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The Risk Factors of Acute Lung Injury in Acute Stage in Patients with Severe Acutepancreatitis

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Abstract: Severe acute pancreatitis (SAP) is prone to develop acute lung injury (ALI), leading to early death, but there is a lack of early warning methods in clinical practice. To identify risk factors, this study first retrospectively enrolled 158 SAP patients, then systematically collected their clinical data, screened independent predictive indicators through univariate and multivariate analyses, and finally constructed a risk prediction model. The APACHE II score, hypocalcemia, and C-reactive protein were shown to be separate ALI risk factors, and the predictive power of the model was significant (AUC=0.89). Research has shown that the risk assessment system based on conventional indicators can identify high-risk patients early and provide effective basis for precise clinical intervention.

1. Introduction

Severe acute pancreatitis (SAP) is a common and critical illness in clinical practice. Its effects are typically not limited to the pancreas, but often trigger a systemic inflammatory response, leading to multi-organ dysfunction. Among the many complications of SAP, ALI and its potential progression to acute respiratory distress syndrome (ARDS) are particularly dangerous and have become a leading cause of early mortality. Once ALI develops, the patient's condition often deteriorates rapidly, making treatment more challenging and significantly increasing the risk of death. Currently, clinical diagnosis of ALI relies on conventional methods such as imaging and blood gas analysis. While these methods can help confirm the diagnosis, they can often only confirm it after lung damage has already occurred. Due to the lack of early warning methods, treatment is often delayed, and the optimal time for prevention and intervention is easily missed.

Given this, it is of great significance to delve into the driving factors of ALI in the course of SAP and construct an effective risk prediction model. This study systematically analyzed the components of ALI in SAP patients during the acute phase of their disease. By constructing a risk prediction model, this study hopes to provide clinicians with a practical tool to identify high-risk patients before ALI occurs. This article first describes the research background and methods, then reports the results of univariate and multivariate analyses, identifies key risk indicators, and evaluates the

effectiveness of the prediction model. Finally, the article conducts an in-depth discussion of the research results in conjunction with existing literature, explains its underlying mechanisms, and explores its potential value in guiding the clinical implementation of phased and precise prevention and control strategies. Notably, the development of ALI during the course of SAP exhibits a distinct temporal pattern. During the acute phase, an overactive systemic inflammatory response is the primary driver of lung injury; in the secondary infection phase, immune dysregulation and secondary infection become key drivers of disease progression. This heterogeneity across stages suggests that the weight of risk factors may change dynamically as the disease progresses.

2. Related Works

Currently, many studies have explored the relationship between acute pancreatitis and acute lung injury. For example, Hu et al. reported that the therapeutic effect of emodin in alleviating severe acute pancreatitis-associated acute lung injury was partly dependent on exosomal mechanisms [1]. Acute pancreatitis is one of the leading causes of gastrointestinal hospitalization in the United States, with approximately 300,000 visits annually. Its prognosis is affected by factors such as risk stratification, fluid nutrition management, and follow-up care, which are the research topics of Mederos et al [2]. Szatmary et al. believed that acute pancreatitis is a common indication for hospitalization, with an increased incidence and serious impact, so some patients require long-term management to prevent recurrence, progression of chronic pancreatitis, and the risk of pancreatic cancer [3]. The etiology and natural history of acute pancreatitis are diverse, some patients have other complications, and the mortality rate is high; Lee and Cho outlined the available scoring systems and biochemical markers [4]. Dang et al. explored the possibility of using gene expression of monocytes/macrophages as a biomarker [5]. Long et al. reviewed the pathogenesis of pneumonia and acute lung injury and outlined the role of respiratory microorganisms, lung microbiome, and interventions, noting that the effects of these interventions in clinical trials were mixed [6]. Multiple organ failure is linked to the inflammatory condition known as acute pancreatitis. Data from Fan et al. showed that pyroptosis and ferroptosis play a crucial role in acute pancreatitis, and inhibition of glutathione peroxidase 4-mediated pyroptosis and ferroptosis can alleviate acute pancreatitis and related lung injury [7]. Feng et al. explored the possible mechanism of action of the Qingjie Huagong formula on acute lung injury associated with severe acute pancreatitis through network pharmacology and verified it through animal experiments [8]. However, most existing studies lack in-depth analysis of patients with pancreatitis at different clinical stages and have failed to fully reveal specific biomarkers and clinical risk factors.

To address these issues, Zhao et al. retrospectively selected 139 patients with acute pancreatitis who visited the Department of Endocrinology and Metabolism and the Department of Gastroenterology at the Second Hospital of Lanzhou University from September 2019 to September 2023 [9]. Zhang et al. associates investigated the risk factors for acute respiratory distress syndrome in patients with acute pancreatitis using univariate and multivariate logistic regression [10]. In summary, although existing research provides a basis for understanding the association between SAP and ALI, there are still obvious deficiencies in dynamic assessment and stage-specific analysis. Most models rely on static data at admission and fail to fully reflect the evolution of risk factors during disease progression. Existing prediction models mostly focus on static assessments immediately after admission, but ignore the dynamic evolution of biomarkers during the course of the disease. Especially in the critical time window when SAP patients progress from systemic inflammatory response to organ dysfunction, the changing trajectory of continuous monitoring indicators may have stronger predictive value than single measurements. This requires researchers to shift from static risk assessment to a dynamic early warning model. This study systematically analyzes the triggers of ALI in SAP patients during the acute phase of their disease.

3. Materials and Methods

3.1 Subjects

To clarify the trigger of ALI in patients with severe SAP, this study constructed a retrospective observational cohort. Patients with SAP who were hospitalized at hospital between January 2020 and December 2023 and met the diagnostic criteria of the revised Atlanta classification were included.

In order to more accurately evaluate the causal relationship between SAP and ALI and to control the influence of confounding factors as much as possible, this study has established clear inclusion and exclusion criteria. Patients who meet the following conditions are included in the study: ① diagnosed with SAP; ② within the time range specified by the study; ③ aged 18 years and above. The exclusion criteria are mainly used to exclude respiratory insufficiency caused by non-SAP, specifically including: ① individuals who have previously been diagnosed with interstitial lung disease, chronic heart failure, or chronic obstructive pulmonary illness (NYHA grade III–IV); ② ALI/ARDS already existed at the time of admission to ensure that the ALI studied was a new onset after SAP; ③ the proportion of missing key clinical data exceeded 20% to avoid the impact of incomplete data on the results.

3.2 Design

This design can efficiently explore the association between SAP and subsequent ALI within a clear time frame based on previously prospectively collected clinical data.

In this study cohort, all patients were observed starting with the diagnosis of SAP (i.e., the exposure factor) and subsequently underwent continuous monitoring during the acute phase (within one week of onset) to determine whether ALI (i.e., the study outcome) occurred. This temporal relationship of "exposure (SAP) first, outcome (ALI) later" is an important logical basis for establishing causal relationships between risk factors. The advantage of a retrospective design is that it fully utilizes existing clinical diagnosis and treatment data, allowing for a systematic analysis of the spectrum of complications of SAP, a critical illness, in a relatively short period of time, thereby providing timely evidence to support the identification of early warning indicators for ALI.

To ensure data quality and reproducibility, a standardized data extraction process was developed for this study. Two researchers, all trained in the same discipline, independently extracted data using a pre-defined electronic data collection form. After extraction, data was cross-checked. Any inconsistencies were resolved through negotiation or adjudication by a third researcher to ensure accuracy and consistency in data entry.

3.3 Diagnostic Criteria for ALI/ARDS

This study used the internationally recognized Berlin definition of ARDS to diagnose ALI and its severe form, ARDS. This definition categorizes the severity of ARDS based on onset time, chest imaging, oxygenation status, and the exclusion of pulmonary edema due to heart failure.

To ensure that cases of lung injury earlier in the course of SAP can be identified, this study included patients who met the diagnostic criteria of "mild ARDS" in the Berlin definition into the category of "ALI" for analysis. This operational definition aimed to improve the sensitivity of identifying early lung injury related to SAP, thereby more comprehensively capturing the role of risk factors. All diagnoses were jointly confirmed by two or more senior physicians who were unaware of the specific grouping of this study, after independently reviewing the patient's medical records, arterial blood gas analysis results, and serial chest imaging data. Adopting this authoritative

and objective diagnostic standard can minimize the misclassification bias and ensure the internal authenticity of the study and the external comparability between different studies [11]. To minimize subjective bias in the diagnostic process, this study conducted unified training on the application of the Berlin criteria for physicians involved in diagnostic assessment.

3.4 Data Collection

To systematically identify the triggers of acute lung injury (ALI) in SAP patients, this study collected complete clinical data from four dimensions. All data were collected using standardized forms.

Data collection dimensions included: ① baseline information (age, sex, BMI, and SAP etiology); ② disease severity scores (APACHE II and SOFA scores); ③ laboratory indicators (CRP, PCT, serum calcium, amylase, lipase, white blood cell count, and PaO_2); and ④ imaging data (chest X-ray and CT reports). The completeness of data collection for each dimension is shown in Figure 1.

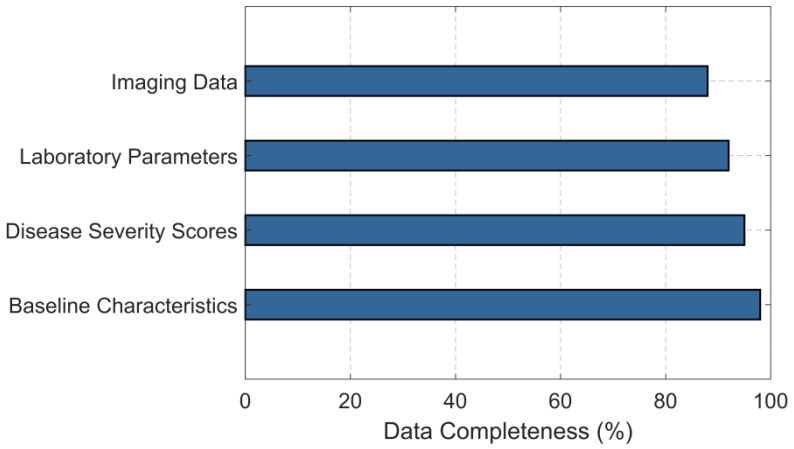

Figure 1. Data collection completeness for each clinical dimension

This bar chart illustrates the collection completeness of four core data dimensions. Baseline characteristics had the highest completeness (98%), followed by disease severity score (95%), laboratory parameters (92 %), and imaging data (88%). All dimensions maintained a completeness above 85%, providing a reliable data foundation for subsequent risk factor analysis. This study used multiple imputation to address missing data that occurred during the data collection process. Specifically, assuming data were missing at random, chain equations are used to generate five complete data sets using information on other observed variables. These data sets were analyzed separately and the results were aggregated to ensure robust statistical conclusions and maximize the use of available data. All data were logically checked and range-checked after entry into the database to identify and correct potential data entry errors.

3.5 Statistical Methods

All statistical analyses in this study were conducted using SPSS 26.0 software. For measurement data that conformed to normal distribution, independent sample t-test was used for comparison between groups. The median (interquartile range) was used to characterize quantitative data that were not normally distributed, and the Mann-Whitney U test was used for comparisons [12].

To identify a single generating element of ALI,a multivariate logistic regression model was first constructed using variables that were statistically significant in univariate analysis. Variables were

selected using forward stepwise regression, and the odds ratio (OR) and its 95% confidence interval (CI) were calculated for each variable. Model goodness of fit was examined using the Hosmer-Lemeshow test, and receiver operating characteristic curves were drawn and the area under the curve was computed to measure the model's predictive ability. All statistical analyses were two-sided.

4. Results

4.1 Basic Characteristics of Patients

A total of 158 patients with severe acute pancreatitis who met the criteria were enrolled in this study. Of these, 97 were male (61.4%) and 61 were female (38.6%), with a mean age of 52.7 ± 11.4 years, ranging from 28 to 76 years. Biliary etiology was the most common (76 patients, 48.1%), followed by hyperlipidemia (46 patients, 29.1%) and alcohol (25 patients, 15.8%). Other etiologies were reported in 11 patients (7.0%). All patients were severely ill, with a mean APACHE II score of 14.3 ± 5.2 and a mean SOFA score of 5.1 ± 2.3 within 24 hours of admission, indicating a significant risk of systemic inflammation and multi-organ dysfunction in this cohort. This provides a reliable research basis for subsequent analysis of the causes of acute lung injury.

4.2 Incidence of Acute ALI

Among the 158 patients included in this study,49 were diagnosed with acute lung injury (ALI) during the defined acute phase (i.e., within 1 week of onset), with an acute ALI incidence of 31.0% (49/158). No statistically significant differences were found in terms of age, gender, or etiology between the two groups when comparing baseline patient data, as seen in Table 1 (P>0.05). However, patients in the ALI group had significantly higher disease severity at admission, with significantly higher APACHE II and SOFA scores than those in the control group (both P<0.001).

Table 1. Comparison of basic characteristics of acute ALI patients and non-ALI patients

Characteristic	Total Patients (n=158)	Non-ALI Group (n=109)	ALI Group (n=49)	P-value
Age (years, Mean ± SD)	52.7 ± 11.4	51.5 ± 11.9	55.3 ± 9.8	0.058
Male, n (%)	97 (61.4)	68 (62.4)	29 (59.2)	0.698
Etiology, n (%)				0.205
Biliary	76	48	28	
Hyperlipidemic	46	30	16	
Alcoholic	25	19	6	
Other	11	9	2	
APACHE II Score (points, Mean ± SD)	14.3 ± 5.2	12.6 ± 4.6	18.2 ± 4.3	<0.001
SOFA Score (points, Mean ± SD)	5.1 ± 2.3	4.4 ± 1.9	6.7 ± 2.1	<0.001

4.3 Results of Univariate Analysis

Univariate analysis showed that patients who developed ALI in the acute phase had significant

differences in multiple clinical indicators compared with those who did not. Patients in the ALI group showed more severe systemic inflammation and organ function damage.

Specifically, the C-reactive protein level in ALI patients was significantly higher than that in the control group (187.4 ± 39.1 mg/L vs 116.7 ± 49.9 mg/L, t(156) = 8.77, P < 0.001), with a mean difference of 70.7 mg/L (95% confidence interval: 54.8-86.6) and an effect size Cohen's d of 1.58. This difference is large enough to affect the treatment plan.

In terms of other indicators, the APACHE II score (18.2 ± 4.3 vs 12.6 ± 4.6) and SOFA score (6.7 ± 2.1 vs 4.4 ± 1.9) of the ALI group performed best. Furthermore, the ALI group had significantly higher procalcitonin levels (12.5 (5.4, 25.1) ng/mL vs 3.2 (1.5, 7.8) ng/mL) and significantly lower serum calcium levels (1.75 ± 0.21 mmol/L vs 2.02 ± 0.18 mmol/L) (both P < 0.001). No statistical difference was observed in white blood cell counts between the two groups.

To visually demonstrate this key finding, Figure 2 presents a comparison of the distribution of C-reactive protein levels in the two groups of patients.

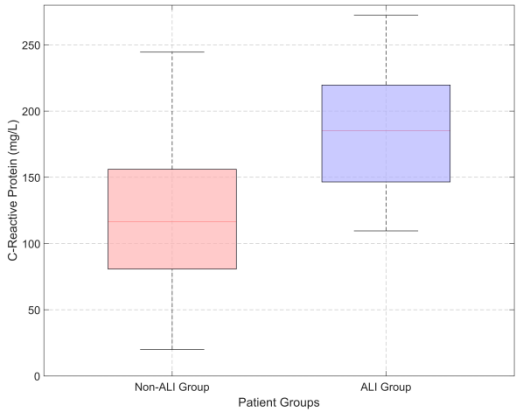

Figure 2. Comparison of C-reactive protein levels in patients with acute ALI and those without ALI

The box plot visually shows that the levels of patients in the ALI group were significantly higher than those in the non-ALI group (187.4 ± 39.1 mg/L vs 116.7 ± 49.9 mg/L, P < 0.001), with a mean difference of 70.7 mg/L. This finding suggests that ALI patients have a more severe systemic inflammatory response, consistent with the pathophysiology of SAP-ALI.

4.4 Results of Multivariate Logistic Regression Analysis

Three independent risk factors were shown to be significantly linked to acute ALI in SAP patients using multivariate logistic regression analysis. APACHE II (Acute Physiology and Chronic Health Evaluation II) score (odds ratio (OR) = 1.32, 95% CI: 1.17-1.49, P < 0.001), low serum calcium level (OR = 1.57, 95% CI: 1.26-1.95, P < 0.001), and protein (OR = 1.09, 95% CI: 1.03-1.16, P = 0.002) all showed significant predictive value. With a predictive accuracy of 85.4% and an operational characteristic curve area beneath the receiver of 0.89(95% CI: 0.84-0.94), the prediction model showed outstanding discriminative capacity.

Figure 3 uses a forest plot to visually display the effect size and precision of each independent risk factor.

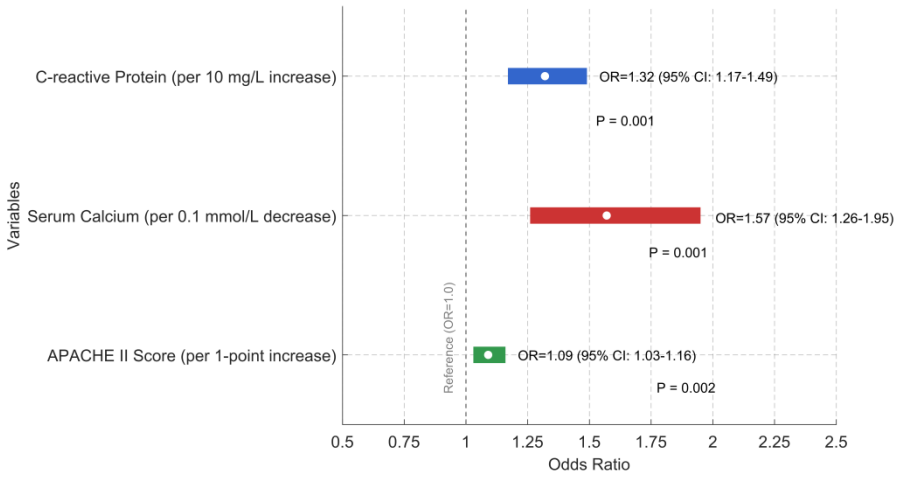

Figure 3. Forest plot of independent risk factors for ALI in SAP patients

The figure presents not only the odds ratio and confidence interval for each factor, but also the corresponding percentage increase in clinical risk, visualized in the right panel. Serum calcium level shows the strongest predictive effect. All factors achieve high statistical significance.

5. Discussion

This study systematically explored the causes of acute lung injury thorough retrospective analysis in individuals suffering from severe acute pancreatitis. The analysis results clearly identified the APACHE II score, blood calcium level, and C-reactive protein as three key independent predictors of ALI. This finding is highly consistent with the pathophysiological mechanism of SAP-ALI. As a comprehensive indicator for assessing the severity of systemic disease, an increase in the APACHE II score directly reflects the imbalance of the body's physiological homeostasis and the risk of multiple organ failure, making it the most powerful predictive signal for ALI. Notably, hypocalcemia demonstrated a high odds ratio in this study, which profoundly reflects its special significance in SAP: it is not only a laboratory abnormality but also a direct consequence of extensive necrosis and saponification of the peripancreatic adipose tissue. Its severity is closely related to the intensity of the systemic inflammatory response and poor prognosis.

From a pathological perspective, SAP-induced acute lung injury (ALI) is essentially the pulmonary manifestation of a systemic inflammatory response initiated by local pancreatic injury. The independent risk factors identified in this study outline the key pathways of this inflammatory cascade at the clinical level. When TNF-α, IL-1β, etc. enter the circulation in large quantities, they directly damage the alveolar capillary endothelial cells, destroy the intercellular junctions, significantly increase vascular permeability, and cause protein-rich fluid to penetrate into the pulmonary interstitium and alveolar cavity, forming non-cardiogenic pulmonary edema - this is the core pathological feature of ALI. During this process, elevated APACHE II and the occurrence of hypocalcemia can be regarded as important indirect markers of the severity of systemic inflammatory response.

The results of this study have clear clinical implications and phased management value. The risk prediction model has good discriminatory ability, which means that in clinical practice, high-risk groups can be identified very early before ALI occurs. Patients with high APACHE II scores, hypocalcemia, and high CRP levels on admission should be considered as individuals at very high

risk of ALI, and early warning intervention should be initiated immediately. In the acute phase (within 1 week of onset), management strategies should focus on "prevention and interruption", including precise fluid resuscitation to avoid volume overload, strengthening respiratory function monitoring (such as daily arterial blood gas analysis), and considering early, short-term lung protective ventilation strategies, which may prevent the occurrence of ALI or reduce its severity.

Although this study controlled for some confounding factors through multiple regression analysis and established a well performing predictive model, there are still some limitations. Firstly, research design may introduce selection bias and limit the broad applicability of research results. Second, the relatively limited sample size may have affected the power to detect certain potential risk factors. Future studies can require further validation of the conclusions of this study in large, prospective, multicenter cohorts, and the integration of more novel biomarkers (such as cytokine profiles) into the prediction model to further enhance its accuracy.

In summary, this study confirms that APACHE II score, blood calcium, and CRP are the elements that contribute to acute ALI in SAP patients. A risk assessment system based on these readily available clinical indicators can provide clinicians with an effective decision-making tool, enabling early identification of high-risk patients and targeted, phased intervention, ultimately improving the overall prognosis of SAP patients.

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