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Correlation between serum levels of PTX-3, SIL-2R, inflammatory markers, and APACHE II scores in patients with severe acute pancreatitis

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Abstract

To investigate the correlation of serum pentraxin 3 (PTX-3), soluble interleukin-2 receptor (SIL-2R), C-reactive protein (CRP), procalcitonin (PCT) levels, and acute physiology and chronic health evaluation II (APACHE II) scores in patients with severe acute pancreatitis (SAP). A total of 30 patients with SAP from October 2020 to October 2021 were selected as the SAP group, and 42 patients with mild acute pancreatitis (MAP) or moderate-severe acute pancreatitis (MSAP) was selected as the control group. The serum levels of PTX-3, SIL-2R, CRP, PCT, and APACHE II scores were evaluated. The serum levels of PTX-3, SIL-2R, CRP, PCT, and APACHE II scores at admission in the SAP group were significantly higher than those in the control group (all $P < .05$). Spearman analysis showed that serum PTX-3, SIL-2R, CRP, and PCT levels were positively correlated with APACHE II scores (all $P < .05$). The mortality rate within 28 days was 26.7% in the SAP group; moreover, the serum PTX-3, SIL-2R, CRP, and PCT levels and APACHE II scores at admission in the death group were significantly higher than those in the survival group (all $P < .05$). The receiver operating curve showed that the combined prediction value of all indicators (PTX-3 + SIL-2R + CRP + PCT + APACHE II) was superior to the single indicators, and the diagnostic sensitivity and specificity were 90.9% and 84.2%, respectively. Serum PTX-3, SIL-2R, CRP, and PCT levels and APACHE II scores have high guiding significance in early diagnosis and prognostic evaluation of SAP patients.

Abbreviations: AP = acute pancreatitis, APACHE II = acute physiology and chronic health evaluation II, AUC = area under curve, CRP = C-reactive protein, MAP = mild acute pancreatitis, MSAP = moderate-severe acute pancreatitis, PCT = procalcitonin, PTX-3 = serum pentraxin 3, ROC = receiver operating characteristic, SAP = severe acute pancreatitis, SIL-2R = soluble interleukin-2 receptor.

Keywords: C-reactive protein, procalcitonin, serum pentraxin 3, severe acute pancreatitis, soluble interleukin-2 receptor

1. Introduction

Acute pancreatitis (AP) is a common acute abdomen.[1] The main symptoms of AP are abdominal pain, abdominal distension, nausea, vomiting, and radiating pain in the lower back, accompanied by changes in serum enzymes such as amylase and lipase.[2] AP was classified into 3 categories according to the Revised Atlanta Classification, which were mild acute pancreatitis (MAP), moderate-severe acute pancreatitis (MSAP), and severe acute pancreatitis (SAP).[3,4] MAP is defined as AP clinical manifestations that are mild, with no organ failure and complications occur, and low mortality rate. SAP is described as critical AP clinical signs, accompanied by organ failure lasting more than 48 hours, with a severe condition and a high fatality rate. SAP has an acute onset and rapid progress, with intractable complications and increased mortality. Hence, it is essential to evaluate the severity and prognosis of SAP.

AP is essentially an inflammatory reaction of the tissue.[5] Inflammatory mediators and cytokines play an essential role in the pathogenesis of AP. Studies have suggested that both procalcitonin (PCT) and C-reactive protein (CRP) inflammatory parameters are associated with the occurrence and development of AP.[6]

At present, there are many predictive indicators for the severity of AP, including independent biochemical indicators[7] (such as amylase/lipase, serum creatinine, and urine urea nitrogen), biomolecular inflammatory markers[8] (such as PCT, CRP, and interleukin), and scoring system containing laboratory test results such as Acute Physiology and Chronic Health Evaluation II (APACHE II) scores.[9] In addition, the progression of SAP is closely related to the inflammatory response and immune function. Studies have shown that serum pentraxin 3 (PTX-3) and soluble interleukin-2 receptor (SIL-2R) levels are closely related to the inflammatory response in systemic infectious diseases.[10,11]

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PTX-3, CRP, and PCT have been reported as prognostics biomarkers of SAP as they have the early evaluation and prediction value of the SAP; moreover, PTX-3 as acute phase proteins achieve earlier peak levels compared to CRP and PCT when SAP occurs.[12] Moreover, the development of SAP is positively correlated to the changes in the immune system, and in the early phase of SAP, the expression of SIL-2R is increased as an immunosuppressive inhibitor to the inflammatory cascade; hence, SIL-2R levels are closed to SAP progression and can be used as indicator for determining the severity of SAP.[13]

Although the progress of the above prognostic biomarkers have been investigated, PTX-3, SIL-2R, CRP, and PCT combined with APACHE II scores for assessing early severity of SAP are rarely reported. Therefore, this study aimed to investigate the predictive value of PTX-3, SIL-2R, CRP, PCT combined with APACHE II score on the prognosis of SAP patients.

2. Materials and Methods

2.1. General information

A retrospective case-control study was conducted. A total of 72 patients with AP admitted to the Fourth Affiliated Hospital of Anhui Medical University from October 2020 to October 2021 were selected. According to clinical guidelines, 30 patients with SAP were assigned to the SAP group, and 42 patients with MAP and MSAP were assigned to the control group. The patients' demographic information and characteristics data, including age, gender, AP etiology, Ranson score, white blood cell count, body mass index, and blood pressure, were collected. This study was reviewed and approved by the Ethics Committee of the Fourth Affiliated Hospital of Anhui Medical University. All subjects gave informed consent and signed a consent form.

2.2. Inclusion criteria

The inclusion criteria were as follow: The selected patients met the AP diagnostic criteria in the Chinese Guidelines for the Diagnosis and Treatment of Acute Pancreatitis[4]: patients were diagnosed AP by CT or abdominal ultrasonography, combined with abdominal pain symptoms, and the time from onset to admission was <24 hour. SAP patients should meet one of the following conditions: organ failure, pseudocyst, pancreatic abscess or necrosis, or modified CT severity index[14] in AP scores > = 7. The clinical data of all patients were complete. The age of patients ranged from 18 to 80 years.

2.3. Exclusion criteria

The exclusion criteria were as follows: Patients who died within 48 hours after admission at the hospital. Patients with related hematological diseases leading to neutrophil dysfunction. Patients with thyroid or parathyroid diseases. Patients with hepatitis cirrhosis, liver cancer, or abnormal liver function. Patients with malignant tumors. Patients with morbidity caused by trauma or surgical procedures.

2.4. Reagents and instruments

After emergency admission, the patients were divided into SAP and non-SAP groups according to the severity of the disease according to the diagnostic guidelines for AP. Blood samples were collected at emergency admission (within 24 h). Serum PTX-3, SIL-2R, CRP, and PCT were measured by enzyme-linked immunosorbent assay. PCT was measured on Roche e411 immunoassay analyzer (Roche Diagnostics). Serum PCR level was detected using AU680 automatic biochemical analyzer (Beckman Coulter, Brea, CA). For serum PTX-3 and SIL-2R levels, the kits were purchased from Suzhou Huayimei Biotechnology Co., Ltd.

2.5. APACHE II

APACHE II score consists of the acute physiology score, the patient's age, and chronic health status. Acute physiology score includes 12 physiological indicators, including body temperature, blood pressure, heart rate, etc, and the worst value within the first 24 hours after admission at the hospital shall be selected. Patients with chronic organ dysfunction or suppressed immune function have a chronic health status score (2 points for admission to intensive care unit after elective surgery or 5 points for admission to intensive care unit after emergency surgery or non-surgery). The highest theoretical value of the APACHE II score was 71 points, and the higher the score value, the more critical the patient's condition. The above scores were scored by the participation of relevant specialist medical staff. All the above operations were carried out strictly following the relevant operating standards.

2.6. Observation indicators

Serum PTX-3, SIL-2R, CRP, and PCT levels and APACHE II scores at admission were compared between ASP and non-ASP groups. The correlation between serum PTX- 3, SIL-2R, CRP, PCT levels, and APACHE II score were analyzed. The survival of patients within 28 days was counted and recorded, and they were divided into the death group and survival group according to the prognosis.

2.7. Statistical analysis

For all statistical analysis, the SPSS Statistics software (version 26.0; IBM, Chicago, IL) was utilized. The number of cases (%) was employed to characterize categorical variables, and a *Chi-square* test or *Fisher exact* probability method was used to analyze the difference. The mean standard deviation was calculated for all continuous variable data that followed the normal distribution. The quartile M (P_{25}, P_{75}) described non-normally distributed variables. Comparisons between multiple groups were performed by 1-way analysis of variance, pairwise comparisons were performed by *t* test, and correlation analysis was performed using Pearson correlation analysis. Mann–Whitney *U* test was performed for non-normally distributed variables. The receiver operating characteristic (ROC) analysis and area under curve (AUC) were performed. The Youden index of the ROC curve was calculated to determine the optimal diagnostic cutoff value. $P < .05$ was considered statistically significant.

3. Results

3.1. Demographic information and clinical data

The mean ages of the SAP group and the non-SAP group were 51.90 ± 10.27 (between 40 and 63) and 48.50 ± 9.91 (between 38 and 60) years, respectively. In the SAP group, 13 patients (43.3%) had biliary AP due to gallstone, 4 patients (13.3%) had alcoholic AP, and 5 patients (16.7%) had hyperlipidemic AP. There were significant differences in white blood cell count and Ranson scores between the SAP and non-SAP groups. Moreover, the SAP group had a higher mortality rate than the non-SAP group in 28 days (8 patients vs 0 patients), with a mortality rate of 11.1% in all AP patients cohort. The demographic and general clinical information of the patients is provided in Table 1.

Table 1

Demographic information and clinical data (mean ± SD, n).

Variables	SAP (n = 30)	Non-SAP (n = 42)	*P* value
Age, yrs	51.90 ± 10.27	48.50 ± 9.91	.081
Male, n (%)	13 (43.3)	20 (47.6)	.129
BMI, kg/m^2	20.91 ± 1.88	21.45 ± 2.03	.205
SBP, mm Hg	127.3 ± 5.66	127.77 ± 4.37	.687
DBP, mm Hg	87.30 ± 3.71	87.77 ± 4.12	.578
Etiology, n (%)			.947
Gallstone	13 (43.3)	16 (38.1)	
Hyperlipidemia	5 (16.7)	7 (16.7)	
Alcoholic	4 (13.3)	6 (14.3)	
Others	8 (26.7)	13 (30.9)	
WBC, $\times 10^9$	18.91 ± 1.86	13. 51 ± 1.49	.001
Ranson score	4.74 ± 0.69	1.56 ± 0.22	.001
Underlying medical conditions			
Hypertension, n (%)	8 (26.7)	12 (28.6)	.060
Diabetes mellitus, n (%)	6 (20.0)	8 (19.0)	.919
28-day mortality, n (%)	8 (26.7)	0 (0.0)	.002

BMI = body mass index, DBP = diastolic blood pressure, SAP = severe acute pancreatitis, SBP = systolic blood pressure, WBC = white blood cell.

3.2. Comparison of difference indicators

Both serum CRP and PCT levels of the SAP group and the non-SAP group were significantly different (CRP, $P = .001$; PCT, $P = .001$). In addition, the results demonstrated that the SAP group showed higher serum PTX-3 and SIL-2R levels than the non-SAP group (PTX-3, $P = .001$; SIL-2R, $P = .001$). The APACHE II score was higher in the SAP patients than non-SAP patients. The APAPCHE II score of each patient are listed in Table S1 (Supplemental Digital Content, http://links.lww.com/MD/H673). Table 2 presents the comparison of indicators between the SAP and the non-SAP group.

Of the patients with SAP, 8 patients died, and 22 patients survived within 28 days after admission at the hospital. The comparative analysis found that the serum CRP, PCT, PTX-3, and SIL-2R levels and APACHE II scores in the death group were higher than in the survival group, and the differences were significant (All $P < .05$). Table 3 shows the comparison of indicators between the death group and survival group in SAP patients.

3.3. Correlation analysis between laboratory-related parameters and APACHE II

Spearman correlation analysis demonstrated that serum CRP, PCT, PTX-3, and SIL-2R levels were positively correlated with APACHE II scores. The serum CRP level had the highest correlation with the APACHE II score among the laboratory-related parameters. The correlation coefficient was $r_s = 0.828$ ($P = .001$). Table 4 presents the correlation between laboratory-related parameters and APACHE II score.

Table 2

Comparison of indicators between SAP and non-SAP group (mean ± SD, M [P_{25}, P_{75}]).

Variable	SAP (n = 30)	Non-SAP (n = 42)	*P*
CRP, mg/L	106.90 ± 8.41	72.95 ± 7.07	.001
PCT, ng/mL	3.73 ± 0.84	2.38 ± 0.71	.001
PTX-3, ng/mL	15.34 ± 1.39	7.67 ± 1.39	.001
SIL-2R, pg/mL	53.39 ± 4.08	36.39 ± 4.62	.001
APACHE II score	12 (9, 15)	7 (4.25, 9)	.001

APACHE II = acute physiology and chronic health evaluation II, CRP = C-reactive protein, PCT = procalcitonin, PTX-3 = pentraxin 3, SAP = severe acute pancreatitis, SIL-2R = soluble interleukin-2 receptor.

Table 3

Comparison of indicators between death group and survival group in SAP patients (mean ± SD).

	Death group (n = 8)	Survival group (n = 22)	*P* value
CRP, mg/L	113.23 ± 7.03	104.60 ± 7.78	.001
PCT, ng/mL	4.38 ± 0.62	3.49 ± 0.78	.010
PTX-3, ng/mL	16.19 ± 2.84	13.47 ± 3.13	.032
SIL-2R, pg/mL	56.85 ± 3.08	51.97 ± 4.02	.004
APACHE II score	16.86 ± 2.1	10.55 ± 2.42	.001

APACHE II = acute physiology and chronic health evaluation II, CRP = C-reactive protein, PCT = procalcitonin, PTX-3 = pentraxin 3, SAP = severe acute pancreatitis, SIL-2R = soluble interleukin-2 receptor.

Table 4

Correlation of laboratory-related parameters and APACHE II.

Variables	r_s	*P* value
CRP	0.828	.001
PCT	0.794	.001
PTX-3	0.717	.001
SIL-2R	0.691	.001

CRP = C-reactive protein, PCT = procalcitonin, PTX-3 = pentraxin 3, SAP = severe acute pancreatitis, SIL-2R = soluble interleukin-2 receptor.

3.4. Predictive value of indicators on the prognosis of SAP patients

ROC curve analysis of CRP, PCT, PTX-3, SIL-2R, APACHE II score, and combined indicators (CRP + PCT + PTX-3 + SIL-2 R + AHAPHE II) for SAP prognosis is illustrated in Figure 1 and Table 5. Among the laboratory-related parameters, serum CRP levels showed the maximum AUC (0.766) and maximum sensitivity (81.8%), but its specificity (68.4%) was lower than that of PCT (72.3%). The results showed that APACHE II score combined with CRP, PCT, PTX-3, and SIL-2R reached the highest AUC (0.952). ROC curve showed that the optimal cutoff value of combined indicators for SAP prognosis was 0.33, providing a sensitivity of 90.9% and a specificity of 84.2% (Fig. 1).

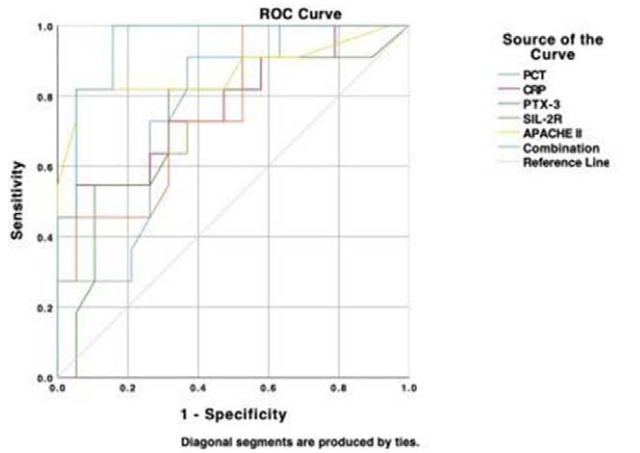

Figure 1. ROC curve of indicators for predicting the prognosis of patients with SAP (combination: CRP + PCT + PTX-3 + SIL-2R + APACHE II). APACHE II = acute physiology and chronic health evaluation II, CRP = C-reactive protein, PCT = procalcitonin, PTX-3 = serum pentraxin 3, ROC = receiver operating characteristic, SAP = severe acute pancreatitis, SIL-2R = soluble interleukin-2 receptor.

Table 5

Comparative analysis of the predictive value of single or combined indicators for SAP prognosis.

Variables	AUC	95% CI	Cutoff value	Sensitivity	Specificity	*P* value
CRP	0.775	0.593–0.957	108.80	0.818	0.684	.017
PCT	0.766	0.594–0.937	3.85	0.727	0.723	.013
PTX- 3	0.737	0.542–0.932	15.55	0.636	0.684	.033
SIL-2R	0.758	0.583–0.933	53.85	0.727	0.632	.020
APACHE II score	0.871	0.710–0.992	8.50	0.818	0.842	.001
Combination	0.952	0.991–0.997	0.33	0.909	0.842	.001

Combination: CRP + PCT + PTX-3 + SIL-2R + APACHE II.

APACHE II = acute physiology and chronic health evaluation II, CRP = C-reactive protein, PCT = procalcitonin, PTX-3 = pentraxin 3, SAP = severe acute pancreatitis, SIL-2R = soluble interleukin-2 receptor.

4. Discussion

SAP can lead to organ failure and induce systemic response syndrome, characterized by rapid onset, complex changes in the condition, and poor prognosis, with a mortality rate ranging from 15% to 30%.[15,16] Therefore, early diagnosis of SAP and more accurate prediction and evaluation of its severity are essential. Many laboratory-related markers have been used to diagnose and assess AP in recent years. As an inflammatory disease, the pathogenesis of AP is closely related to inflammatory mediators and inflammatory factors[17]; hence, the inflammation-related substances can be used as reference indicators.

This study demonstrates that serum CRP levels are higher in patients with SAP and in the death group. CRP reacts with the polymer of capsular C polysaccharide of Streptococcus pneumoniae, and the acute phase protein secreted by liver cells is directly involved in the body's inflammatory response.[18] Serum CRP levels are very low (<5 mg/L) in healthy physiological conditions and rise dramatically in bacterial infections or inflammatory injuries.[19] CRP is often used as a sensitive indicator for acute and chronic inflammation clinical diagnosis. Some studies have pointed out that the level of CRP is closely related to the severity of AP and its prognosis, and CRP can directly promote the inflammatory response of vascular endothelium.[20,21] Moreover, serum CRP reaching 150 mg/L within 48 hours is a marker of critical condition in AP.[22] Together with the above, there is some correlation between the mechanism of action of CRP and the pathogenesis of SAP, especially with regard to inflammatory mediators. The results of this study show that CRP levels can reflect the prognosis of SAP. The AUC of CRP is 0.775. When the CRP value is 108.80 mg/L, the sensitivity for predicting the prognosis of SAP is 81.8% and the specificity is 68.4%.

In this study, PCT measures were increased in patients with SAP compared with PCT levels in patients without SAP. PCT is a substance secreted by thyroid C-cells.[23] In a healthy physiological state, PCT is converted into calcitonin, so it is difficult to detect the concentration of PCT in healthy conditions (<0.1 ng/mL).[24] PCT can be significantly increased in the infected state, and its concentration may change very early compared with other cytokines and may be involved in the regulation of other cytokines.[25] The imbalance of intestinal bacteria caused by SAP may increase PCT levels.[26] The hypothesis has been confirmed by some scholars that PCT has a certain correlation with the severity of SAP.[27,28] Choudhuri AH et al[29] reported that AP patients might experience a significant increase in serum PCT levels and the serum PCT levels were positively correlated with mortality rate in AP patients. Our results show that PCT has the strongest specificity (72.3%) among the serological parameters.

PTX-3 is a nonspecific inflammatory factor.[30] Studies have pointed out that PTX-3 plays a significant role in evaluating the severity of sepsis and predicting the risk of prognosis and can be used as an independent predictor of systemic infectious diseases.[31,32] It has been reported that serum PTX-3 is positively correlated with CRP levels in septic patients.[32] At the same time, PTX-3 can affect cell membrane calcium channel opening and aggravate calcium load in pancreatic tissue.[33] This study shows that the serum PTX-3 levels in the SAP group are higher than that in the non-SAP group, while the serum PTX-3 levels in the death cases are higher than that in the surviving patients, suggesting that there is a certain correlation between the serum PTX-3 level and the severity of the disease in SAP patients. Spearman correlation analysis shows that serum PTX-3 levels are positively correlated with APACHE II scores ($P < .001$), demonstrating that the higher the serum PTX-3 level, the more severe the SAP condition.

SIL-2R is an immunosuppressive mediator released by monocytes and activated T cells, regulating interleukin-2/interleukin-2 receptor system function.[34] SIL-2R binds interleukin-2 competitively with the interleukin-2 receptor, reducing its secretion level to inhibit lymphocyte proliferation and decrease the immune response.[35] Elevated SIL-2R levels are accompanied mainly by decreased CD4 +/CD8 + levels, resulting in reduced immune function and weakened B cell function.[36,37] It has been shown that SIL-2R levels can be used to assess the immune function status of SAP patients, thereby further predicting disease changes.[13] Patients with SAP present early with an excessive inflammatory response. Increased serum SIL-2R levels can cause immune escape, reduce interleukin-2 expression, and lead to a massive release of inflammatory factors, leading to systemic organ function syndrome and threatening the life safety of patients.[38] This study revealed that the serum SIL-2R levels in the SAP group are higher than that in the non-SAP group at admission, while the serum SIL-2R level in the death cases was higher than that in the surviving group patients. Moreover, Spearman correlation analysis shows that serum SIL-2R levels are positively correlated with APACHE II scores ($P < .001$), suggesting that serum SIL-2R levels indicate SAP severity.

The APACHE II scoring is objective and comprehensive, not limited by spatial time, continuously and dynamically monitoring multiple organ involvement in SAP.[39] An APACHE II score of 8 and above was generally judged as SAP.[40] The results of relevant studies showed that the mortality rate of patients with APACHE II score >8 was much higher than that of patients with a score <8. In this study, APACHE II had the largest AUC (0.880) than the laboratory-related indicators in ROC analysis. APACHE II > 8.5 points indicates that the highest sensitivity of SAP is 81.8%, and the specificity is 84.2%. In this study, every indicator is relevant for the predictive assessment of prognosis in SAP, with the APACHE II having the most significant AUC and the highest sensitivity. The results show that APACHE II score combined with CRP, PCT, PTX-3, and SIL-2R reached the highest AUC, suggesting the best predicting effect for SAP prognosis. APACHE II score combined with serological indicators CRP, PCT, PTX-3, and SIL-2R provides a more accurate indicator in the early evaluation and prediction of SAP and a certain scientific basis for early clinical diagnosis and accurate assessment of SAP.

There are several limitations in this current study: Our research is a case-control study of AP patients. Given the nature of the retrospective study, the evident and inherent selection bias of this research methodology exists. Due to the limited sufficient data and information, we did not conduct an analysis or a comparison in the SAP, MAP, and MSAP patients regarding different severities

assessments. The sample size is limited, and we failed to stratify the patients by age to perform a sub-group analysis since age is a confounder in this study for the prognosis of SAP. Hence, future large-sample and multicenter studies are required to reduce the confounding effect of the result and demonstrate the advantages of the indicators in this study in the prognostic prediction of SAP.

5. Conclusions

To sum up, CRP, PCT, PTX-3, SIL-2R, and APACHE II can reflect the severity of AP and predict the prognosis of SAP. The APACHE II has the strongest predictive power, and CRP has the highest sensitivity among laboratory-related indicators. When CRP, PCT, PTX-3, and SIL-2R are combined with APACHE II, higher sensitivity and specificity in predicting the prognosis of SAP are found. Therefore, we can regard the combined indicators as a valuable predictive evaluation with great reference value and guiding significance for early disease evaluation, accurate diagnosis, and prognosis of SAP in clinical practice.

Author contributions

Conceptualization: Yang Bao.
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Investigation: Yang Bao.
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