

# Clinical characteristics and outcomes of acute pancreatitis following spinal surgery: a systematic review

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## Abstract

**Objective:** This study reviewed the current evidence on the clinical characteristics and outcome of acute pancreatitis (AP) following spinal surgery.

**Methods:** A systematic search was performed to identify English articles published through May 2020 in PubMed, Scopus, EMBASE, Latin American & Caribbean Health Sciences Literature, and Cochrane Library. Data on clinical characteristics, risk factors, and outcomes were analyzed.

**Results:** Eleven papers (including six case reports) were included, with 306 patients (incidence, 23.0%) developing AP after spinal surgery (mean age, 14.2 years). Of the studies that specified symptoms (55 patients), abdominal pain (43.6%), nausea and vomiting (32.7%), and abdominal distension (7.27%) were most prevalent. The mean duration from surgery to symptom onset was 6.15 days (range, 1–7). The most common complications of AP were glucose intolerance (25%), peritonitis (2%), pseudocyst formation (2%), and fluid collection (2%) were most prevalent. Prolonged fasting time (13.6%), intraoperative blood loss (9.09%), gastroesophageal reflux disease (9.1%), age > 14 years (9.1%), and low BMI (9.1%) were most commonly associated with AP. Two deaths (0.6%) were reported.

**Conclusion:** AP remains an important complication of spinal surgery because of its morbidity and mortality. Avoiding major risk factors can reduce the incidence of AP following spinal surgery.

## Keywords

Acute pancreatitis, spinal surgery, scoliosis, systematic review, postoperative complication, abdominal pain, nausea, vomiting, multiorgan failure

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## Introduction

Acute pancreatitis is a known postoperative complication of many abdominal and extra-abdominal surgeries.<sup>1-5</sup> Postoperative pancreatitis is associated with a higher risk of local and systemic complications as well as high morbidity and mortality rates.<sup>6</sup> The severity of pancreatitis ranges from mild to severe, with increasing mortality observed in patients with severe pancreatitis, necrotizing pancreatitis, and multiorgan failure.<sup>7</sup> In patients with postoperative pancreatitis, the mortality rate has been reported to be as high as 50%.<sup>1</sup> Although the incidence of postoperative pancreatitis is low, routinely monitoring with clinical and biochemical parameters can facilitate early diagnosis and treatment, especially among patients undergoing surgeries with a known high risk of pancreatitis.<sup>8</sup>

A diagnosis of acute pancreatitis is considered if a patient satisfies at least two of the following criteria: clinical features including abdominal pain, nausea, and vomiting; biochemical features including serum lipase levels three times above the upper limit of normal; and characteristic findings in imaging including computed tomography (CT) or magnetic resonance imaging (MRI).<sup>9</sup>

The pathogenesis of pancreatitis following spinal surgery is attributed to multiple factors such as splanchnic hypoperfusion caused by intraoperative hemodynamic instability,<sup>8,10</sup> mechanical compression caused by spinal correction mainly in individuals with lower body mass index (BMI), pancreatic ischemia caused by lower intraoperative mean arterial pressures,<sup>8,11</sup> and depressed trypsin inhibitor activity leading to reduced immunity to autodigestion postoperatively.<sup>2</sup> It has been observed that patients with neurofibromatosis type 1, Marfan syndrome, and cerebral palsy are at higher risk of developing acute pancreatitis following spinal surgery, although the

exact mechanism of the higher risk among these patients is poorly understood.<sup>8</sup>

The available literature on acute pancreatitis following spinal surgery is limited. Therefore, we conducted this systematic review to describe the clinical characteristics, risk factors, and outcomes of acute pancreatitis among patients undergoing spinal surgeries.

## Methods

A systematic review of all studies on pancreatitis following spinal surgeries, including prospective and retrospective cohort analysis and experimental studies, was performed. Because of the limited number of studies, we decided to include case reports in this review. Studies describing patients meeting at least two of the three criteria of acute pancreatitis after any spinal surgery were eligible. As a systematic review, ethics committee approval and patient consent were not required.

The primary objective was to describe the clinical characteristics, risk factors, and outcomes of acute pancreatitis following spinal surgeries. We also aimed to describe attempted treatment modalities and their outcomes when relevant. The methodology of this review followed the PRISMA recommendations.<sup>12</sup>

## Search strategy

All articles published before May 2020 were searched electronically using PubMed/Medline, Scopus, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), and Latin American & Caribbean Health Sciences Literature (LILACS) without any restrictions regarding language or the publication status. Keywords related to acute pancreatitis and its complications and various types of spinal surgeries were searched in the title and abstract fields. The detailed search

strategy is presented in the supplementary file (Annexure 1). Furthermore, the list of references of eligible articles was manually searched, and relevant articles were added to the review.

The initial eligibility screening was performed by two investigators using the titles, abstracts, and keywords of the citations. Thereafter, the full text of all relevant records was assessed according to the inclusion criteria. In cases of disagreement, a consensus was reached after input from the senior authors. All data pertaining to the clinical presentation, risk factors, investigations, treatment and outcomes were extracted, categorized, and tabulated. Finally, qualitative analysis was performed using the available data. A meta-analysis could not be performed because of the heterogeneity in the study methodology, treatment options, and description of outcomes. The risk of bias assessment of eligible studies was performed using the Downs and Black checklist, which is a valid and a reliable tool for assessing both randomized and non-randomized control studies (external validity, KR20 = 0.54; internal consistency, KR20 = 0.89),<sup>13</sup> and the findings are presented in Table S1.<sup>8,10,13–30</sup>

## Results

### *Overall summary and patient characteristics*

The search of PubMed/Medline, Scopus, EMBASE, CENTRAL, and LILACS resulted in 687 citations. After excluding duplicates, 620 were evaluated for eligibility. Of these, 598 papers were excluded after reviewing the titles and abstracts. The full texts of the 22 remaining papers were assessed for eligibility. Of these papers, 11 were excluded because the full text did not meet the inclusion criteria. Finally, 11 manuscripts, including six case reports and five cohort studies, were included in this

systematic review. No relevant unpublished studies were obtained. The included studies described a total of 1326 patients, of whom 306 patients (23%; mean age, 22.2 years; 68.3% female [n = 209]). Three studies included children with cerebral palsy, and eight studies included patients undergoing surgery for scoliosis (Supplementary File S1).

### *Clinical symptoms and signs*

Of the studies that specified symptoms (n = 55), abdominal pain (43.6%, n = 24), nausea and vomiting (32.7%, n = 18), and abdominal distention (7.3%, n = 4) were most prevalent. The other described features included reduced bowel sounds (5.4%, n = 3), food intolerance (3.6%, n = 2), and prolonged ileus (3.6%, n = 2). These clinical features appeared after a mean of 6.1 days after surgery (Table 1).

### *Biochemical findings*

Only studies reporting serum amylase elevation of more than three times the upper limit of normal were included; therefore, all studies and case reports reported an elevation of serum amylase levels. Serum lipase elevation was observed in 65% of patients (n = 199; Table 2).

### *Imaging findings*

Only studies that included definitive imaging evidence of acute pancreatitis were included. Although, all studies and case reports included imaging findings, only 24.5% (n = 75) of patients had detailed imaging data. Of these patients, 81.3% (n = 61) underwent abdominal ultrasound, and the remaining 18.6% (n = 14) underwent CT (Table 2).

### *Treatments used*

All but one patient was treated non-operatively nil by mouth with nasogastric

**Table 1.** Clinical characteristics of acute pancreatitis following spinal surgeries.

Author, year	Study design	Participants	Total number of patients	Patients with AP	Incidence with AP of AP	Mean age, years	Sex (F)	Spinal deformity	Type of surgery	Clinical symptoms	Mean duration of symptoms (postoperative days)	Serum amylase >3 times upper limit of AP	Definitive imaging evidence
<i>Core studies</i>													
Abousamra 2016 (1)	Case control study	Cerebral palsy children with scoliosis	300	165	55%	14.5	135	CP, scoliosis	Posterior spinal fusion ± anterior release, unit rod fixation, pedicle screw fixation, mixed implants	Signs of feeding intolerance such as abdominal distention or vomiting	6	Yes	Yes
Borkhuu 2009 (2)	Retrospective cohort study	Cerebral palsy patients, who received spine fusion with rod instrumentation	355	109	30.1%	14.07	60	CP, scoliosis.	Posterior spinal instrumentation and fusion/spine fusion with rod instrumentation	Persistent vomiting, poor feeding tolerance, abdominal pain, and tenderness	NA	Yes	Yes
Elbouyouf 2016 (3)	Retrospective cohort study	Adolescents after spine fusion surgery for scoliosis	571	14	2.4 %	16.025	NA	CP, scoliosis.	Scoliosis surgery	Diffused abdominal pain, pain in the right upper quadrant and epigastric pain	9.5	Yes	Yes
He 2004 (4)	Prospective cohort study	Patients with neuromuscular scoliosis who underwent posterior spinal fusion and central line placement	17	5	29.4%	15	2	Neuromuscular scoliosis	Posterior spinal fusion	Upper abdominal pain, epigastric or left upper quadrant tenderness, abdominal distension, nausea and vomiting, and persistent ileus	2	yes	Yes
Lapaza 2002 (5)	Retrospective cohort study	Patients undergoing surgery for adolescent idiopathic scoliosis	80	7	9%	16	6	Adolescent idiopathic scoliosis	Isolated posterior spinal arthrodesis; Isola instrumentation, Cotrel-Dubousset instrumentation, and Texas Scottish Rite Hospital system	Abdominal pain, nausea, or vomiting	NA	Yes	Yes

(continued)

**Table 1.** Continued.

Author, year	Study design	Participants	Total number of patients	Patients with AP	Incidence of AP	Mean age, years	Sex (F)	Spinal deformity	Type of surgery	Clinical symptoms	Mean duration of symptoms (postoperative days)	Serum amylase > 3 times upper limit of AP	Definitive imaging evidence
<i>Case studies</i>													
Ghisi 2018 (6)	Case report	Severe idiopathic scoliosis	1	1	NA	15	1	Scoliosis	Two-stage posterior arthrodesis including first-stage instrumentation with growing magnetic rod and second-stage posterior fixation	Nausea and mild abdominal pain during pressure and vomiting; abdominal distension and hypoactive bowel sounds	1	Yes	Yes
Hewavitharane 2020 (7)	Case report	Severe proximal thoracic scoliosis with deformity (Cobb's angle of 84°)	1	1	NA	13	1	Scoliosis	Single-stage posterior or correction of scoliosis	Abdominal pain, mild distension, nausea, vomiting, low grade fever and diminished bowel sounds	3	Yes	Yes
Juricic 2017 (8)	Case report	Scoliosis	1	1	NA	14	1	Scoliosis	Posterior instrument-tation, correction and, fusion from T2 to S1 using hybrid implants	Mild abdominal pain, vomiting, and abdominal distension	7	Yes	Yes
Korovessis 1996 (9)	Case report	Thoracolumbar kyphosis	1	1	NA	28	1	Kyphosis	Short apical anterior (Zielke operation) and a posterior rods-sublaminar wires plus Texas Scottish Rite Hospital procedure	Severe abdominal pain associated with severe back pain and repeated vomiting, epigastric tenderness on examination with abdominal distention and absent bowel sounds	1	Yes	Yes

(continued)

**Table 1. Continued.**

Author, year	Study design	Participants	Total number of patients	Patients with AP of AP	Incidence	Mean age, years	Sex (F)	Spinal deformity	Type of surgery	Clinical symptoms	Mean duration of symptoms (postoperative days)	Serum amylase >3 times upper limit of AP	Definitive imaging evidence
Rajaraman 2000 (10)	Case report	Grade I spondylolisthesis with mild lumbar spinal stenosis and degenerative disc disease	1	1	NA	60	1	Spondylolisthesis	Anterior lumbar interbody fusion	Nausea, vomiting, and abdominal distension	3	Yes	Yes
Tauchi 2013 (11)	Case report	Grade I spondylolisthesis, severe lumbar spinal canal stenosis	1	1	NA	53	1	Spondylolisthesis	Posterior lumbar interbody fusion	Persisting mild abdominal pain, nausea and vomiting starting several hours after surgery	1	Yes	Yes

AP, acute pancreatitis; NA, not available.

**Table 2.** Investigation findings of acute pancreatitis following spinal surgeries.

Author, year	Biochemical investigations		Imaging	
	Hyperamylasemia, n (%)	Hyperlipasemia, n (%)	Positive ultrasonography, n (%)	Positive CT, n (%)
<i>Core studies</i>				
Abousamra 2016 (1)	3 (2%)	147 (89%)	10 (3.33%)	Not performed
Borkhuu 2009 (2)	6 (5.5%)	34 (31.2%)	37 (10.42%)	Not performed
Elbouyoufi 2016 (3)	NA	NA	2 (0.35%)	9 (1.57%)
He 2004 (4)	NA	NA	4 (23.52%)	Not performed
Laplaza 2002 (5)	12 (15%)	12 (15%)	NA	NA
<i>Case studies</i>				
Ghisi 2018 (6)	1	1	Negative	1
Hewavitharane 2020 (7)	1	NA	1	1
Juricic 2017 (8)	NA	1	Not performed	1
Rajaraman 2000 (10)	1	1	Not performed	1
Tauchi 2013 (11)	1	NA	Not performed	1
Korovessis 1996 (9)	1	NA	1	Not performed

CT, computed tomography; NA, not available.

suction, intravenous fluids, somatostatin, and intravenous antibiotic prophylaxis until clinical improvement was observed. Four patients received total parenteral nutrition, and one patient needed total parenteral nutrition. One patient underwent surgery for corporeal fracture of the pancreas postoperatively after correction of the spinal deformity (Table 3).

### Risk factors

Three studies identified a prolonged fasting time (13.6%), intraoperative blood loss (9.1%), gastroesophageal reflux disease (9.1%), age >14 years (9.1%), low BMI (9.1%), and an anterior or combined approach (9.1%) as the most common risk factors of acute pancreatitis. Risk factors such as the duration of surgery, total parenteral nutrition, feeding difficulty, reactive airway disease, increased TNF-alpha levels, urine trypsin-associated peptide levels, male sex, gastrointestinal tube placement, reactive airway disease, anemia, and the

duration of surgery were also associated with acute pancreatitis, albeit at lower frequencies (4.5%, n = 1).

### Complications

The common complications of acute pancreatitis were glucose intolerance (25%, n = 4), peritonitis (12.5%, n = 2), pseudocyst formation (12.5%, n = 2), and fluid collection (12.5%, n = 2). Other complications including pancreatic pseudocyst formation, pancreatic ascites, and fluid collection were found in 7.1% of patients (n = 2). A minority (6.2%, n = 1) of patients had complications including septicemia, severe pancreatitis, multiorgan failure, phrenic abscess, ascites, and pancreatic duct rupture. The mean hospital stay and intensive care unit stay were 22.1 and 5.4 days, respectively. Two deaths (0.6%) were reported. Of these deaths, one patient died of severe pancreatitis 48 hours after surgery, and the other died 1 month after surgery from multiorgan failure

**Table 3.** Management, complications, and outcomes of acute pancreatitis following spinal surgeries.

Author, Year	Management	Complications		Outcome			
		Spinal surgery-related	Local	Acute systemic	Mean postoperative ICU stay, days	Mean postoperative hospital stay, days	Mortality
<p><i>Core studies</i> Abousamra 2016 (1)</p>	NA	Postoperative fever; postoperative atelectasis, postoperative pneumonia, postoperative pleural effusion, postoperative pneumothorax, superficial wound infection, deep wound infection, postoperative constipation, postoperative UTI, postoperative blood transfusion reaction	None	Postoperative septicemia	3	20	None
Borkhuu 2009 (2)	NA	Ascending paralysis	Severe pancreatitis with pseudocyst formation	Hepatitis, hypotension, and coagulopathy attributable to severe hemorrhagic pancreatitis	NA	23.1	Seven-year-old girl with severe quadriplegic pattern CP had an uneventful spine fusion but developed hemorrhagic pancreatitis 48 hours postoperatively and died
Elbouyoufii 2016 (3)	NA	Pneumonia and surgical site infection	Peritonitis and phrenic abscess in the pouch of Douglas, multi-organ failure	Peritonitis, glucose intolerance needing insulin, peritonitis following peripancreatic effusion, shock with respiratory and neurological failure	28.25	51	None

(continued)



**Table 3.** Continued.

Author, Year	Management	Complications				Outcome		
		Spinal surgery-related	Local	Acute systemic	Acute pancreatitis-related	Mean postoperative ICU stay, days	Mean postoperative hospital stay, days	Mortality
He 2004 (4)	NA	NA	Not mentioned	Sepsis	NA	28	None	
Laplaza 2002 (5)	Non-operative management; symptomatic patients were treated with bowel rest, intravenous fluids, and fasting until clinical improvement was observed; two patients required total parenteral nutrition	NA	Abdominal pain, nausea, or vomiting	NA	NA	9	None	
<i>Case studies</i>								
Hewavitharane 2020 (7)	Non-operative management	Intraoperative blood loss	None	None	6	10	None	
Ghisi 2018 (6)	Non-operative management	Intraoperative blood loss	Ascites	None	NA	19	None	
Rajaraman 2000 (10)	Non-operative management	Postoperative ileus	None	None	10 days	21	None	
Tauchi 2013 (11)	Non-operative management	Intraoperative blood loss	Acute fluid collection	None	NA	30	None	
Jurjic 2017 (8)	Abdominal exploration confirmed pancreatic fracture; a jejunal lesion was resected with direct anastomosis; drains were placed around the pancreatic area	Pancreatic fracture with pancreatic ductal disruption	Pancreatic duct rupture, acute fluid collection, and ascites	None	NA	NA	One death after 6 months	
Korovessis 1996 (9)	Non-operative management	Intraoperative blood loss	None	None	NA	NA	None	

ICU, intensive care unit; UJI, urinary tract infection; NA, not available; CP, chronic pancreatitis

attributable to complications of pancreatitis, including pancreatic duct rupture and leakage with pseudocyst formation and acute digestive peritonitis (Table 3).

## Discussion

Acute pancreatitis occurring following spinal surgery can severely disrupt the postoperative course, leading to unexpected morbidity and mortality.<sup>15</sup> It is associated with a relatively high mortality rate of 10% to 45% because of its potential to evolve into life-threatening systemic disease.<sup>31,32</sup> Postoperative pancreatitis occurs following several surgeries, including both abdominal and extra-abdominal surgeries, although it occurs mostly following gastric and hepatobiliary surgery.<sup>2</sup> However, few studies have described its occurrence following spinal surgery. To our knowledge, this is the first systematic review of the clinical characteristics and outcomes of acute pancreatitis following spinal surgery.

Overall, the evidence suggests that acute pancreatitis is an uncommon yet important postoperative complication following spinal surgery. The studies included in our review described 306 patients who developed AP postoperatively. The incidence of acute pancreatitis ranged from 0.2% to 7.4% in the published studies.<sup>8</sup>

The exact cause for postoperative pancreatitis has not been identified, although several mechanisms have been postulated. A study by Curtin *et al.* found that suboptimal positioning during surgery causing trauma to the pancreas might be a contributing factor.<sup>33</sup> Korovessis *et al.* identified a prolonged surgical time and the receipt of hypotensive anesthesia, which can cause ischemic injury in the pancreas, as potential causes of acute pancreatitis.<sup>30</sup> A study by Leichtner *et al.* found that intraoperative blood was significantly higher in patients who developed postoperative pancreatitis than in their counterparts. However, this

study failed to demonstrate a relationship with hypotension.<sup>23</sup> Although medications are well-known causes of acute pancreatitis, its true incidence is low, ranging from 0.1% to 2%.<sup>34,35</sup> Direct trauma in the abdominal region has been found to play a role in the development of acute pancreatitis following gastric and hepatobiliary surgery.<sup>2</sup> However, causes such as perioperative hypotension and reduced cardiac output were identified as major risk factors for postoperative acute pancreatitis in surgeries performed in non-abdominal regions.<sup>31</sup> A study by Rajaraman *et al.* on acute pancreatitis following anterior lumbar interbody fusion concluded that significant blood loss, the use of hypotensive anesthesia, and an anterior spinal approach should make surgeons take extra caution and stay vigilant concerning a possibility of acute pancreatitis, especially when patients develop prolonged postoperative ileus. Several common risk factors for developing acute pancreatitis were identified in the current review. A prolonged fasting time (13.6%), intraoperative blood loss (9.1%), gastroesophageal reflux disease (9.1%), age >14 years (9.1%), low BMI (9.1%), and an anterior or combined approach (9.1%) were the most common risk factors, whereas the duration of surgery, total parenteral nutrition, feeding difficulty, reactive airway disease, increased TNF alpha levels, urine trypsin-associated peptide levels, male sex, gastrointestinal tube placement, reactive airway disease, anemia, and the duration of surgery were also associated with acute pancreatitis, albeit in fewer patients.

A study by El Bouyousfi *et al.* on acute pancreatitis following scoliosis surgery revealed that pancreatitis occurred in the first 10 days after surgery, in line with the present study, in which symptoms appeared a mean of 6.2 days after surgery. Furthermore, they concluded that abdominal pain in postoperative acute pancreatitis was less typical and less frequent in

comparison to that caused attributable to other common etiologies including alcohol or gallstones. However, symptoms such as nausea, prolonged ileus, and vomiting were more common in acute pancreatitis following surgery, possibly caused by the combined effect of acute pancreatitis and surgery itself.<sup>16</sup> Among patients receiving systemic opioids after surgery, prolonged ileus beyond 48 to 72 hours after surgery suggests the possibility of pancreatitis because these symptoms typically should regress within 48 to 72 hours.<sup>36,37</sup> Although the most common symptoms identified in the current review were abdominal pain, nausea and vomiting, and abdominal distention, other symptoms including food intolerance, prolonged ileus, and reduced bowel sounds were described in a minority of patients. It is often difficult to link postoperative fever to acute pancreatitis because postoperative inflammation and infection must be excluded before seeking an alternative diagnosis, including acute pancreatitis.<sup>16</sup>

Biochemical testing for serum lipase and amylase is performed to establish a diagnosis of acute pancreatitis, with serum lipase being superior to serum amylase, even in the postoperative setting.<sup>38</sup> In the present review, only 65% of patients displayed elevated serum lipase levels. Early imaging is unlikely to be useful in patients with typical clinical features of acute pancreatitis, even with supportive abnormal biochemistry to establish a positive diagnosis, in the postoperative setting.<sup>39</sup> Abdominal ultrasonography has proven to be of little benefit in the diagnosis of acute pancreatitis in adults; thus, CT is the most commonly used imaging modality in adults.<sup>40</sup> The drawbacks of abdominal ultrasound include its operator-dependent nature and poor visualization attributable to interposition of the hollow viscera, leading to a higher rate of false negatives that is more pronounced in patients who underwent abdominal surgery.<sup>23,38</sup>

In the present review, 81.3% (61/75) of patients underwent abdominal ultrasound, and the remaining patients (18.6%, n = 14) underwent CT.

Postoperative acute pancreatitis is associated with a high mortality rate, reaching 12% to 13%, and approximately 27% and 53% of patients develop severe pancreatitis and other major complications associated with pancreatitis, respectively.<sup>6</sup> The mortality rate of patients in the present study was 0.7%, which was considerably lower than the rates reported in the literature. However, complications such as sepsis were relatively more common (28.5%). Only 6.2% of patients in the present review developed severe pancreatitis, which was a much lower rate than those described in the literature for postoperative acute pancreatitis. Other complications of pancreatitis including pancreatic pseudocyst formation, pancreatic ascites, and fluid collection were found in a minority (6.2%) of patients.

There were several limitations in the present review. The main limitation was that the patient populations, clinical characteristics, types of spinal surgery, and outcomes varied widely across the included studies. Furthermore, there was considerable variability in the quality of studies because most studies were cohort studies and there were no published randomized control trials providing high-quality evidence. However, the risk of bias of the selected studies was minimal.

## Conclusions

Although uncommon, acute pancreatitis remains an important postoperative complication of spinal surgery because of its associated morbidity and mortality. Avoiding major risk factors including prolonged fasting and minimizing intraoperative blood loss can help to reduce the incidence of acute pancreatitis in patients

undergoing spinal surgery. Delays in diagnosis because of masked symptoms in patients after spinal surgery remain a challenge. A high index of suspicion and a low threshold for both biochemical and radiological investigations could facilitate an earlier diagnosis and thereby minimize both short- and long-term complications.

### Author contributions

UJ and SS conceived the research idea. RJ, SR, CK, and UJ were involved in data curation, analysis, investigation, methodology, and initial draft writing. CK was involved in the formal academic literature search and methodology. SS was the senior author and supervisor, and he revised the final manuscript. All authors have read and agreed to the published version of the manuscript.

### Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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### Declaration of conflicting interest


All authors declare that there is no conflict of interest.

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### Supplemental files

S1: PRISMA flowchart

Table S1: Risk of bias analysis of the included studies

S2: PRISMA checklist

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