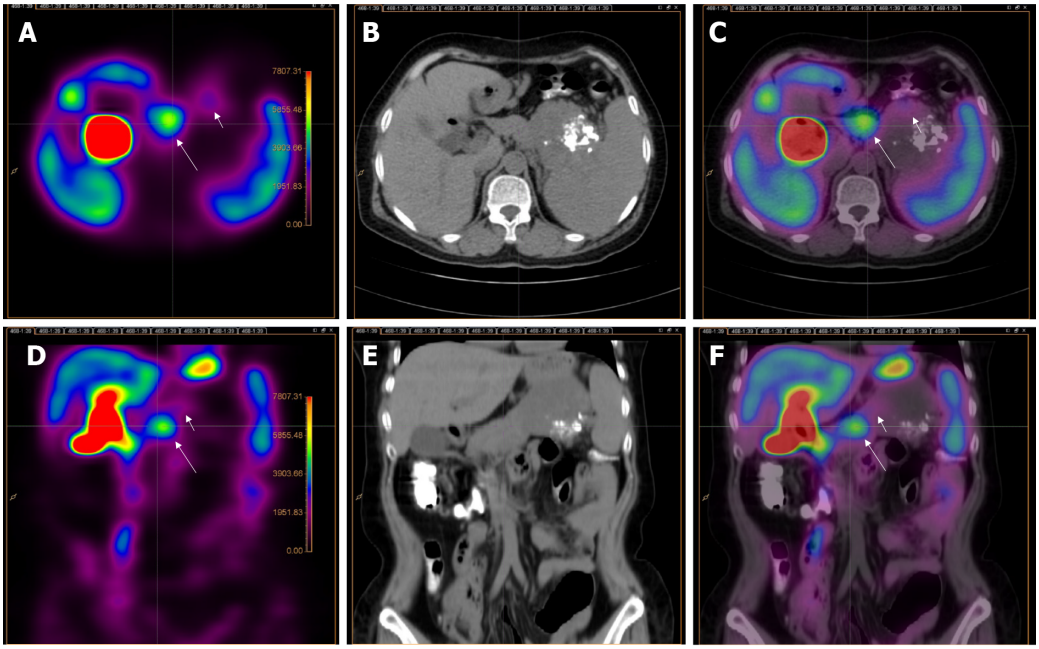
DOI: 10.12998/wjcc.v11.i12.2825

Figure 2 Abdominal computed tomography with contrast showed that the upper abdominal mass was unevenly and gradually enhanced (arrow). A: Arterial time; B: Venous time.

More than 90% of well-differentiated GEP NETs express somatostatin receptors[8]. Functional imaging technique of gallium-68 dota-octreotate (^{68}Ga-DOTATATE) positron emission tomography (PET)/CT uses radiolabeled somatostatin analogs to localize NETs. Research showed that the sensitivity of ^{68}Ga-DOTATATE PET/CT was about 95% for detecting pancreatic NETs[7]. Unlike ^{68}Ga-DOTATATE, ^{99m}Tc-MIBI is a nonspecific tumor imaging agent. However, compared with ^{68}Ga-DOTATATE PET/CT, ^{99m}Tc-MIBI SPECT/CT is a relatively cheap and easily available imaging modality. Herein, we present a case of pancreatic NETs detected by ^{99m}Tc-MIBI SPECT/CT.

^{99m}Tc-MIBI is a lipophilic univalent cationic agent. Driven by cytoplasmic and mitochondrial transmembrane potential gradients, ^{99m}Tc-MIBI penetrates reversibly into the cytoplasm and concentrates in mitochondria[9]. In one study, there were greater electrical gradients from outside the cell to the mitochondria in carcinoma cells than in normal epithelial cells, and the uptake of ^{99m}Tc-MIBI increased tenfold in carcinoma cells[9].

^{99m}Tc-MIBI SPECT/CT may be a useful tool for detecting lymph node and lung metastases in patients with differentiated thyroid carcinoma[10]. Additionally, ^{99m}Tc-MIBI SPECT can be used to differentiate benign from malignant solitary pulmonary nodules and thyroid nodes[11,12]. Lu *et al*[13] reported a



DOI: 10.12998/wjcc.v11.i12.2825

Figure 3 Abdominal technetium-99m methoxy-2-isobutylisonitrile single photon emission computed tomography/computed tomography. Technetium-99m methoxy-2-isobutylisonitrile single photon emission computed tomography (SPECT)/CT of the abdomen showed that a focal radioactive concentration (long arrow) with mild radioactive concentration (short arrow) was present on SPECT (A, D) and technetium-99m methoxy-2-isobutylisonitrile SPECT/CT fusion images (C, F) at the sites corresponding to the pancreatic body and tail and the upper abdominal mass discovered by CT (B, E). A-C: Transverse axis; D-F: Coronal axis.

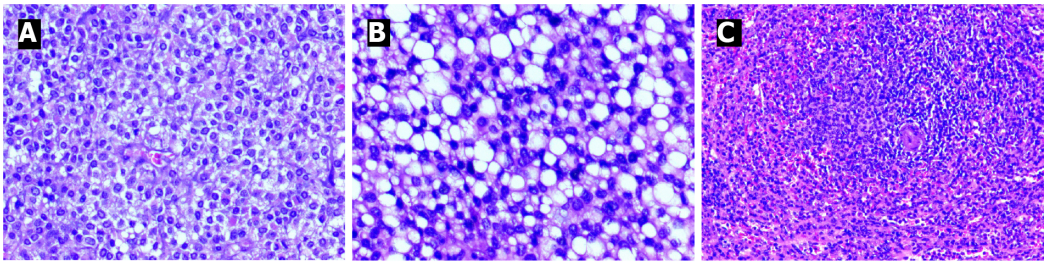


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Figure 4 Hematoxylin and eosin staining. A: The pathology of the focal radioactive concentration of the pancreatic body and tail shown on technetium-99m methoxy-2-isobutylisonitrile single photon emission computed tomography (CT)/CT indicated a well-differentiated pancreatic neuroendocrine tumor *via* hematoxylin and eosin staining (× 200); B: The pathology of the upper abdominal mass shown on CT indicated a well-differentiated pancreatic neuroendocrine tumor *via* hematoxylin and eosin staining (× 200); C: Normal spleen cells observed after hematoxylin and eosin stain (× 100).

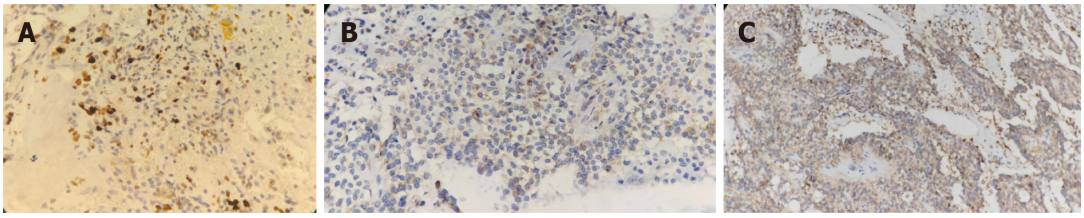

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Figure 5 Immunohistochemical staining of tumor cells. A: Positive for insulinoma-associated protein 1; B: Positive for synaptophysin; C: Positive for cluster of differentiation 56 (× 200).

case of mediastinal typical carcinoid tumor detected by ^{99m}Tc-MIBI SPECT/CT.

Our patient was a 57-year-old woman with symptoms that started 1 d previously. The age for the occurrence of pancreatic NETs is equivalent to the mean age (57-58 years) previously identified for this type of tumor[5]. The patient's abdominal CT showed a mass with multiple calcifications between the

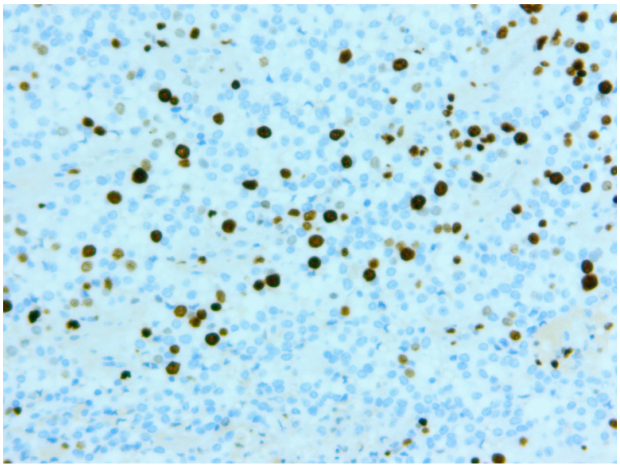

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Figure 6 Immunohistochemical staining (EnVision technique) showed Ki-67 (marker of proliferation Ki-67) proliferative index of 10% (× 400).

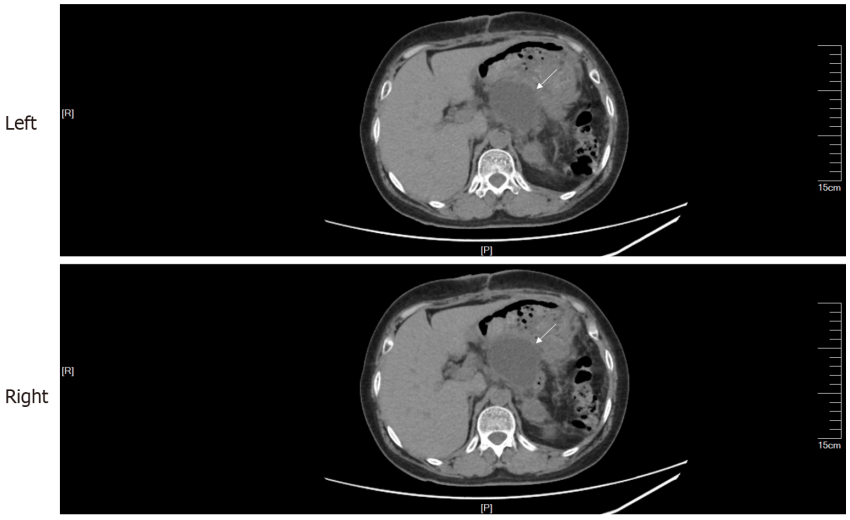

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Figure 7 Encapsulated effusion (arrow) in the surgical area.

pancreas and spleen. The boundary between the mass and pancreas and spleen was poorly defined. These findings indicated that the tumor might have originated from the spleen or pancreas. Contrast-enhanced CT revealed that the mass was unevenly and gradually enhanced. This indicated the possibility of a malignant tumor. However, ^{99m}Tc-MIBI SPECT/CT showed the presence of a focal radioactive concentration, with mild radioactive concentration extending into the upper abdominal mass at the pancreatic body and tail. This finding strongly suggested that the upper abdominal mass originated from the pancreas. The CT manifestations of the pancreatic tissue corresponding to the focal radioactive concentration were solid and homogenous. A previous study reported that pancreatic NETs tended to appear as solid and homogenous lesions on CT imaging[7]. In our case study, the ^{99m}Tc-MIBI SPECT/CT manifestations were consistent with the final pathological diagnosis of pancreatic NET.

CONCLUSION

^{99m}Tc-MIBI SPECT/CT appears to be valuable for diagnosing pancreatic NETs. However, subsequent large-sample studies are needed to confirm this finding.

FOOTNOTES

Author contributions: Liu CJ and Yang HJ conceived the idea; Liu CJ designed the research; Liu CJ, Yang HJ, Peng YC, and Huang DY analyzed the data and wrote the manuscript; all authors have read and agreed to the published version of the manuscript.

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CASE REPORT

Furazolidone-induced pulmonary toxicity in *Helicobacter pylori* infection: Two case reports

Yao Ye, Zi-Ling Shi, Zhuo-Chao Ren, Yi-Lan Sun

Specialty type: Medicine, research and experimental

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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Grade C (Good): C, C, C
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Abstract

BACKGROUND

Helicobacter pylori (*H. pylori*) infection is a global problem, causing significant morbidity and mortality. Furazolidone is recommended to eradicate *H. pylori* infections in China owing to the highly associated antibiotic resistance.

CASE SUMMARY

This article presents two cases of lung injury caused by furazolidone treatment of *H. pylori* infection and the relevant literature review. Two patients developed symptoms, including fever, cough, and fatigue after receiving a course of furazolidone for *H. pylori* infection. Chest computed tomography showed bilateral interstitial infiltrates. Laboratory studies revealed elevated blood eosinophil count. After discontinuing furazolidone with or without the use of corticosteroids, the symptoms improved rapidly. A PubMed database literature search revealed three reported cases of lung injury suggestive of furazolidone-induced pulmonary toxicity.

CONCLUSION

Clinicians should be aware of the side effects associated with the administration of furazolidone to eradicate *H. pylori* infection.

Key Words: Furazolidone; *Helicobacter pylori* infection; Pulmonary hypersensitivity; Case report

Core Tip: Furazolidone should be used as a treatment option for *Helicobacter pylori* (*H. pylori*) eradication in China because of high antibiotic resistance. We present two cases of furazolidone-induced pulmonary hypersensitivity determined by the Naranjo Adverse Drug Reaction Probability Scale score. Clinicians should be aware of the adverse effects of furazolidone, especially as it is widely used in the treatment of *H. pylori* infection in China.

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INTRODUCTION

Helicobacter pylori (*H. pylori*) infection is highly prevalent worldwide and is the leading cause of gastritis, peptic ulcers, and gastric cancer[1]. *H. pylori* remains the most common human bacterial pathogen, infecting approximately half of the global population[2]. The overall *H. pylori* infection rate has declined gradually over the past 3–4 years owing to ongoing interventions, education, improved sanitation, and water quality. However, the incidence was high (46.7%) between 2006 and 2018[3]. The most commonly recommended therapy worldwide is a standard dose of proton-pump inhibitor (PPI)-based regimen consisting of a PPI, clarithromycin, amoxicillin, and/or metronidazole[4]. However, the eradication rate of standard therapy is less than 80%, with the increasing drug resistance of *H. pylori*[5]. Furazolidone, a conventional drug administered for decades in the developing countries to eradicate *H. pylori* infections, has low resistance rates[6]. The Fifth Chinese National Consensus Report recommended the administration of furazolidone as a treatment option for *H. pylori* eradication in China because of its high antibiotic resistance[7].

The side effects of furazolidone are mild and well-tolerated by most patients[8]. Common furazolidone side effects include gastrointestinal reactions[4], including nausea, vomiting, diarrhea, and allergic reactions characterized by fever and rash[9]. Pulmonary hypersensitivity induced by furazolidone administration for the treatment of *H. pylori* infection is uncommon and rarely reported. Therefore, furazolidone-induced pulmonary toxicity goes largely unrecognized, prolonging diagnosis and leading to irreversible pulmonary complications.

Here, we present two cases of furazolidone-induced pulmonary hypersensitivity determined using the Naranjo Adverse Drug Reaction Probability Scale score (score: 11). Furthermore, we review the literature to improve our understanding of the side effects of furazolidone.

CASE PRESENTATION

Chief complaints

Case 1: Progressive fatigue and cough lasting 1 wk.

Case 2: A 1d history of fever and a mild cough.

History of present illness

Case 1: A 38-year-old woman presented at our hospital complaining of progressive fatigue and cough lasting 1 wk. There was no history of pyrexia, weight loss, night sweats, chest tightness, dyspnea, or rash.

Case 2: A 36-year-old woman presented with a 1-d history of fever and a mild cough. She did not complain of weight loss, night sweats, chest tightness, dyspnea, or rash.

History of past illness

Case 1: Her medical history revealed that she underwent cesarean section in 2017. Chronic non-atrophic gastritis caused by *H. pylori* infection was diagnosed 6 mo before her presentation. Eighteen days prior, she was prescribed rabeprazole (10 mg), potassium bismuth citrate (600 mg), amoxicillin (1 g), and furazolidone (100 mg) twice daily for 2 wk, to treat the *H. pylori* infection.

Case 2: Twelve days before her presentation, she was diagnosed with *H. pylori* infection and treated with omeprazole (20 mg), potassium bismuth citrate (600 mg), amoxicillin (1 g), and furazolidone (100) mg twice daily.

Personal and family history

Case 1: Furthermore, the patient had never smoked and had no occupational exposure or a history of allergies.

Case 2: The patient had never smoked and denied alcohol consumption.

Physical examination

Case 1: Physical examination revealed the following vital signs: Temperature, 37 °C; heart rate, 95 beats/min; respiratory rate, 20 breaths/min; blood pressure, 112/86 mmHg; and oxygen saturation, 98% in room air. Pulmonary examination revealed bilateral coarse breath sounds. Other physical examinations, including cardiac examinations, were unremarkable.

Case 2: Her vital signs at the outpatient clinic were as follows: Temperature, 38.5 °C; respiratory rate, 18 breaths/min; heart rate, 80 beats/min; and blood pressure, 116/74 mmHg. Chest auscultation revealed bilateral coarse breath sounds, while the other general examination results were normal.

Laboratory examinations

Case 1: Routine blood tests revealed an elevated eosinophil ratio (10.9%; reference range, 0.4%–8%) and blood eosinophil count (0.55 × 10^9/L; reference range, 0.02–0.52 × 10^9/L). We observed a rapid erythrocyte sedimentation rate (44 mm/h; reference range, 0–26 mm/h) and elevated immunoglobulin E (966 IU/mL; reference range, 0–87 IU/mL). The electrolyte panel, renal function, hepatic function, thyroid function, glucose level, tumor markers, and antinuclear antibodies were normal.

Case 2: Although the white blood cell and neutrophil counts were within the normal ranges, the eosinophil ratio (9.8%) and C-reactive protein (11.2 mg/L; reference range, 0–10 mg/L) were elevated. The electrolyte panel, renal function, hepatic function, and cardiac workup results were normal.

Imaging examinations

Case 1: Computed tomography (CT) of the chest revealed bilateral interstitial infiltrates, mainly manifested as interlobular septal thickening and nodules (Figure 1A).

Case 2: Chest CT showed bilateral interstitial infiltrates, including patchy hyperdense foci, combined with thickening of the interlobular septa and nodules (Figure 2A).

FINAL DIAGNOSIS

The two patients were diagnosed with furazolidone-induced lung injury based on the findings.

TREATMENT

For case 1, the patient received a 6 d treatment with intravenous prednisone (40 mg/d). Then the intravenous administration of prednisone was replaced with oral administration, and the dose was gradually reduced over a week. For case 2, due to the adamant refusal of oral corticosteroids administration and hospitalization, only furazolidone was discontinued, and antipyretic treatment was administered.

OUTCOME AND FOLLOW-UP

For case 1, the fatigue and cough rapidly subsided. The eosinophil ratio was 0.3%, and chest CT showed significant absorption of bilateral interstitial infiltrates (Figure 1B). The patient did not show any similar symptoms during the follow-up period. For case 2, the symptoms improved rapidly, and chest CT after 1 mo revealed obvious absorption of bilateral interstitial infiltrates (Figure 2B).

DISCUSSION

H. pylori infection is a family-based, population-wide disease that causes significant morbidity and mortality as it causes peptic ulcers and gastric cancer. It poses a major health threat to the Chinese families and society through increasing the economic and medical burden of the country[3]. In 2020, a meta-analysis, including 670572 participants from 26 provinces of mainland China, reported that the overall prevalence was 63.8% between 1983 and 1994, 57.5% between 1995 and 2005, and 46.7% between

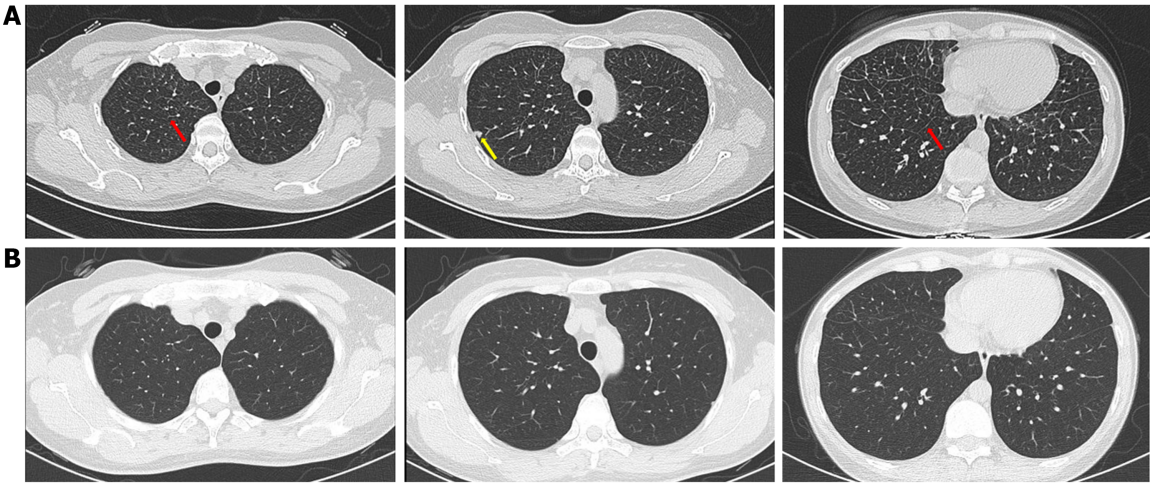

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Figure 1 Radiological changes of furazolidone-induced pulmonary toxicity in case 1. A: Bilateral interstitial infiltrates on chest computed tomography (CT) scan on admission. Red arrows indicate interlobular septal thickening. Yellow arrow indicate nodule; B: After treatment, the interstitial infiltrates on chest CT absorbed.

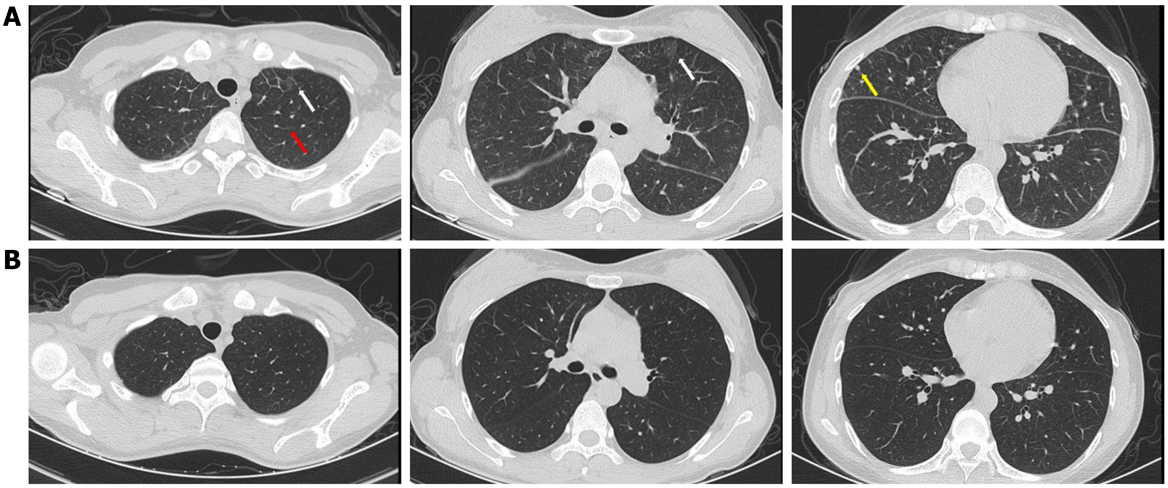

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Figure 2 Radiological changes of furazolidone-induced pulmonary toxicity in case 2. A: Bilateral interstitial infiltrates on chest computed tomography (CT) scan on admission. Red arrow indicate interlobular septal thickening. Yellow arrow indicate nodule. White arrows indicate patchy hyperdense foci; B: After treatment, the interstitial infiltrates on chest CT were absorbed.

2006 and 2018[10]. The infection rates vary greatly among different geographical regions and are much higher in the rural areas[10]. The discovery that *H. pylori* causes most duodenal ulcers and approximately two-thirds of gastric ulcers is seminal. Furthermore, *H. pylori* has been estimated to increase lifetime risk of gastric cancer by 1.5%–2.0%[11]. Previous studies reported that *H. pylori* eradication for gastric cancer prevention is cost-effective in China[12].

Optimal clinical management and treatment approaches are unknown and evolve in response to the changing antimicrobial resistance patterns[11]. In many parts of the world, triple therapy with PPI, clarithromycin, amoxicillin, or bismuth-based quadruple therapy with PPI, bismuth, tetracycline, and metronidazole, is the most commonly administered first-line treatment regimen[4]. In China, the rate of *H. pylori* resistance to antibiotics, including clarithromycin, metronidazole, and levofloxacin, is increasing[7]. Recent studies reported that the resistance rates to clarithromycin, metronidazole, and levofloxacin were 20%–50%, 40%–70%, and 20%–50%, respectively[13]. Furthermore, *H. pylori* can be resistant to multiple antibiotics[13]. Previous studies reported that the dual resistance of *H. pylori* to clarithromycin and metronidazole is approximately 25%[14]. Therefore, implementing these regimens in China may result in significantly lower eradication rates.

Furazolidone is a synthetic nitrofuran monoamine oxidase inhibitor with broad-spectrum antimicrobial activity[15]. However, its therapeutic effect on *H. pylori* infection cannot be ignored. Currently, the resistance rates of *H. pylori* to furazolidone are low (0%–1%)[13]. Because it rarely produces resistance, it can be readministered after a treatment failure. Therefore, some national and regional

Table 1 Summary of furazolidone-induced pulmonary hypersensitivity (literature review)

Ref.	Furazolidone administration time and dosage	Purpose of using furazolidone	Symptoms	Physical examination	Laboratory studies	Image test	Treatment
Cortez and Pankey[18], 1972	A 4 d course, 100 mg twice daily	To prevent diarrhea	Fever, dyspnea, headache, and pleuritic chest pain	Dry, crackling rales	Eosinophils elevated	Diffuse, bilateral Infiltrates (X-ray)	15 mg of prednisone orally followed by 40 mg daily
Collins and Thomas [19], 1973	A 5 d course, dose not mentioned	To treat a gastrointestinal infection	Fever, rigors, generalized rash, breathless on slight exertion, and night sweats	No abnormal physical signs	Eosinophils and ESR elevated	Diffuse mottling (X-ray)	not mentioned
Kowalski *et al*[20], 2005	A 10 d course, 125 mg 4 times daily	To treat Isospora Belli infection	Fever, dyspnea, and nonproductive cough	Bibasilar crackles	Eosinophil ratio elevated	Bilateral interstitial infiltrates (X-ray)	Prednisone 40 mg/day

ESR: Erythrocyte sedimentation rate.

guidelines for *H. pylori* infection recommend furazolidone as a component of rescue therapy[11]. However, furazolidone has been administered in a few high-quality eradication studies, and there is a lack in randomized trials. Additionally, concerns about its safety and use have resulted in its unavailability in the United States and European Union[4]. However, due to antibiotic resistance, it is recommended as empirical first-line therapy for *H. pylori* infection in China[7]. With the increasing use of furazolidone in China, its related side effects should be fully recognized and monitored.

The most common side effects of furazolidone are gastrointestinal reactions, including nausea and abdominal pain[4,15]. Furazolidone-related allergic reactions are clinically common and are characterized by fever (1.8%) and rash (0.3%)[10]. One study reported that rash and fever were the most frequent clinical findings in antibiotic-induced drug reactions, with eosinophilia and systemic symptoms[16]. Pulmonary hypersensitivity is uncommon; however, it often leads to fatal damage[16]. Drug-induced pulmonary hypersensitivity and interstitial lung disease may mediated by T cells; however, they are primarily affected by antibody-mediated factor functions (I–III)[17].

Following furazolidone treatment for *H. pylori* infection, the patients reported in this case report developed pulmonary hypersensitivity. The Naranjo probability score indicated that the adverse events could be drug-related. Using the search algorithm "furazolidone" and "pulmonary" or "lung", we searched the PubMed database (as of May 2022). Three cases of pulmonary hypersensitivity were attributed to furazolidone; however, these included other bacterial infections. In all the reported patients, symptoms developed during or immediately after furazolidone administration, with prominent pyrexia and dyspnea (Table 1)[18-20]. Chest radiograph revealed bilateral interstitial infiltrates with subsequent eosinophilia.

Our cases were similar to the three previously reported cases of furazolidone pulmonary hypersensitivity, with minor differences. Both patients developed symptoms during their furazolidone treatment. The three previously reported cases had severe symptoms, including significant pyrexia, dyspnea, and bibasilar crackles. The symptoms and physical signs in our cases were milder than those of the previous studies as there was no dyspnea or obvious crackles. This could be attributed to racial differences with respect to drug susceptibility or factors related to medication dosage and duration. However, the eosinophil levels were elevated during the early disease stages. Lung imaging revealed bilateral interstitial infiltrates. However, since only the radiographs of the patients have been shown in the past, the specific imaging findings of the chest CT are unknown. Both cases in our report showed interlobular septal thickening and nodules on the chest CT. Furthermore, the symptoms improved rapidly and significantly without recurrence after discontinuing furazolidone and the concurrent steroid administration.

CONCLUSION

This report highlights two rare cases of pulmonary hypersensitivity caused by furazolidone during treatment of *H. pylori* infection. Clinicians should be aware of the side effects of furazolidone, especially because it is widely used in China to treat *H. pylori* infection. The possibility of furazolidone-induced pulmonary hypersensitivity can be recognized based on the medical history, elevated eosinophil levels, and pulmonary interstitial infiltrates. Appropriate and timely treatment is required to prevent drug-induced damage.

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FOOTNOTES

Author contributions: Ye Y, Shi ZL, Ren ZC, and Sun YL conceptualized and designed the study, collected and analyzed data, they have read and approved the final manuscript; Ye Y and Shi ZL contributed to writing-original draft preparation; Ye Y, Ren ZC and Sun YL contributed to writing-review and editing, treatment of the patient; Sun YL contributed to supervision.

Informed consent statement: Written informed consent was obtained from the patients for the publication of this case report.

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

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CASE REPORT

Efficacy of anlotinib combined with radioiodine to treat scalp metastasis of papillary thyroid cancer: A case report and review of literature

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Abstract

BACKGROUND

Papillary thyroid cancer (PTC) is one of the well-differentiated thyroid tumors. Cutaneous metastasis from differentiated thyroid cancers occurs in < 1% of primary thyroid carcinomas but produces the worst survival prognosis. The multi-targeting tyrosine kinase inhibitor anlotinib has been approved to treat refractory advanced non-small-cell lung cancer as well as advanced soft-tissue and clear cell sarcomas in China.

CASE SUMMARY

In a patient with scalp metastasis caused by PTC, thyroid and skull metastasis tumor sizes were significantly reduced after a trial of neoadjuvant anlotinib therapy for 3 cycles. Anlotinib maintenance medication after thyroidectomy further reduced the metastatic skull tumor size thereby preventing the requirement for craniotomy.

CONCLUSION

The outcome of the present trial confirmed the potential of anlotinib therapy to treat scalp metastasis induced by PTC and point the way for the treatment of similar diseases in the future.

Key Words: Papillary thyroid cancer; Tyrosine kinase inhibitor; Neoadjuvant anlotinib therapy; Literature review; Case report

Core Tip: Cutaneous metastasis to the scalp is a site in patients which occurs after papillary thyroid cancers (PTC). Tyrosine kinase inhibitors represent a new approach to treat certain types of thyroid cancer. Here we report a case of scalp metastasis caused by PTC, in which neoadjuvant therapy of anlotinib before thyroidectomy was beneficial in reducing the thyroid and skull metastasis tumor sizes. Anlotinib maintenance regimen after thyroidectomy reduced the size of the metastatic skull tumor further, which successfully avoided the need for craniotomy.

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INTRODUCTION

Papillary thyroid cancer (PTC) and follicular thyroid cancer (FTC) are the two most common differentiated thyroid tumors (DTC)[1,2], with lymph nodes metastasis occurring frequently, but cutaneous metastasis to the scalp being a rare site. The average survival time for patients with thyroid carcinoma skin metastasis was about 19 mo from the end of the last century[1]. Most patients with thyroid cancer undergo surgery combined with subsequent radioactive iodine (RAI) therapy to clear any remaining tumor tissue and to prevent thyroid cancer recurrence[3]. RAI therapy is also given for more advanced cancers and/or cancers that have spread to lymph nodes or distant areas[4]. Apart from these regular treatment regimens, novel target therapies including a tyrosine kinase inhibitor (TKI) has become a new approach to treat certain types of thyroid cancer.

For example, sorafenib was approved by the United States Food and Drug Administration (FDA) in 2014 for the treatment of radioiodine-resistant DTC with metastasis[5]. Anlotinib is a new TKI that targets the vascular endothelial growth factor, fibroblast growth factor and platelet-derived growth factor receptors as well as c-kit[6]. Anlotinib was approved as third-line therapy for refractory advanced non-small-cell lung cancer in 2018, and as second-line treatment for advanced soft-tissue and clear cell sarcomas in 2019 in China[7]. In a preclinical study, anlotinib inhibited the cell viability of PTC, suppressed migration of thyroid cancer cells *in vitro* and also xenograft thyroid tumor growth in mice [8]. In a phase 2b study of medullary thyroid cancer patients treated with anlotinib, the median progression free survival (PFS) was found to be significantly prolonged (20.7 *vs* 11.1 mo)[9]. Another recent case of a patient with recurrent and metastatic radioactive iodine-refractory DTC (RAIR-DTC) treated with anlotinib showed a partial response after 2 cycles of anlotinib treatment and a PFS of 37 mo [10].

CASE PRESENTATION

Chief complaints

A 72-year-old woman presented to our hospital with a scalp mass on November 3, 2020.

History of present illness

A scalp mass biopsy puncture indicated that thyroid cancer metastasis.

History of past illness

The patient had no previous history of any illnesses.

Personal and family history

The patient had no previous personal and family history.

Physical examination

On December 4, 2020, a 3.0 cm × 3.0 cm nodule was palpable on the left thyroid and a 4.0 cm × 3.0 cm nodule was palpable on the right thyroid. In addition, a 6.5 cm × 5.0 cm mass was palpable in the left temporoparietal junction region.

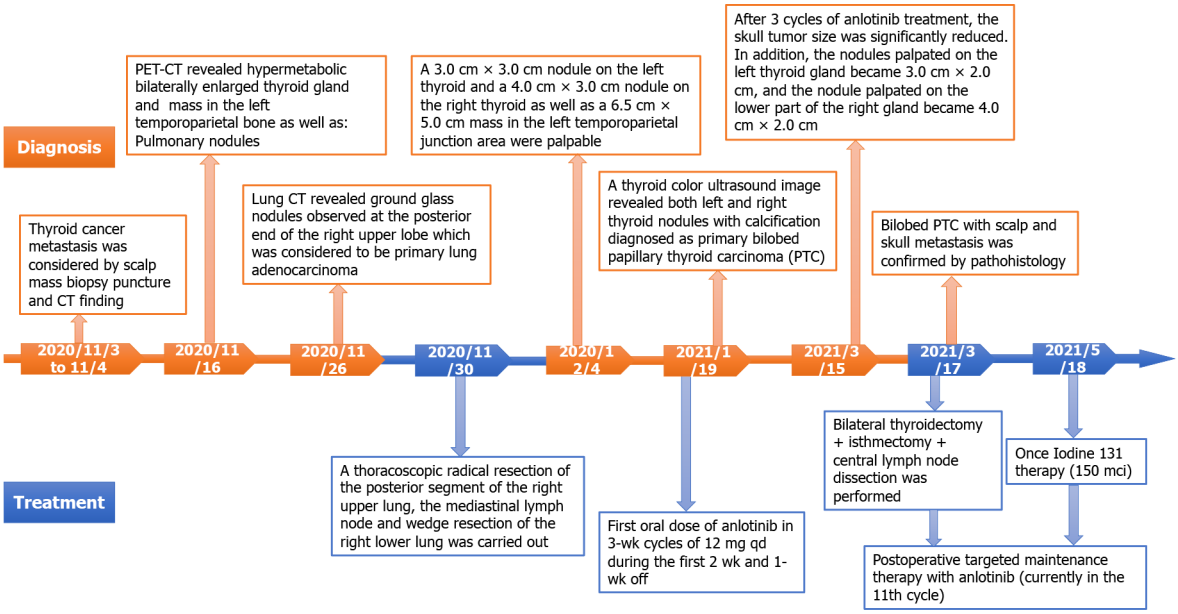

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Figure 1 A scheme of the diagnoses and treatments in chronological order. PTC: Papillary thyroid cancer; PET-CT: Positron emission tomography-computed tomography.

Laboratory examinations

Immunohistochemical results: TTF-1 (+), CK7 (+), NapsinA (+), CDX-2 (-).

Imaging examinations

A scheme of the diagnoses and treatments in chronological order is provided in Figure 1. On November 16, 2020, a positron emission tomography-computed tomography (PET-CT) imaging diagnosis was conducted in which a hypermetabolic mass was revealed in the left parietal skull bone, indicating skin metastasis (Figure 2A), which was confirmed by a fine-needle aspiration biopsy diagnosis (Figure 2B). In addition, a bilaterally enlarged thyroid gland with increased metabolism was found (Figure 2C).

Lung CT was performed on November 26, 2020, which revealed ground glass nodules at the posterior end of the right upper lung lobe and in the dorsal portion of the right lower lung lobe. The ground glass nodules observed at the posterior end of the right upper lobe may correlate with the possibility of primary lung adenocarcinoma and oblique fissure. Both lungs exhibited scattered ground glass patches, likely due to chronic inflammation.

On January 19, 2021, A thyroid color ultrasound image revealed a left thyroid nodule with calcification (Chinese TI-RADS category 4) and a right thyroid nodule with calcification (Chinese TI-RADS category 3c)[11] (Figure 3).

FINAL DIAGNOSIS

According to the findings, bilobed PTC with scalp and skull metastasis was diagnosed based on histopathology data and PET-CT imaging. Next-generation sequencing (NGS) by an Illumina Novaseq 6000 system (Illumina, San Diego, CA, United States) revealed mutations in the BRAF, KRAS and IGF1R genes of the PTC. In addition, neck metastasis of the PTC and primary lung cancer were provisionally diagnosed.

TREATMENT

On November 30, 2020, a thoracoscopic radical resection of the right upper lung cancer (resection of the posterior segment of the right upper lung + mediastinal lymph node sampling) plus wedge resection of the right lower lung were carried out. The operation went without complications and the postoperative recovery of the patient was good.

On January 19, 2021, the patient was given the first oral dose of anlotinib in 3-wk cycles of 12 mg qd during the first 2 wk and 1-wk off (Figure 3B). After 3 cycles of anlotinib treatment, the skull tumor size was significantly reduced. The nodule palpated on the left thyroid gland became 3.0 cm × 2.0 cm, and

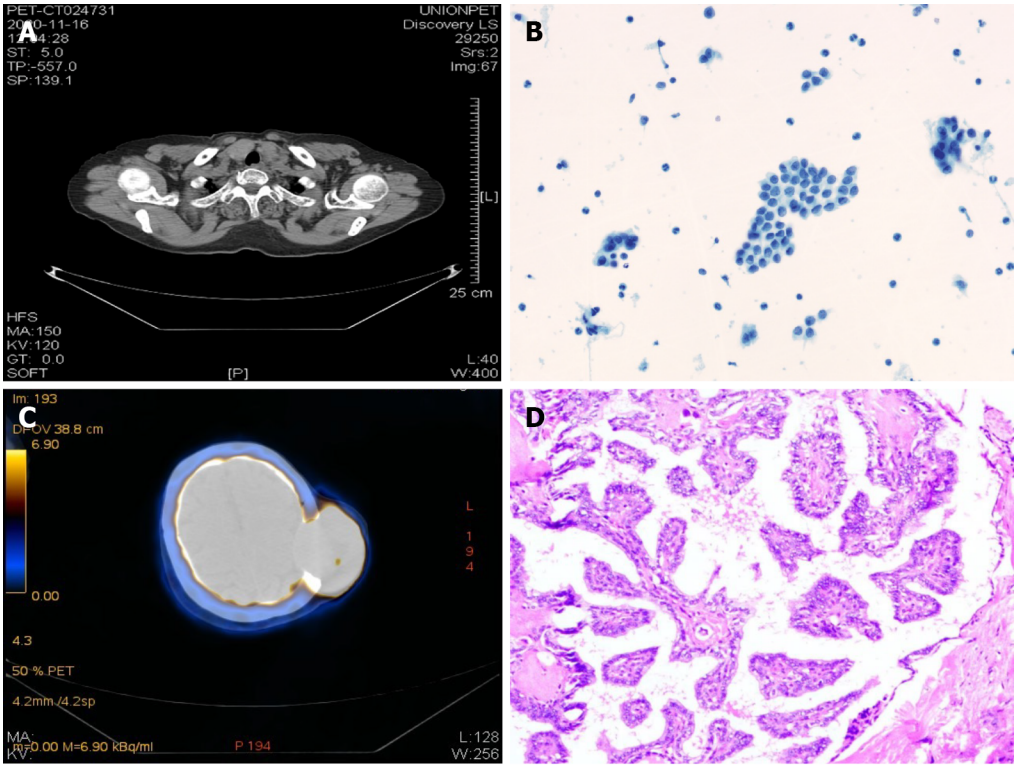

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Figure 2 Histological and computed tomography images of the skull tumor. A: positron emission tomography-computed tomography (PET-CT) imaging of the thyroid performed on initial diagnosis of the patient (November 16, 2020); B: Pathology of scalp mass biopsy (November 3, 2020). Scalp tumor histology similar to papillary thyroid carcinoma; papillary thyroid carcinoma metastasis was considered; C: PET-CT imaging of scalp metastasis (November 16, 2020). Note the hypermetabolic mass in the left temporoparietal bone, thinning of the corresponding temporoparietal bone due to compression, and local disappearance of the cerebral sulcus on the left side; D: Postoperative thyroid nodule pathology (paraffin) (March 18, 2021). Papillary thyroid carcinoma, classical type, interstitial fibrosis, no nerve infiltration or blood vessel invasion were observed. The tumor involved extra-glandular fibrofatty tissue.

the nodule palpated on the lower part of the right gland became 4.0 cm × 2.0 cm. In addition, preoperative color ultrasonography also showed that the thyroid tumor size was significantly reduced after neoadjuvant anlotinib therapy (Figure 3E).

A thyroidectomy was performed on March 17, 2021 with the left thyroid lobule and isthmus and the right thyroid lobule and lymph nodes in the central region successfully removed. The histopathology confirmed PTC (Figure 2D). Targeted maintenance therapy of anlotinib was administered after the operation in order to avoid craniotomy (Figure 3C).

OUTCOME AND FOLLOW-UP

By postoperative day 2 (March 18 2021), the neck incision had healed and the patient recovered well. The intact parathyroid hormone concentration was 1.10 pmol/L and the electrolytic calcium concentration was 2.21 mmol/L.

Once iodine-131 therapy (dosage: 150 mci) was performed after the operation on May 18, 2021 and continued in combination with anlotinib (currently in the 11th cycle), a regimen which successfully avoided the need for craniotomy.

DISCUSSION

The 4 main subtypes of thyroid carcinoma are papillary, follicular, medullary and anaplastic forms[12], with PTC being the most frequently occurring followed by FTC[13,14]. In this case report, the potential of anlotinib therapy to treat scalp metastasis induced by PTC was demonstrated. Scalp metastasis of thyroid cancer has been also been described in other case reports[15-22] (Table 1). Most of the patients were females of advanced age with FTC and in the majority of the cases the scull metastasis had been diagnosed before thyroid cancer, as in the present case. Only 2 patients received post-operative TKI medication and the lung was the major organ of cancer lesions, which were supposed to be metastatic (Table 1). TKIs are small molecules which inhibit the activity of tyrosine kinases (Figure 4).

Table 1 List of case reports about scalp metastasis of thyroid cancer published during the last decade

Gender	Age	Type	Time of diagnosis	Metastasis	Treatment	Ref.
Female	51	Follicular	Before thyroid cancer	Lung, bone	Surgery, I-131	[15]
Female	64	Papillary	After medical history of total thyroidectomy	Lung, liver	Excisional biopsy I-131	[16]
Female	37	Follicular	Before thyroid cancer	Lung, bone, cranium	Resection, I-131, post-operative TKI	[17]
Female	60	Follicular	Before thyroid cancer	No	Surgery	[18]
Female	70	Follicular	Before thyroid cancer	Lung	Surgery, I-131	[19]
Female	75	Follicular	1 year after thyroidectomy	Lung	Surgery, I-131	[20]
Male	65	Papillary	Before thyroid cancer	Vertebral and iliac lesions	Shave biopsy, I-131, post-operative sorafenib	[21]
Female	49	Follicular	4 years after thyroidectomy	No	Surgery, I-131	[22]

TKI: Tyrosine kinase inhibitor.

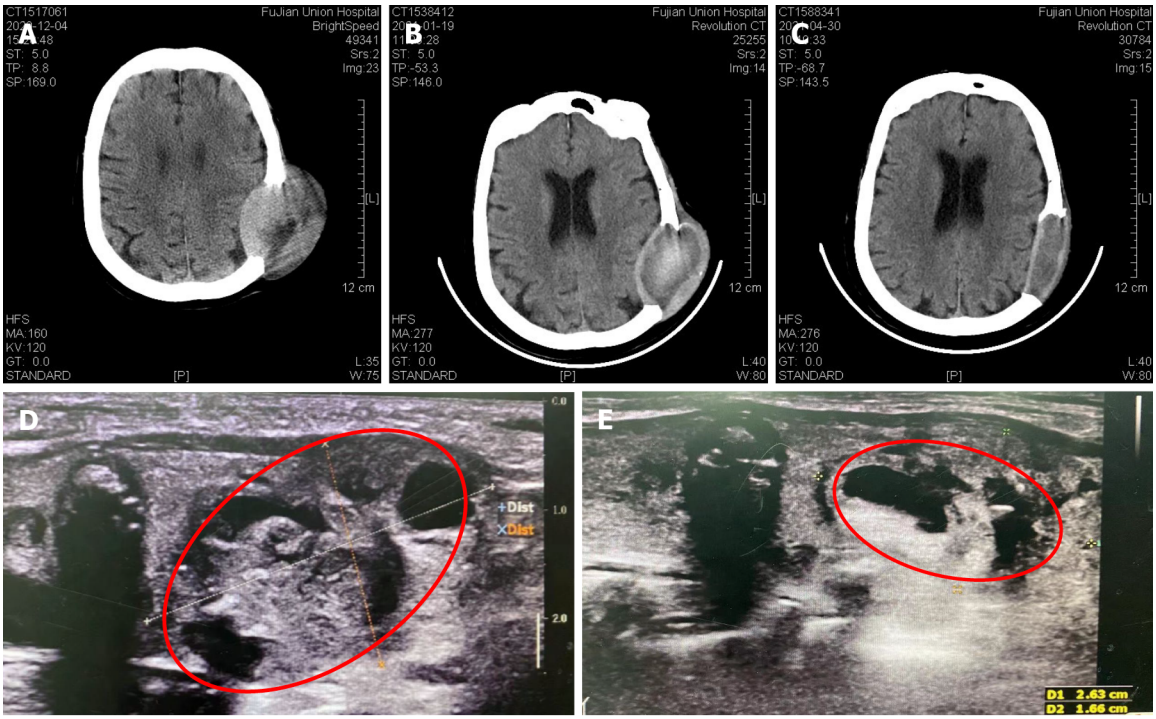

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Figure 3 Computed tomography image and color ultrasound of the skull throughout the treatment course and of the thyroid gland. A-C: Computed tomography images at admission (November 4, 2020; A), at the start of anlotinib treatment (January 19, 2021; B), and during maintenance medication (April 30, 2021; C); D: Color ultrasound images of a thyroid nodule with calcification (January 19, 2021); E: Preoperative color ultrasonography showed that the thyroid tumor size was significantly reduced after neoadjuvant anlotinib therapy (March 15, 2021).

TKI therapy is usually the final option for metastatic lesions, which are normally incurable by surgery and/or RAI therapy combined, but encouragingly a study involving 147 patients demonstrated that TKI treatment improved the prognosis of patients with distant metastasis and progressive disease[23]. A number of TKIs have been approved by the FDA to treat thyroid cancer, including vandetanib, cabozantinib, sorafenib and lenvatinib (Table 2). Vandetanib and cabozantinib were the first and second approved drugs for the therapy of advanced and progressive and/or symptomatic medullary thyroid cancer[24,25]. Sorafenib was approved for the treatment of ^{131}I-refractory DTC after the findings of the phase 3 DECISION clinical trial[26]. Lenvatinib is an anti-angiogenic TKI that has been approved for the treatment of advanced and progressive ^{131}I- refractory DTC[27]. A real-world study conducted in the United States demonstrated that treatment with first-line lenvatinib followed by subsequent second-line therapy delivered a clear clinical benefit[28]. A study carried out in Korea mainly focused on the adverse events of TKIs (lenvatinib and sorafenib) elicited in patients with DTC. Seventy-one cases (lenvatinib, n = 23; sorafenib, n = 48) were involved without new safety concerns being identified for either drug. Most AEs were managed with dose modification and medical therapy[29]. In former *in vitro*

Table 2 Tyrosine kinase inhibitors for treatments of thyroid cancer

Medication	Target	Indication	Ref.
Vandetanib	RET-tyrosine kinase, VEGFR and EGFR	Unresectable locally advanced or metastatic thyroid cancer	[24]
Cabozantinib	c-Met- tyrosine kinase, VEGFR 2, RET-tyrosine kinase, AXL	RAIR locally advanced or metastatic thyroid cancer after VEGFR-targeted therapy	[25]
Sorafenib	VEGFR 1-3, PDGFR and RAF and RET-kinases	Metastatic RAIR thyroid cancer	[26]
Lenvatinib	VEGFRs 1-3, FGFRs 1- 4, PDGFR-α, RET and KIT signaling	RAIR thyroid cancer	[27]

AXL: Tyrosine-protein kinase receptor UFO; FGFR: Fibroblast growth factor receptor; PDGFR: Platelet-derived growth factor receptor; RAIR: Radioactive iodine-refractory; VEGFR: Vascular endothelial growth factor receptor.

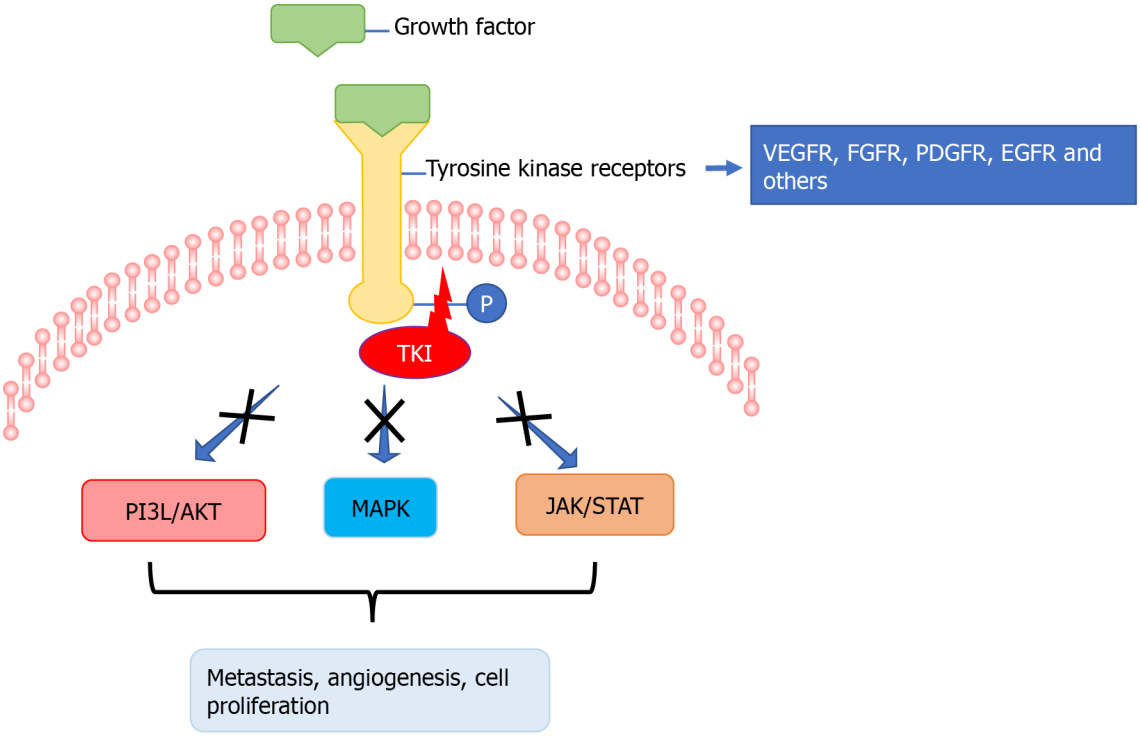

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Figure 4 Scheme of tyrosine kinase inhibitor activity. In order to activate signal transduction cascades, tyrosine kinase receptors must be phosphorylated by a tyrosine kinase in addition to binding with their specific ligands. Tyrosine kinase inhibitors block the activity of tyrosine kinases *via* different mechanisms. TKI: Tyrosine kinase inhibitor; P: Phosphate; PI3L/Akt: Phosphatidylinositol-3-kinase/Akt; MAPK: Mitogen-activated protein kinase; JAK/STAT: Janus kinase/signal transducer and activator of transcription.

experiments, anlotinib reduced the viability of PTC and anaplastic thyroid cancer cell lines, most likely due to aberrant spindle assembly, G2/M arrest and TP53 activation, while in a murine model anlotinib suppressed migration and growth of thyroid tumor xenografts[8]. Recently, a phase 2 trial of anlotinib in Chinese patients with radioiodine-refractory DTC showed promising results with a median PFS of 40.54 mo in the treatment group compared to 8.38 mo in the placebo group at a data cutoff date of January 2020[30].

Nevertheless, the present case report can be considered as a kind of pilot study. Besides conservative treatments, anlotinib has been used as neoadjuvant therapy, which significantly reduced the sizes of a metastatic skull tumor and of the primary PTC, while in combination with anlotinib maintenance medication a craniotomy was avoided.

NGS analysis of the PTC found mutations in the *BRAF*, *KRAS* and *IGF1R* genes, which did not match with the previously described undeferential thyroid cancer specific mutations of the *TERT* promoter, *RET* fusion and *TP53*[31]. On the other hand, *BRAF* mutations have been found to be key drivers of DTC, leading to the proposal of BRAF-directed therapies[32]. In line with the findings of the present study, a recent case report found that anlotinib was effective for the treatment of a RAIR-DTC patient with *TERT* promoter and *BRAF* mutations[10]. Another case report of a RAIR-DTC PTC patient with a $BRAF^{V600E}$ mutation noted that the patient developed tumor progression, with clinical symptoms that

worsened after dabrafenib-trametinib withdrawal[33]. In our case we will continue to monitor the outcome of anlotinib maintenance therapy.

A limitation of the present study was the lack of NGS and histopathology data about the lung lesions and the neck lymph nodes, which had been provisionally diagnosed as primary lung cancer and PTC metastasis into the neck.

CONCLUSION

Neoadjuvant therapy of anlotinib before surgery was beneficial in reducing the thyroid tumor volume, but also that of the metastatic skull tumor. A craniotomy was thus avoided by using anlotinib maintenance therapy. Our findings point the way for the treatment of similar diseases in the future.

FOOTNOTES

Author contributions: Zhang LY and Zhao WX contributed to the study design; Liang BY and Yan SY contributed to the data collection; Cai SJ, Wang B and Li MY contributed to the data analysis and interpretation; Zhang LY, Cai SJ and Yan SY wrote the draft; Wang B, Li MY and Zhao WX contributed to the revising/editing draft; all authors read and approved the final manuscript.

Informed consent statement: Informed written consent was obtained from the patient for publication of this report and any accompanying images.

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CASE REPORT

Endoscopic ultrasound-guided transrectal drainage of a pelvic abscess after Hinchey II sigmoid colon diverticulitis: A case report

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Abstract

BACKGROUND

Acute diverticulitis is one of the most prevalent complications of diverticular disease and may result in abscess formation, perforation, fistula formation, obstruction, or bleeding. Diverticular abscesses may be initially treated with antibiotics and/or percutaneous drainage and/or surgery. Endoscopic ultrasound (EUS)-guided drainage techniques are increasingly used as a minimally invasive alternative to percutaneous or surgical approaches, as they are associated with better treatment outcomes, shorter recovery time and duration of hospitalization.

CASE SUMMARY

A 57-year-old female presented to the emergency department on account of abdominal pain and fever. Clinical examination revealed tenderness in the left lower abdominal quadrant, with elevated inflammatory markers in laboratory tests. Abdominal computed tomography (CT) revealed an 8 cm × 8 cm × 5 cm well-encapsulated abscess of the sigmoid colon, surrounded by numerous diverticula. A diagnosis of Hinchey II diverticular abscess was made, and the patient was admitted and commenced on appropriate antibiotic treatment. A transrectal EUS showed a fluid collection in direct contact with the sigmoid colon. Transluminal drainage was performed, and a lumen-apposing metal stent was inserted into the abscess collection. A follow-up CT scan showed a regression of the collection. The patient's general condition improved, and the stent was removed during a follow-up transrectal EUS that revealed no visible collection.

CONCLUSION

We report the first successful management of a pelvic abscess in patient with

Hinchey II acute diverticulitis using EUS-guided transluminal drainage in Slovenia. The technique appears effective for well-encapsulated intra-abdominal abscesses larger than 4 cm in direct contact with the intestinal wall of left colon.

Key Words: Acute diverticulitis; Diverticular disease; Pelvic abscess; Endoscopic drainage; Case report

Core Tip: The incidence of colonic diverticulosis and its complications is rising in developed countries. An abscess due to acute diverticulitis may be initially treated with antibiotics and/or percutaneous drainage and/or surgery. Since percutaneous drainage of an abscess is not always feasible, endoscopic ultrasound-guided transluminal drainage seems to be an effective minimally invasive alternative for well-encapsulated intra-abdominal abscesses lying in direct contact with the intestinal wall, which reduces the need for surgery and stoma formation in selected patients. However, given the limitations of the supporting evidence, the optimal treatment strategy should be determined on a case-by-case basis by a multidisciplinary team.

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INTRODUCTION

Diverticulosis of the colon is defined as the existence of false diverticula or outpouchings of the mucosa and serosa through openings in the muscular layer of the bowel known as *locus minoris resitentiae*. The condition is remarkably prevalent in Western countries, affecting a substantial proportion of the middle-aged and elderly populations. Inflammation of a colonic diverticulum, or acute diverticulitis, is one of the most prevalent complications of diverticular disease and represents an abdominal emergency[1]. The incidence of acute diverticulitis is rising, especially among individuals under the age of 50. This is likely attributable to factors such as a low-fibre diet, obesity, smoking, physical inactivity, and a diet high in red meat[2-4]. Approximately 5% of patients with known diverticula are estimated to develop an episode of acute diverticulitis[5].

Numerous classifications and modifications describe the various stages of diverticular disease. The first widely used classification by Hinchey was intended as an intra-operative stratification of perforated diverticulitis with abscess or peritonitis, enabling surgeons to adjust the surgical approach. The treatment of acute diverticulitis depends on whether the presentation is uncomplicated or complicated. Complicated presentation occurs in approximately 12% of patients. An intraabdominal abscess (Hinchey Ib or II) can be managed non-operatively, but an abscess larger than 4 cm in diameter must be drained[3,6,7].

In recent years, minimally invasive methods have replaced classical surgical techniques where possible. Drainage is usually performed percutaneously by an interventional radiologist. However, percutaneous drainage is not always feasible, and endoscopic ultrasound (EUS)-guided drainage represents a compelling alternative that eliminates the need for an invasive surgical approach.

In the present report, we describe the clinical presentation, management, and outcome of EUS-guided drainage of a pelvic abscess due to complicated Hinchey II acute sigmoid diverticulitis. The management approach is discussed in the context of available literature.

CASE PRESENTATION

Chief complaints

A 57-year-old otherwise healthy female was admitted to the abdominal emergency department on account of abdominal pain and a fever of up to 38 ˚C since the preceding five days.

History of past illness

A patient's history of past illness is unremarkable.

Personal and family history

A patient's personal and family history is unremarkable.

Physical examination

Clinical examination revealed localized tenderness in the left lower abdominal quadrant without clinical signs of diffuse peritonitis.

Laboratory examinations

Laboratory tests at admission showed elevated inflammatory markers with a C-reactive protein (CRP) value of 353 mg/L and a leucocyte count of 12.4 × 10^9/L.

Imaging examinations

An urgent abdominal computed tomography (CT) scan revealed a well-encapsulated pelvic abscess measuring 8 cm × 8 cm × 5 cm, located in the proximity of a very long sigmoid colon surrounded by numerous diverticula (Figure 1). There was only a small amount of free fluid in the lesser pelvis with no other pathological findings.

FINAL DIAGNOSIS

Pelvic abscess due to acute sigmoid diverticulitis (Hinchey II) without evidence of diffuse peritonitis.

TREATMENT

The patient was hospitalized at the department of abdominal surgery, and empirical antibiotic treatment with amoxicillin and clavulanic acid was commenced, in line with national guidelines for acute complicated diverticulitis. Additionally, in the first 48 h she was put on nil by mouth and received intravenous fluids and analgesics. Due to the size of the abscess and the elevated inflammatory markers despite antibiotic treatment, an interventional radiologist was consulted to perform percutaneous drainage. However, the collection was not safely approachable *via* the percutaneous route. After consulting a gastroenterologist, a decision was jointly made to attempt draining the collection transrectally under EUS guidance.

On the third day of admission, a transrectal EUS scan was performed, which showed an encapsulated fluid collection lying in direct contact with the wall of the sigmoid colon. Transluminal drainage of the collection was performed by placing a lumen-apposing metal stent (LAMS) into the collection (Figure 2). The procedure was completed without complications, and purulent content was observed leaking through the open stent. The patient's condition gradually improved over the first few days after the procedure; she started with enteral nutrition, abdominal pain diminished, and defecation was normal. The previously elevated inflammatory parameters also began to decline.

A follow-up abdominal CT scan showed an appropriate stent position and regression of the collection with only some residual gas at the site (Figure 3). As the patient was asymptomatic, the antibiotic treatment was switched from intravenous to enteral route by the 9th day after admission. She was temporarily discharged home with the prescribed antibiotic and care instructions.

The patient returned as scheduled on the 16th day after the primary admission and repeat laboratory studies showed complete normalization of inflammatory parameters (CRP 6 mg/L, leukocytes 6.6 × 10^9/L). She reported no complaints and was discharged from the hospital on the same day. The antibiotic treatment was also discontinued after 16 d of administration (9 d intravenously and 8 d enterally).

OUTCOME AND FOLLOW-UP

Thirty days after the stent insertion, an elective follow-up transrectal EUS was performed at the outpatient clinic. The endoscopic view demonstrated almost complete closure of the abscess cavity, surrounded by granulation tissue; accordingly, the LAMS was endoscopically removed during the same procedure (Figure 4). The procedure was uneventful, and at a subsequent follow-up clinical review, the patient remained well without any complaints. Three months after the LAMS removal, we additionally performed a colonoscopy and noted the disappearance of the fistular canal at the previous puncture site and no other remarkable findings.

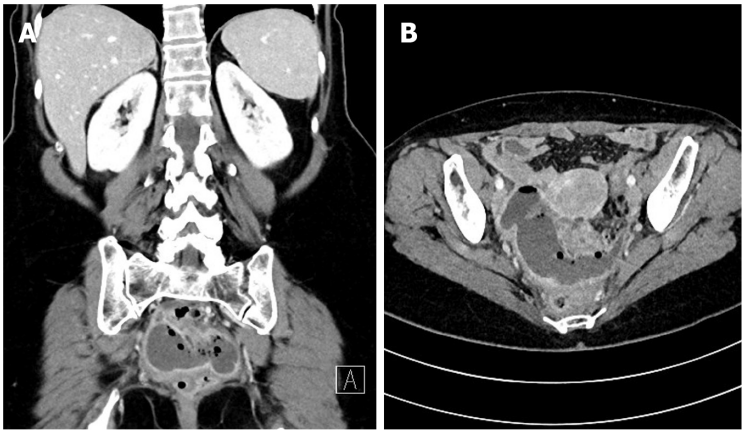

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Figure 1 Abdominal computed tomography scan in axial and coronal view. The well-encapsulated pelvic abscess measuring 8 cm × 8 cm × 5 cm is seen as a dense air-fluid collection in the proximity of the sigmoid colon. A: Axial view; B: Coronal view.

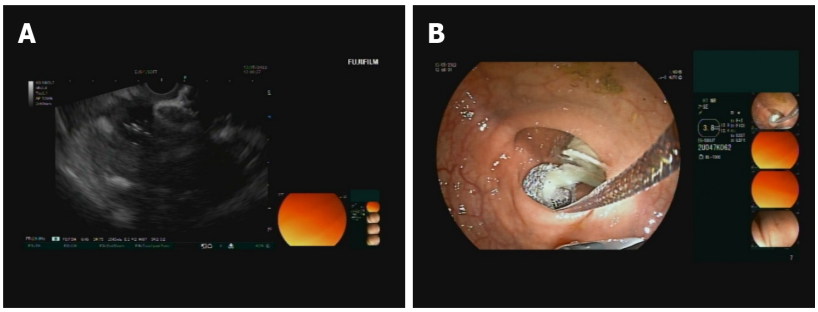

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Figure 2 Endoscopic ultrasound scan during lumen-apposing metal stent insertion. A: An Endoscopic ultrasound image of the inserted lumen-apposing metal stent (LAMS), connecting the bowel lumen and the abscess collection; B: An endoscopic view of in-situ LAMS, draining the pus from the abscess collection.

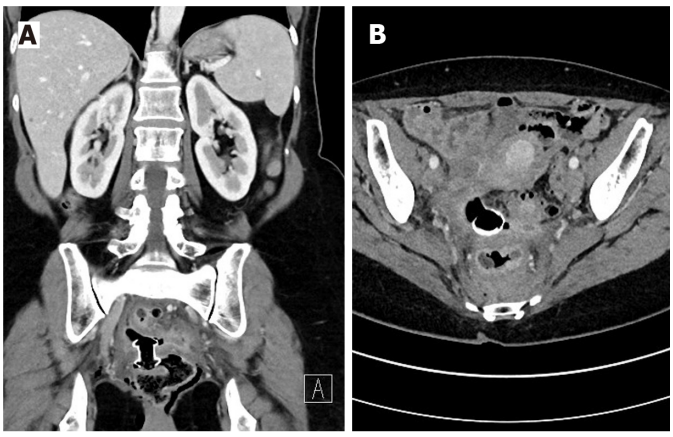

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Figure 3 Follow-up abdominal computed tomography scan in axial and coronal views. The lumen-apposing metal stent position is appropriate and lies transluminal in the sigmoid wall. Regression of the collection is seen with only some gas remaining at the site. A: Axial view; B: Coronal view.

DISCUSSION

We present a case of successful EUS-guided drainage of a pelvic abscess due to complicated Hinchey II acute sigmoid diverticulitis. Because the percutaneous route of abscess drainage was not safely accessible, the decision was made to use this alternative option after interdisciplinary consultations and discussions. The EUS-guided transrectal drainage with LAMS insertion was performed and, in

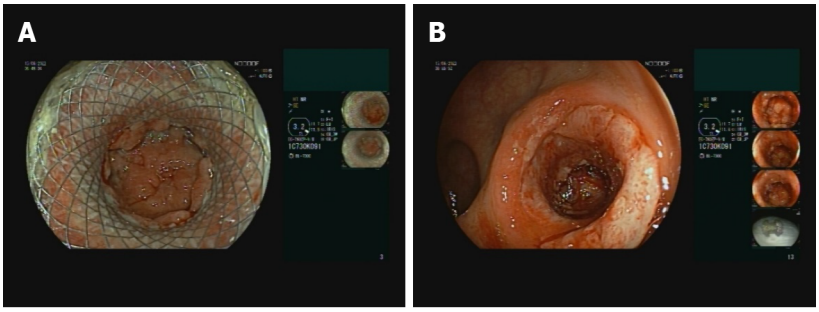

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Figure 4 The findings during the removal of the lumen-apposing metal stent. A: The lumen-apposing metal stent (LAMS) is seen in situ with regression of the abscess cavity; B: The remaining fistular canal is covered with granulation tissue after the removal of LAMS.

combination with antibiotic treatment, proved effective for managing the diverticular abscess. LAMS removal was performed 30 d after the insertion uneventfully.

There are several classification systems for describing acute diverticulitis, but the modified Hinchey classification, introduced in 1978 and revised by Wasvary *et al*[8] in 1999, remains the most commonly used in the international literature[8-12]. In general, the management of acute diverticulitis is well-established in the guidelines[6,7,12,13]. For the Hinchey stages 0 and Ia, antibiotic treatment is usually sufficient; stages Ib and II require additional drainage if an abscess is larger than 4 cm[6,7,13]. The drainage may be performed surgically, percutaneously or endoscopically[11,13].

However, the most appropriate drainage method for the patient may not always be accurately determined, and treatment choice must be individualized. The surgical treatment being the most invasive and associated with the highest morbidity and mortality, should be performed as a last resort and only when other methods fail. The most widely accepted clinical practice is to perform percutaneous drainage *via* transabdominal anterior or transgluteal posterior approach; however, percutaneous drainage is not always feasible[11-14]. Additionally, even though it is considered safe, the complication rate of percutaneous drainage is 2.5% (ranging from 0 to 12.5%), and possible complications include enterocutaneous fistulas, small bowel lesions, and sciatic nerve injuries[15].

Deep pelvic abscesses often present a clinical challenge, since they are surrounded by intra-abdominal organs and other structures, which may interfere with safe percutaneous drainage route. Over the past few decades, endoscopic drainage has emerged as a compelling and feasible option when percutaneous drainage cannot be performed safely, reducing the need for surgery and stoma formation in selected patients[11]. However, endoscopic drainage of diverticular abscess is not yet reflected in the major guidelines, and its supporting evidence is currently limited to only several retrospective case studies or case reports[6,12-17]. In contrast, the experience with endoscopic drainage of intraabdominal abscesses is rich. Besides acute diverticulitis, an intraabdominal abscess may also be associated with other inflammatory gastrointestinal or urogenital conditions or may occur as a complication after surgical procedures. Appropriate drainage is of vital importance for a successful treatment of an intra-abdominal abscess[18,19]. Extensive and positive experiences with LAMS in treating peripancreatic collections also open new possibilities for treating other types of fluid collections. Their characteristic shape prevents stent dislocation, and the diameter of the lumen allows efficient drainage and further endoscopic necrosectomy *via* an open stent. EUS-guided transluminal drainage might be a safer procedure in comparison to surgical or percutaneous drainage techniques as the risk of vessel injury and a puncture site leakage are neglectable. Interestingly, fecal contamination in the abscess cavity is unlikely as the intrinsic negative luminal pressure ensures adequate drainage. Thus, EUS-guided transluminal drainage is a suitable drainage method of all pelvic abscesses, regardless of their etiology.

The crucial abscess characteristics for a safe EUS drainage are size larger than 4 cm, a well-formed capsule and the position in close contact with the intestinal wall of the left colon[14,19]. As already noted, although percutaneous drainage is considered the method of choice in the existing guidelines, it is not always feasible. In the event of a failed or impractical percutaneous approach, an attempt at endoscopic drainage should be considered in any patient without evidence of sepsis before initiating surgical therapy. Meanwhile, more case reports or larger prospective studies are needed to evaluate and compare both drainage methods. Because EUS-guided drainage is not included in the guidelines, the exact role of endoscopic drainage in the treatment of diverticular abscesses remains unclear.

CONCLUSION

Since percutaneous drainage of diverticular abscess is not always feasible, EUS-guided transluminal drainage appears to be a promising and practical alternative for managing well-encapsulated intra-abdominal abscesses that lie in direct contact with the intestinal wall of left colon, reducing the need for

surgery and stoma formation. However, given the limited evidence, a careful interdisciplinary review of each clinical case by the abdominal surgeon, gastroenterologist, and interventional radiologist is required to determine the optimal treatment strategy.

FOOTNOTES

Author contributions: Drnovšek J and Janež J conceived and designed the study; Čebron Ž contributed to the collection, analysis and interpretation of data; Čebron Ž and Drnovšek J drafted the manuscript; Grosek J and Janež J contributed to the critical revision; all authors issued final approval for the version to be submitted.

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