EURASIAN JOURNAL OF EMERGENCY MEDICINE
Original Article
DOI: 10.4274/eajem.galenos.2025.39112
Eurasian J Emerg Med.

Cholesterol, Urea Nitrogen, CRP, And IL-4 as Independent Predictors for Severe Acute Pancreatitis: A Retrospective Study

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Abstract

Aim: To investigate the expression and correlation between laboratory indicators, such as urea nitrogen, cholesterol, and inflammatory markers in patients with severe acute pancreatitis (AP) within 24 hour of admission and provide new insights for the early identification of severe acute pancreatitis (SAP).

Materials and Methods: A retrospective study was conducted on patients with AP admitted between January 2022 and December 2022. According to the revised atlanta classification, patients were categorized into the mild acute pancreatitis (MAP) group (N=112) and the moderately severe acute pancreatitis/severe acute pancreatitis (MSAP)/SAP group (N=45). Clinical data were compared between two groups. Univariate and multivariate logistic regression analyses were performed to identify independent risk factors for severe AP. The predictive value of the model was assessed using the area under the ROC area under the curve (AUC).

Results: Compared with the MAP group, The MSAP/SAP group exhibited significantly higher proportions of fatty liver, diabetes, and hypertriglyceridemia, along with elevated levels of cholesterol, fibrinogen, urea nitrogen, bilirubin, neutrophil-to-lymphocyte ratio, C-reactive protein, D-dimer, interleukin-4, interleukin-6, and interleukin-10 ($p<0.05$). The multivariate logistic regression analysis revealed that cholesterol [odds ratio (OR): 1.278, 95% confidence interval (CI): 1.085-1.562, $p=0.007$], urea nitrogen (OR: 1.478, 95% CI: 1.203-1.976, $p=0.002$), C-reactive protein (OR: 1.016, 95% CI: 1.006-1.027, $p=0.002$), and interleukin-4 (OR: 2.151, 95% CI: 1.470-3.564, $p<0.001$) were the independent risk factors for early severe AP. The AUC of the combined prediction model incorporating these four factors was 0.932 (95% CI: 0.884-0.979), demonstrating a sensitivity of 97% and a specificity of 75%. It exhibited superior diagnostic efficacy compared to any single indicators and the commonly used BISAP scoring system.

Conclusion: This study identified cholesterol, urea nitrogen, C-reactive protein, and interleukin-4 as significant independent risk factors for the early development of severe AP. A novel predictive model was developed incorporating these four biomarkers, which demonstrated superior diagnostic efficacy compared with any single indicator and the conventional BISAP score. This model assists clinicians with a simple, objective, and powerful tool for early risk stratification of AP patients within 24 hour of admission.

Keywords: Urea nitrogen, cholesterol, CRP, IL-4, acute pancreatitis, ROC

Introduction

Acute pancreatitis (AP) is an acute life-threatening inflammatory disease characterized by abnormal activation of pancreatic enzymes, leading to autodigestion of the pancreas and injury to surrounding organs. As one of the most common causes of acute abdomen, AP can trigger systemic inflammatory response syndrome and multiple organ dysfunction syndrome in the early stage, with mortality rates reaching 20-30% (1,2). Based on disease severity, AP is classified as mild acute pancreatitis (MAP), moderately severe acute pancreatitis (MSAP), and severe acute pancreatitis (SAP) (1). Early Identification of MSAP and SAP remains crucial yet challenging for improving patient survival.

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Cite this article as: Chen Y, Mo J, Qiao G, He Y. Cholesterol, urea nitrogen, CRP, and IL-4 as independent predictors for severe acute pancreatitis: a retrospective study. Eurasian J Emerg Med. [Epub Ahead of Print].

Received: 07.08.2025
Accepted: 18.09.2025
Epub: 23.10.2025

At present, no standardized and universally accepted assessment system exists in clinical practice for evaluating the severity of AP, as each available scoring method has its own advantages and limitations (3,4). Laboratory indicators are still under investigation due to their objectivity and reproducibility. biochemical parameters, such as blood urea nitrogen (BUN), and cholesterol (CHO), have been reported to correlate with AP severity in previous studies (5,6). The inflammatory cascade is recognized as a key pathophysiological mechanism of AP (7), and inflammatory markers, such as C-reactive protein (CRP) (8) and [interleukin (IL)], (7), have also been confirmed to be associated with disease severity. However, few studies have evaluated the predictive potential of combining routine biochemical indicators with inflammatory markers, including cytokines, for the early identification of severe AP. In this study, changes in clinical indicators across various severities of AP were analyzed, and the predictive value of integrating biochemical and inflammatory markers for severe AP was investigated; aiming to provide a reliable reference for the early diagnosis and timely intervention.

Materials and Methods

Research Participants

Total of 157 patients with AP diagnosed and treated between January 2022 and December 2024 were included in this study. Of these, 112 were classified as MAP and 45 as MSAP/SAP.

Patients were included if they met the following study inclusion criteria: 1) Met the diagnostic criteria specified in section 1.3 of Chinese guidelines for the diagnosis and treatment of AP (2021) (1); 2) Were stratified by AP severity according to the revised Atlanta classification (9): MAP patients assigned to the Mild group, and MSAP/SAP patients assigned to the Severe group; 3) Aged >18 years; 4) Underwent relevant examinations, including abdominal computed tomography, ultrasound, and laboratory testing within 24 hour after admission. Laboratory tests included bilirubin (BIL), CHO, BUN, creatinine (CREA), uric acid (URIC), neutrophils-to-lymphocytes ratio (NLR), platelet-to-lymphocyte ratio (PLR), CRP, fibrinogen (FIB), D-dimer (DD), interleukin-2 (IL-2), IL-4, IL-6, IL-10, tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ), and glycosylated hemoglobin type A1c (HbA1c); 5) had complete medical records.

Patients were excluded if they met the following study exclusion criteria: 1) Having recurrent or chronic pancreatitis; 2) Having tumors, pregnancy, or severe pre-existing organ dysfunction prior to disease onset.

Ethics Approval and Consent to Participate

Case data were collected from the electronic medical record system of Yixing People's Hospital, for retrospective analysis of patients with AP. The study was approved by the ethics committee of Yixing People's Hospital, which waived the requirement for informed consent based on the following considerations: (1) All data were de-identified prior to analysis, with direct identifiers such as name, ID number, and contact information removed; and (2) The research involved minimal risk to participants, as no additional interventions or contact with patients were required. The informed consent was obtained from all patients and their families, and the study was approved by the hospital's medical ethics committee. This study was approved by the Medical Ethics Review Committee of Yixing People's Hospital (desicion number: 2025 141-01, date: 15.09.2025).

Statistical Analysis

Data analysis was performed using SPSS 26.0. Continuous variables with normal distribution were expressed as ($X \pm S$), and the LSD-T test was used for comparison. Abnormally distributed data were presented as [M (P25, P75)], and the Mann-Whitney U test was applied to determine intergroup differences. Spearman's correlation test was used to evaluate the correlation among variables. Categorical variables were expressed as count and percentage, and the chi-square test was used to compare the rates between two groups. Multivariate analysis was performed using a logistic regression model, and the discriminative ability of the model was assessed by calculating the area under the ROC curve area under the curve (AUC). P-value<0.05 was considered statistically significant.

Results

Comparison of the Clinical Data in AP Patients with Different Severities

As presented in Table 1, a total of 157 AP patients were included, comprising 112 cases in the MAP group and 45 cases in the MSAP/SAP group. No significant differences were observed between the two groups in terms of gender, age, body mass index, or prevalence of hypertension (p>0.05). The distribution of etiologies significantly varied between the two groups. Biliary AP was the most common subtype in the MAP group (56.25%), whereas hypertriglyceridemic AP predominated in the MSAP/SAP group (53.66%). In addition, the proportions of patients with fatty liver or diabetes were significantly associated with AP severity. Laboratory tests indicated that levels of CHO, FIB, BUN, BIL, NLR, CRP, DD, IL-4, IL-6, and IL-10 were significantly higher in the MSAP/SAP group compared with those in the MAP group (p<0.05). However, there are no significant differences in indicators, such as HbA1c, aspartate aminotransferase, CREA, URIC, PLR, IL-2, IFN-γ, and TNF-α, between the two groups (p>0.05).

Table 1. Basic clinical data of patients in MAP And MSAP/SAP groups

Variable	MAP (N=112)	MSAP/SAP (N=45)	c^2/Z/T	p
Sex			1.175	0.278
Female	58 (51.79%)	19 (42.22%)		
Male	54 (48.21%)	26 (57.78%)		
Age	55.88±17.96	51.13±16.17	1.54	0.125
BMI (Kg/M^2)	24.90±4.06	24.79±3.96	0.115	0.908
Etiology			7.082	0.029
Biliary	63 (56.25%)	16 (35.56%)		
Hypertriglyceridemia	29 (25.89%)	21 (53.66%)		
Else	20 (17.86%)	8 (17.78%)		
Hypertension			1.181	0.277
No	75 (66.96%)	26 (57.78%)		
Yes	37 (33.04%)	19 (42.22%)		
Fatty liver			6.674	0.01
No	77 (68.75%)	21 (46.67%)		
Yes	35 (31.25%)	24 (53.33%)		
Diabetes			5.69	0.017
No	92 (82.14%)	29 (64.44%)		
Yes	20 (17.86%)	16 (36.36%)		
HbA1c (%)	6.05 (5.5, 8.00)	5.80 (5.45, 7.65)	-0.524	0.6
BIL (Mmol/L)	16.95 (11.92, 27.92)	14.62 (8.59, 19.72)	-2.166	0.03
CHO (Mmol/L)	5.03±2.27	7.48±5.41	-4.007	0
AST (IU/L)	26.75 (16.95, 153.50)	41.71 (19.50, 70.15	-0.082	0.935
BUN (Mmol/L)	5.24±2.84	7.48±5.41	-3.346	0.001
CREA (Mmol/L)	74.04±88.30	92.34±71.70	-1.236	0.218
URIC (Mmol/L)	306.94±120.47	342.52±132.48	-1.626	0.106
NLR (%)	6.34 (4.13, 9.90)	15.20 (6.44, 22.05)	-3.952	0
PLR (%)	195.61±119.92	238.06±171.12	-1.763	0.08
CRP (Mg/L)	22.99 (8.28, 91.06)	123.47 (53.26, 167.03)	-4.115	0
FIB (G/L)	3.86±1.17	4.52±1.41	-3.02	0.003
DD (Mg/ML)	876 (526, 1391)	3373 (1946, 6813)	-6.941	0
IL-2 (Pg/ML)	1.11 (0.47, 1.77)	0.75 (0.09, 1.35)	-0.257	0.797
IL-4 (Pg/ML)	0.98 (0.73, 1.55)	2.18 (1.06, 7.10)	-4.767	0
IL-6 (Pg/ML)	12.75 (5.45, 47.71)	101.76 (36.74, 208.68)	-6.429	0
IL-10 (Pg/ML)	1.51 (0.91, 2.50)	7.02 (5.17, 15.73)	-6.318	0
TNF-A (Pg/ML)	10.28±9.91	8.39±13.40	0.969	0.334
IFN-Γ (Pg/ML)	13.26±17.77	9.75±9.04	1.261	0.209

BMI: Body mass index, HbA1c: Hemoglobin A1c, BIL: Bilirubin, CHO: Cholesterol, AST: Aspartate aminotransferase, BUN: Blood urea nitrogen, CREA: Creatinine, URIC: Uric acid, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, CRP: C-reactive protein, FIB: Fibrinogen, DD: D-dimer, IL: Interleukin, TNF-A: Tumor necrosis factor-alpha, IFN-Γ: Interferon-gamma, MAP: Mild acute pancreatitis, MSAP/SAP: Moderately severe acute pancreatitis/severe acute pancreatitis, Z/T: Z test/T tes

Screening the Independent Predictors and Developing a Model for Severe AP

Using AP severity (MAP: 0, MSAP/SAP: 1) as the dependent variable, 13 clinical indicators, including etiology, fatty liver, diabetes, BIL, CHO, BUN, NLR, CRP, FIB, DD, IL-4, IL-6, and IL-10, That were significantly associated with AP severity were involved in the univariate analysis. As presented in Table 2, multivariate analysis identified CHO, BUN, CRP, and IL-4 as independent predictors of AP severity ($p<0.05$)

Table 2. Multivariate logistic regression analysis of the risk factors for severe acute pancreatitis

Variable	B	OR	Wald	p	OR (95% CI)
Etiology	0.333	0.726	0.210	0.647	1.395 (0.336, 5.792)
Fatty liver	1.303	1.033	1.589	0.207	3.679 (0.486, 27.871)
Diabites	-0.700	1.039	0.453	0.501	0.497 (0.065, 3.807)
CHO (Mmol/L)	0.245	0.091	2.694	0.007	1.278 (1.085, 1.562)
BUN (Mmol/L)	0.391	0.124	3.155	0.002	1.478 (1.203, 1.976)
FIB (G/L)	0.529	0.482	1.201	0.273	1.697 (0.659, 4.368)
BIL (Mmol/L)	0.027	0.017	2.694	0.101	1.028 (0.995, 1.062)
NLR (%)	0.129	0.064	4.001	0.050	1.138 (1.003, 1.291)
CRP (Mg/L)	0.016	0.005	3.061	0.002	1.016 (1.006, 1.027)
DD (Mg/ML)	0.000	0.000	2.044	0.153	1.000 (1.000, 1.000)
IL-4 (Pg/ML)	0.766	0.225	3.410	<0.001	2.151 (1.470, 3.564)
IL-6 (Pg/ML)	0.002	0.002	0.586	0.444	1.002 (0.998, 1.005)
IL-10 (Pg/ML)	-0.079	0.051	2.407	0.121	0.924 (0.836, 1.021)
Constant	-7.409	1.556	-4.761	<0.001	-

CHO: Cholesterol, BUN: Blood urea nitrogen, FIB: Fibrinogen, BIL: Bilirubin, NLR: Neutrophil-to-lymphocyte ratio, CRP: C-reactive protein, DD: D-dimer, IL: Interleukin, OR: Odds ratio, CI: Confidence nterval, B: Beta coefficien

Table 3. Multivariate logistic regression analysis of the risk factors of severe acute pancreatitis

Variable	AUC (95% CI)	Sensitivity	Specificity	Youden	Cut-off	p
BUN (Mmol/L)	0.643 (0.543-0.742)	40.00%	86.61%	0.389	7.545	0.005
CHO (Mmol/L)	0.587 (0.472-0.702)	35.60%	92.86%	0.256	7.705	0.059
CRP (Mg/L)	0.762 (0.658-0.866)	72.70%	71.43%	0.442	81.85	<0.001
IL-4 (Pg/Ml)	0.742 (0.650-0.834)	71.10%	69.60%	0.481	1.870	0.047
BISAP	0.719 (0.628-0.811)	48.50%%	78.60%	0.271	1.50	<0.001
Prediction Model	0.932 (0.884-0.979)	97.00%	75.00%	0.720	0.178	<0.001

AUC: Area under the curve, CI: Confidence interval, BUN: Blood urea nitrogen, CHO: Cholesterol, CRP: C-reactive protein, IL: Interleukin, BISAP: Bedside index of severity in acute pancreatitis

Validation of the Prediction Model

Model Discrimination

As shown in Table 3 and Figure 1, the AUC of the combined prediction model was 0.932 (95% confidence interval (CI): 0.884-0.979), with the cut-off value of 0.178, the sensitivity of 97%, and the specificity of 75%. Its performance surpassed that of individual risk factors and the commonly used BISAP scoring system, indicating that the prediction model exhibited high discriminative power.

Discussion

AP is a complex disease characterized by multiple etiologies, variable disease courses, lack of targeted drug therapies, and difficulty in early prediction of its progression, resulting in a high mortality rate. The global incidence of AP ranges from 4.9 to 73.4 per 100,000 population, with approximately 20% of patients progressing to severe AP accompanied by a 20% mortality rate (1,10-12). Supportive therapy, integrated traditional Chinese and Western medicine therapy, and minimally invasive surgical intervention are common treatment modalities for AP, and the selection of treatment strategies depends on the severity of AP (2). Therefore, early prediction of severe AP is crucial for guiding clinical treatment decisions and improving patient prognosis.

In this study, the clinical data and laboratory indicators of patients with different severities of AP were compared. The independent risk factors were assessed, and their predictive values for identifying early severe AP patients were explored. The results revealed that hypertriglyceridemia, fatty liver, diabetes, BIL, CHO, BUN, NLR, CRP, FIB, DD, IL-4, IL-6, and IL-10 were influential factors for severe AP; while CHO, BUN, CRP, and IL-4 were noted as independent risk factors for severe AP. The discriminative performance of the model was validated by comparing the AUC values with those of individual predictors and the commonly used BISAP scoring system.

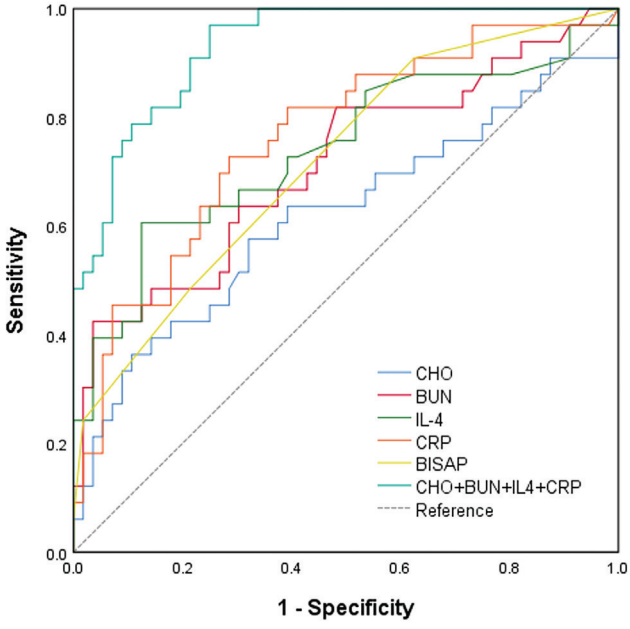

Figure 1. The ROC of the risk factors

CHO: Cholesterol, BUN: Blood urea nitrogen, IL: Interleukin, CRP: C-reactive protein, BISAP: Bedside index of severity in acute pancreatitis

CHO has multiple biological effects. As an essential component of cell membranes, it maintains structural integrity, supports membrane homeostasis, and facilitates signal transduction and material transport. It also serves as an indicator for steroid hormones, such as glucocorticoids, and acts as a metabolic regulator of lipid and glucose homeostasis (6,13). Excessive CHO can trigger inflammatory responses through Toll-like receptor 4 (TLR4) and NOD-like receptor pyrin domain-containing protein 3 (NLRP3) activation (6). Previous research has demonstrated that TLR4 plays a remarkable role in pancreatic injury (14), primarily by activating NF-Kb and upregulating the expression level of NLRP3. NLRP3 subsequently activates pro-inflammatory cytokines (E.G., ILs) leading to their release (15). Inhibition of NLRP3 inflammasome activation has been shown to significantly attenuate pancreatic injury and systemic inflammation (16). Clinically, elevated CHO level (>240 mg/dL) within 24 hour of admission has been identified as an independent risk factor for severe AP (17). Consistently, the present study revealed that CHO level within 24 hour of admission was significantly higher in the MSAP/SAP group compared with that in the MAP group. The cut-off value of CHO for predicting severe AP was 7.705 mmol/L (297.95 mg/dL; conversion factor: 38.67); consistent with previous reports above.

BUN is an integral component of classic scoring systems for predicting severe AP, such as APACHE II And BISAP. Specifically, in the BISAP scoring system, BUN level exceeding 25 mg/dL (8.93 mmol/L, conversion factor 2.8) can contribute 1 point to the assessment of severe AP risk. Results from large-scale multicenter cohort studies demonstrated that early changes in BUN could accurately predict AP outcomes, with BUN measurement within 24 hours of admission recognized as the most valuable single routine parameter for the early prediction of severe AP (18). Yang et al. (19) further confirmed that BUN level within 48 hour of admission was optimal for predicting persistent organ failure in AP. However, a meta-analysis conducted by Wang et al. (20), which included studies on BUN measurements at different time points, failed to identify BUN's predictive value for severe AP. These findings suggest that the predictive utility of BUN depends heavily on strict timing of measurement. Consistent with Wu et al. (18) findings, the BUN level within 24 hour of admission in the MSAP/SAP group was significantly higher than that in the MAP group, and BUN was noted as an independent risk factor for the progression of AP to severe condition. However, the cut-off value derived from univariate analysis (7.545 mmol/L) and the corresponding ROC sensitivity were lower than the BISAP criteria. These results demonstrate that although BUN alone provides early warning value for severe AP, its predictive power is limited, highlighting the need for combination with other indicators.

CRP is an acute-phase reactive protein synthesized by the liver and is commonly used as a non-specific inflammatory marker. Its predictive role in severe AP remains controversial, mainly due to variability in measurement timing, threshold selection, and clinical applicability. On one hand, since CRP synthesis depends on hepatic function, its reliability may be compromised in patients with alcoholic or obesity-related AP; on the other hand, because CRP peaks 24–48 hour after inflammation onset, it may be less appropriate for very early prediction (21,22). Both Stirling et al. (23) and the Chinese guidelines for the diagnosis and treatment of Aps (2021) (1) indicated that a CRP level exceeding 150 mg/mL suggested severe AP, while the former specified that the test should be conducted within 48 hour after admission, and the latter recommended the testing time as 72 hour following the onset of AP. studies by Walker et al. (24), Rao et al. (25), and He et al. (26) support Stirling et al. (23) timing, although they propose different thresholds. Wu et al. (21) further stratified patients by measurement time (≤48 H, 48 H-7 days, ≥7 days), and found that timing did not significantly affect the predictive value of CRP for severe AP. In the present study, CRP was measured within 24 hours of admission, with a predictive threshold of 81.85 mg/L, which is lower than guideline recommendations. Moreover, the 25th percentile of CRP in patients who progressed to severe AP within 24 hour was only 53.26 mg/L. These findings demonstrate that earlier measurement at a lower threshold may hold greater clinical value for early prediction of severe AP.

IL-4 is an anti-inflammatory cytokine. Previous studies have demonstrated that following pancreatic injury, IL-4 promotes The polarization of M2a macrophages via IL-4 receptor signaling, thereby promoting pancreatic repair and regeneration (27). The polarization and subtype diversity of macrophages play a pivotal role in this process (12,27-29). Macrophages, which exhibited similar cellular phenotypes in patients with mild and severe AP and represented the most prominently altered immune cells during AP, exhibited distinct functional effects via cytokine secretion, with variations in cytokine expression levels measured between the recovery and severe phases (29,30). Both clinical and experimental studies have supported the notion that The excessive inflammatory response in AP arises from a dynamic imbalance between anti-inflammatory and pro-inflammatory factors (27,31). In severe AP, overexpression and subsequent exhaustion of IL-4 can lead to immunosuppression, complications, and organ damage, making elevated IL-4 levels a marker of poor prognosis (31). In the present study, IL-4 level in the MSAP/SAP group was significantly higher than that in the MAP group, demonstrating that the development of severe AP may promote the polarization of M1 macrophages toward M2a cells. however, due to the exhaustion of IL-4, its anti-inflammatory effect was remarkably diminished or even abolished. Notably, no counteracting pro-inflammatory cytokines were identified in this study.

Clinical data analysis identified four laboratory indicators (CHO, BUN, CRP, and IL-4) as independent predictors of early severe AP. All four were derived from routine blood tests, providing a more convenient and objective alternative to complex scoring systems.

Study Limitations

However, this study has several limitations. firstly, as a retrospective study, the inclusion of observational indicators was limited, potentially leading to the omission of other risk factors. Secondly, as a single-center study, the study restricted the extrapolation of its findings. Thirdly, when the cost-benefit ratio exceeded 0.7, fluctuations in the decision curve analysis curve were intensified, and further validation of the model still requires data from a larger sample of cases. Fourthly, AP has substantial long-term impacts, even mild cases carry risks of recurrence, progression to chronic pancreatitis, and complications involving endocrine and exocrine insufficiency. Follow-up surveys on readmission rates were limited by variability in measurement methods and small numbers of positive cases, restricting further analysis of risk factors. previous studies by Wu et al. (27) and Yue et al. (28) have highlighted the importance of dynamic cytokine monitoring. The present study analyzed serum cytokine concentrations only at admission, precluding assessment of their real-time significance during disease progression and recovery.

Conclusion

In conclusion, the present study identified CHO, BUN, CRP, and IL-4 as significant independent risk factors for the early development of severe AP. A novel predictive model was developed using four readily available biomarkers, demonstrating superior diagnostic efficacy (AUC: 0.932, Sensitivity: 97%, Specificity: 75%) compared with any single indicator and the conventional BISAP score. This model assists clinicians with a simple, objective, and effective tool for the early risk stratification of AP patients within 24 hours of admission. Despite the limitations of a single-center, retrospective design, the combined biomarker panel showed promising performance for optimizing timely interventions and improving patient prognosis. Future large-scale, prospective studies are warranted to validate these findings and explore the underlying molecular mechanisms.

Ethics

Ethics Committee Approval: This study was approved by the Medical Ethics Review Committee of Yixing People's Hospital (desicion number: 2025 141-01, date: 15.09.2025).

Informed Consent: The informed consent was obtained from all patients and their families, and the study was approved by the hospital's medical ethics committee.

Footnotes

Author Contributions

Concept: Y.C., Design: Y.C., Y.H., Data Collection or Processing: J.M., G.Q., Analysis or Interpretation: Y.H., Literature Search: G.Q., Writing: Y.C., Y.H.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

Availability of Supporting Data

The data that support the findings of this study are available on request from the corresponding author.

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