Postprint: Meta-Analysis of Risk Factors for Acute Lung Injury in Severe Acute Pancreatitis

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Abstract

Background Acute lung injury is the most common extrapancreatic organ injury in the course of severe acute pancreatitis, mainly manifested as respiratory insufficiency accompanied by tachypnea, cyanosis, decreased pulmonary compliance, etc. However, the specific pathogenesis remains unclear. Despite protective treatment, the quality of life of patients with severe acute pancreatitis complicated by acute lung injury remains adversely affected. Objective To systematically evaluate the risk factors for acute lung injury in severe acute pancreatitis. Methods A computer-based search was conducted for relevant studies on risk factors for acute lung injury in severe acute pancreatitis in CNKI, Wanfang Data Knowledge Service Platform, VIP Database, PubMed, Web of Science, and EBSCO databases from inception to October 2023. Two researchers independently screened literature, extracted data, and evaluated literature quality and evidence grade. Meta-analysis was performed using RevMan 5.3 software, and publication bias was analyzed using Begg's test in Stata 17.0. Results A total of 10 articles were included, all being case-control studies, comprising 1,053 patients with severe acute pancreatitis. Meta-analysis results showed that advanced age (SMD=0.58, 95%CI=0.03~1.14, P=0.04), elevated blood glucose (SMD=0.45, 95%CI=0.27~0.64, P<0.000 01), increased respiratory rate (>30 breaths/min) (OR=6.18, 95%CI=3.20~11.94, P<0.000 01), concomitant fever (OR=12.92, 95%CI=4.41~37.84, P<0.000 01), concomitant pleural effusion (OR=7.19, 95%CI=3.25~15.91, P<0.000 01), decreased albumin (SMD=-0.77, 95%CI=-0.98~-0.56, P<0.000 01), concomitant obesity (OR=3.11, 95%CI=1.94~4.98, P<0.000 01), decreased calcium (SMD=-0.63, 95%CI=-0.85~-0.45, P<0.000 01), concomitant acidosis (OR=2.15, 95%CI=1.03~4.49, P=0.04), elevated C-reactive protein (SMD=0.79, 95%CI=0.56~1.03, P<0.000 01), decreased hemoglobin (SMD=-0.77, 95%CI=-1.10~-0.43, P<0.000 01), elevated serum amylase (SMD=0.21, 95%CI=0.01~0.42, P=0.04), elevated urine creatinine

(SMD=0.40, 95%CI=0.03~0.77, P=0.03), increased Ranson score (SMD=0.87, 95%CI=0.66~1.08, P<0.000 01), increased Acute Physiology and Chronic Health Evaluation (APACHE II) score (SMD=0.77, 95%CI=0.58~0.96, P<0.000 01), elevated CT Severity Index score (SMD=0.39, 95%CI=0.19~0.59, P<0.000 01), elevated BISAP (SMD=0.62, 95%CI=0.37~0.88, P<0.000 01), hyperlipidemic acute pancreatitis (OR=1.68, 95%CI=1.05~2.67, P=0.03), concomitant systemic inflammatory response syndrome (SIRS) (OR=9.57, 95%CI=4.03~22.72, P<0.000 01), increased number of organ injuries ($ 2)($OR = 6.94, 95 $2), and infection are risk factors for ALI in SAP patients. Future high-quality studies are needed to validate these findings.

Full Text

Preamble

Evidence-Based Medicine

A Meta-Analysis of Risk Factors for Acute Lung Injury in Severe Acute Pancreatitis

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【Abstract】
Background: Acute lung injury represents the most common organ injury beyond the pancreas during the course of severe acute pancreatitis, primarily manifested as respiratory insufficiency with tachypnea, cyanosis, and decreased lung compliance. However, the specific pathogenesis remains incompletely understood. Despite protective therapeutic measures, the quality of life of patients with severe acute pancreatitis complicated by acute lung injury remains adversely affected.
Objective: To systematically evaluate the risk factors for acute lung injury in severe acute pancreatitis.
Methods: Computerized searches were conducted in CNKI, Wanfang Data, VIP, PubMed, Web of Science, and EBSCO databases for relevant studies on risk factors for acute lung injury in severe acute pancreatitis from database inception to October 2023. Two researchers independently screened literature, extracted data, and assessed study quality and evidence levels. Meta-analysis was performed using RevMan 5.3 software, and publication bias was analyzed using Begg's test in Stata 17.0.

Results: Ten case-control studies involving 1,053 patients with severe acute pancreatitis were included. Meta-analysis results showed that advanced age (SMD=0.58, 95%CI=0.03~1.14, P=0.04), elevated blood glucose (SMD=0.45, 95%CI=0.27~0.64, P<0.00001), increased respiratory rate (>30 breaths/min) (OR=6.18, 95%CI=3.20~11.94, P<0.00001), fever (OR=12.92, 95%CI=4.41~37.84, P<0.00001), pleural effusion (OR=7.19, 95%CI=3.25~15.91, P<0.00001), decreased albumin (SMD=-0.77, 95%CI=-0.98~-0.56, P<0.00001), obesity (OR=3.11, 95%CI=1.94~4.98, P<0.00001), decreased calcium (SMD=-0.63, 95%CI=-0.85~-0.45, P<0.00001), acidosis (OR=2.15, 95%CI=1.03~4.49, P=0.04), elevated C-reactive protein (SMD=0.79, 95%CI=0.56~1.03, P<0.00001), decreased hemoglobin (SMD=-0.77, 95%CI=-1.10~-0.43, P<0.00001), elevated blood amylase (SMD=0.21, 95%CI=0.01~0.42, P=0.04), increased urinary creatinine (SMD=0.40, 95%CI=0.03~0.77, P=0.03), elevated Ranson score (SMD=0.87, 95%CI=0.66~1.08, P<0.00001), increased APACHE II score (SMD=0.77, 95%CI=0.58~0.96, P<0.00001), elevated CT severity index score (SMD=0.39, 95%CI=0.19~0.59, P<0.00001), elevated BISAP (SMD=0.62, 95%CI=0.37~0.88, P<0.00001), hyperlipidemic acute pancreatitis (OR=1.68, 95%CI=1.05~2.67, P=0.03), systemic inflammatory response syndrome (SIRS) (OR=9.57, 95%CI=4.03~22.72, P<0.00001), increased number of organ injuries ($ 2)($OR = 6.94, 95 $2), and infection are risk factors for acute lung injury in patients with severe acute pancreatitis. Future high-level studies are needed to further validate these findings.

【Keywords】 Severe acute pancreatitis; Acute lung injury; Risk factors; Meta-analysis

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Acute pancreatitis (AP) is a common acute abdominal inflammatory condition in clinical practice, characterized by rapid onset, rapid progression, and high mortality. Approximately 20% of patients develop severe acute pancreatitis (SAP), with or without necrosis of the pancreas and peripancreatic tissues, which may ultimately induce systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndrome (MODS) [1-3]. Acute lung injury (ALI) is the most common organ injury beyond the pancreas during the course of SAP [4], yet the specific pathogenesis of ALI induced by SAP remains incompletely

understood [5]. ALI is characterized by acute respiratory insufficiency with tachypnea, refractory hypoxic cyanosis, decreased lung compliance, and diffuse alveolar infiltrates on chest radiography. Recent studies have also defined ALI as moderate or mild acute respiratory distress syndrome (ARDS) [6-7]. ARDS, as a severe form of lung injury, is also a major cause of death in AP patients [8]. However, despite the use of lung-protective ventilation, neuromuscular blockade, and prone positioning, the mortality rate of this syndrome remains around 40%, and long-term quality of life is similarly adversely affected in survivors of the acute phase of ALI [7-8]. Therefore, identifying risk factors for ALI in SAP patients and providing early recognition and therapeutic intervention are crucial for reducing mortality and improving quality of life.

Multiple scholars domestically and internationally have investigated ALI secondary to SAP, but most studies have focused on treatment with various medications and exploration of therapeutic mechanisms, with few systematically discussing the risk factors for ALI induced by SAP. Therefore, this study aims to integrate previous research through meta-analysis to explore risk factors for ALI in SAP patients, providing high-quality evaluative evidence to inform clinical early identification and intervention. This study has been registered in the PROSPERO database (registration number: CRD42023493428).

1.1 Inclusion and Exclusion Criteria

Inclusion criteria: (1) Study population: Patients with SAP complicated by ALI. SAP diagnostic criteria: The Atlanta diagnostic criteria classifying AP into mild acute pancreatitis (MAP), moderately severe acute pancreatitis (MSAP), and SAP [9]; Diagnostic criteria for AP and SAP established by various branches of the Chinese Medical Association; Other explicit SAP diagnostic criteria. ALI diagnostic criteria: Diagnostic criteria for lung injury established by various branches of the Chinese Medical Association; Other explicit ALI diagnostic criteria. (2) Study content: Risk factors for ALI in SAP patients or predictive factors in models predicting ALI development in SAP patients. (3) Study design: Retrospective cohort studies, case-control studies. (4) Language: Limited to Chinese and English articles.

Exclusion criteria: (1) Patients with ALI due to established causes such as lung injury-inducing drugs, pulmonary diseases, or physical injury; (2) Patients who had already developed ALI before SAP onset; (3) Articles with unavailable full text, incomplete research data, or inaccessible study data; (4) Conference papers, duplicate publications, abstracts, reviews, and other literature types.

1.2 Search Strategy

Using the PICOS principle, we defined the study population (P: SAP patients with ALI), outcomes (O: disease-related risk factors), and study design (S: cohort studies, case-control studies, etc.). We conducted searches using a combination of Chinese and English subject headings and free terms. The Chinese search

terms included: severe acute pancreatitis, lung injury, acute lung injury, risk factors, etc. The English search terms included: Severe Acute Pancreatitis, Acute Lung Injury, Risk Factor, etc. Computerized searches were performed in Chinese databases (CNKI, Wanfang Data, VIP) and English databases (PubMed, Web of Science, EBSCO) from database inception to October 2023. Additionally, researchers screened relevant articles from reference lists. The specific search strategy for Web of Science is shown in Table 1 .

1.3 Literature Selection and Data Extraction

Retrieved literature was imported into NoteExpress V3.X, and two researchers independently screened the articles. The software was first used to automatically remove duplicates, after which researchers read titles and abstracts to exclude obviously ineligible studies according to inclusion and exclusion criteria. For remaining articles, researchers read full texts to determine eligibility. Data from final included studies were extracted independently by two researchers, including: (1) First author and publication year, sample size; (2) Types of complications, SAP and ALI diagnostic criteria; (3) Complication risk factors.

1.4 Literature Quality Assessment

Included studies were assessed for quality by two researchers using the Newcastle-Ottawa Scale (NOS) [10]. The NOS comprises three domains (selection of study groups, comparability between groups, and measurement of exposure factors) and eight items including appropriateness of case definition, representativeness of cases, and selection of controls. The total score is 9 points, with scores $ $7, 4-6, and <4 representing high, moderate, and low quality, respectively.

1.5 Statistical Methods

All extracted data were preprocessed in Excel 2019 and then imported into RevMan 5.3 for meta-analysis. Processed data were analyzed using random-effects models. Fixed-effects models were used when the number of included studies was small ($ 5)[11].$Dichotomousvariableswereexpressedasoddsratios(OR),andcontinuousvariablesas$ tests combined with I^2 values (test level α=0.1). P>0.1 and I^2<50% indicated small or no heterogeneity; otherwise, heterogeneity was considered substantial, and sources were examined by sequential exclusion. When $ $3 studies were included, Begg's test in Stata 17.0 was used for publication bias analysis of influencing factors. P<0.05 was considered statistically significant.

1.6 Evidence Evaluation

The GRADE evidence evaluation tool was used to assess the quality of included evidence, including five aspects: risk of bias, imprecision, inconsistency, indirectness, and publication bias [13]. Evidence quality was classified as high (A),

moderate (B), low (C), or very low (D). No downgrading indicated high quality, with each downgrade reducing the level by one grade; three downgrades indicated very low quality.

2.1 Literature Selection Results

The search yielded 545 articles, with 458 remaining after duplicate removal. After reading titles and abstracts, 22 articles were selected for initial screening. Following full-text review, 12 articles were excluded (4 for study type mismatch, 2 for incomplete data, 6 for unclear diagnostic criteria). Ultimately, 10 articles [14-23] were included, comprising 8 Chinese [14,16-22] and 2 English [15,23] studies. The specific literature screening process and results are shown in Figure 1 [Figure 1: see original paper].

2.2 Characteristics and Quality Assessment of Included Studies

The total sample size of included studies was 1,053 patients, all case-control studies conducted in China, each with explicit SAP and ALI diagnostic criteria [9,24-32]. Quality assessment using NOS criteria identified 2 studies [17,21] as moderate quality and 8 [14-16,18-20,22-23] as high quality. Detailed characteristics and quality evaluation of included studies are presented in Table 2 .

2.3 Meta-Analysis Results

Taking age as an example, 9 studies [14-19,21-23] reported the association between age and ALI, including 869 patients. Heterogeneity testing showed substantial heterogeneity among studies (I^2=92%, P<0.00001). Random-effects meta-analysis revealed that advanced age was a risk factor for ALI in SAP patients (SMD=0.58, 95%CI=0.03~1.14, P=0.04), as shown in Figure 2 [Figure 2: see original paper].

Among risk factors, blood glucose, fever, respiratory rate (>30 breaths/min), APACHE II score, CT severity index score, BISAP, hyperlipidemic SAP subtype, SIRS, and infection showed low heterogeneity, while age, blood glucose, pleural effusion, albumin, obesity, calcium, C-reactive protein, hemoglobin, blood amylase, urinary amylase, Ranson score, and number of organ injuries ($ $2) showed high heterogeneity, prompting further analysis of heterogeneity sources.

Meta-analysis results indicated that elevated blood glucose, C-reactive protein, blood amylase, and urinary amylase; decreased albumin, hemoglobin, and calcium concentrations; increased respiratory rate; high Ranson score, APACHE II score, CT severity index score, and BISAP; hyperlipidemic SAP subtype; and presence of fever, acidosis, obesity, pleural effusion, SIRS, number of organ in-

juries ($ $2), and infection were risk factors for ALI in SAP patients (P<0.05), as detailed in Table 3 .

2.4 Sensitivity Analysis

Sensitivity analysis was performed for factors with substantial heterogeneity through sequential exclusion. Results showed that heterogeneity decreased for age, blood glucose, pleural effusion, and Ranson score after removing studies [19], [22], [18], and [19], respectively. Heterogeneity for albumin, obesity, calcium, C-reactive protein, and blood amylase showed no significant change, indicating stable and reliable results. Hemoglobin, urinary amylase, and number of organ injuries ($ $2) were each reported in only 2 studies, precluding sequential exclusion sensitivity analysis. Detailed sensitivity analysis results are presented in Table 4 .

2.5 Publication Bias Analysis

Begg's test in Stata 17.0 was used to assess publication bias for influencing factors. Results showed no significant publication bias for age (P=0.191), obesity (P=0.163), blood glucose (P=0.493), albumin (P=0.562), calcium (P=0.173), C-reactive protein (P=0.156), blood amylase (P=0.093), respiratory rate (P=0.129), Ranson score (P=0.271), APACHE II score (P=0.488), CT severity index score (P=0.204), BISAP (P=0.240), hyperlipidemic SAP subtype (P=0.223), or pleural effusion (P=0.882).

2.6 Evidence Evaluation

The GRADE evidence evaluation for risk factors of ALI in SAP is shown in Table 5 . A total of 11 risk factors (age, respiratory rate, pleural effusion, obesity, hemoglobin, blood amylase, urinary amylase, Ranson score, BISAP, hyperlipidemic acute pancreatitis, and number of organ injuries) were of moderate quality (B), while 10 factors (blood glucose, fever, albumin, calcium, acidosis, C-reactive protein, APACHE II score, CT severity index score, SIRS, and infection) were of low quality (C). Downgrading for risk of bias was primarily due to missing randomization methods and blinding in some studies. Downgrading for imprecision was mainly due to relatively few patients and observed events resulting in wide confidence intervals. Downgrading for inconsistency resulted from inconsistent findings across studies without reasonable explanation.

3.1 General Factors

This study found that age and obesity are risk factors for ALI in SAP. Heterogeneity decreased for age after excluding study [19], while obesity heterogeneity remained high, possibly due to temporal factors and different obesity diagnostic criteria across studies affecting patient inclusion numbers. With advancing age, organ function gradually declines, making elderly patients more susceptible

to organ injury, consistent with Zhang et al.'s findings [19]. Obesity as a risk factor may be mediated by antioxidant consumption, reduced lung volume and chest wall compliance, and increased susceptibility to lung injury. Additionally, as obesity represents a chronic inflammatory state, it can initiate a cascade of inflammatory processes in combination with other inflammatory factors, leading to lung injury [35]. Healthcare providers should focus on elderly and obese populations, strengthen monitoring, and promote exercise to prevent ALI.

3.2 Common Indicators

Results showed that elevated blood glucose, blood amylase, C-reactive protein, and urinary amylase; decreased albumin, hemoglobin, and calcium concentrations; increased respiratory rate; and high Ranson score, APACHE II score, CT severity index score, and BISAP are risk factors for ALI in SAP. Heterogeneity decreased for blood glucose and Ranson score after excluding studies [22] and [19], respectively, while heterogeneity for blood amylase, C-reactive protein, albumin, and calcium remained unchanged after exclusion, likely due to long intervals between studies and different detection methods.

Blood glucose levels were higher in the SAP with ALI group than in the non-ALI group, consistent with findings by Qin et al. [14], Pan et al. [16], and Wei [22]. Pancreatic damage during SAP leads to pancreatic dysfunction, reduced insulin secretion, and subsequent hyperglycemia. Pancreatic destruction also causes amylase to enter the bloodstream, elevating blood amylase. In this study, blood and urinary amylase concentrations were higher in the SAP with ALI group than in the non-ALI group, consistent with Li's findings [18]. Renal injury during SAP progression can also elevate urinary amylase [36]. Elevated blood glucose and amylase together reflect disease progression and increased likelihood of ALI. Pancreatic injury or infection triggers increased C-reactive protein secretion to enhance immune function, activating complement and enhancing phagocytosis. Decreased albumin and hemoglobin may result from early inflammatory exudation from the pancreas and surrounding tissues, excessive serum protein loss, poor gastrointestinal protein absorption, and disease-related protein catabolism [16]. During pancreatitis, low endoplasmic reticulum calcium concentration and open calcium channels allow extracellular calcium to replenish the endoplasmic reticulum [37], reducing serum calcium levels. These changes, consistent with Pan et al.'s findings [16], indicate that continued alteration of these factors signals SAP progression and further ALI induction. ALI in SAP patients causes alveolar epithelial injury and epithelial-endothelial barrier disruption, impairing gas exchange and prompting increased respiratory rate to maintain normal gas exchange [6], consistent with HUANG et al.'s findings [15]. The Ranson score predicts SAP severity and prognosis, with higher scores indicating more severe disease [38]. The APACHE II score is a commonly used tool for SAP with high accuracy and strength in assessing systemic complications [39]; higher scores indicate more severe disease and greater ALI probability. The CT severity index score, based on CT imaging findings, reflects AP severity, with higher scores

indicating greater likelihood of ALI, consistent with Gao et al.'s findings [40]. The BISAP score predicts local and systemic complications in AP patients, with higher scores indicating greater ALI probability, consistent with Jin et al.'s findings [41]. Healthcare providers should monitor laboratory indicators and vital signs, apply scoring systems accurately, and promptly identify abnormal indicators to prevent ALI.

3.3 Etiological Subtype

This study found that hyperlipidemic SAP is a risk factor for ALI. Under hyperlipidemic conditions, fats are broken down into fatty acids by pancreatic enzymes, accumulate in the lungs via systemic circulation, and damage pulmonary capillary endothelium. Elevated lipid peroxide concentrations and insufficient oxygen free radical clearance also exacerbate inflammatory responses, significantly increasing ALI incidence, consistent with Zhao et al.'s findings [42]. Healthcare providers should encourage hyperlipidemic patients to modify dietary patterns, ensure medication adherence, and regularly monitor lipid levels for early detection and intervention.

3.4 Comorbidities

Results showed that infection, fever, SIRS, number of organ injuries ($ 2), $pleural effusion, and acidosis are risk factors for ALI in SAP. Heterogeneity decreased for pleural effusio$ may be due to differences in patient numbers between studies [23] and [19] and the small number of included studies. Early SAP infection most commonly involves the respiratory system [43], causing systemic inflammatory responses and fever. Massive release of inflammatory mediators triggers uncontrolled SIRS, often involving tissues and organs [44], further inducing ALI. Pleural effusion increases pulmonary compression and, combined with pancreatic enzymes, inflammatory factors, and cellular necrosis products within the effusion, induces ALI [45]. Pancreatic destruction reduces insulin secretion, causing hyperglycemia and potentially diabetic ketoacidosis in severe cases [46]. Lung tissue injury impairs gas exchange, and mechanical ventilation may exacerbate hypercapnia, causing respiratory lung injury [47] and leading to ALI.

This study found that advanced age; elevated blood glucose, C-reactive protein, blood amylase, and urinary amylase; decreased albumin, hemoglobin, and calcium concentrations; increased respiratory rate (>30 breaths/min); high Ranson score, APACHE II score, CT severity index score, and BISAP; hyperlipidemic SAP subtype; and presence of fever, acidosis, obesity, pleural effusion, SIRS, number of organ injuries ($ $2), and infection are risk factors for ALI in SAP patients. Additional uninvestigated factors such as D-dimer and fluid retention volume may also represent risk factors. Healthcare providers should strengthen identification and implement timely interventions and targeted treatments to prevent ALI and reduce mortality in SAP patients with ALI.

5 Limitations

Due to limited relevant research, this study included a small number of articles, all single-center, small-sample studies with incomplete risk factors from the same country, potentially introducing bias. Future multi-center, large-sample, multi-national studies incorporating more risk factors are needed to further validate these findings.

Author Contributions: GUO Shengteng and ZHANG Fenfen designed the study, collected data, performed statistical analysis, and drafted and revised the manuscript. WAN Di conducted literature search and screening and database quality control. YU Dongmei performed database quality control and figure/table preparation. WANG Qinghua designed the study, provided quality control, and finalized the manuscript. All authors take responsibility for the manuscript.

Conflict of Interest: The authors declare no conflict of interest.

Note: Figure translations are in progress. See original paper for figures.