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The predictive efficacy of dynamic level changes of plasma endothelial microparticles and plasma soluble thrombomodulin on the prognosis of severe acute pancreatitis

Hu Chen[1] and Xiao Yuan[2,3*]

Abstract

Objective To investigate the predictive efficacy of dynamic level changes of plasma endothelial microparticles (EMP) and plasma soluble thrombomodulin (sTM) on the prognosis of severe acute pancreatitis (SAP).

Methods This study retrospectively selected 128 eligible SAP patients admitted to our hospital from May 2021 to April 2023. According to the final outcome, the patients were grouped as the survival group ($n=95$) and death group ($n=33$). The EMP, sTM and microcirculation related indexes (lactic acid level, central venous pressure (CVP), mean arterial pressure (MAP)) of SAP patients were monitored at admission, 24 h, 48 h and 72 h after admission. Pearson was adopted to analyze the correlation between EMP and sTM levels with microcirculation disorder related indicators. The levels of EMP and sTM were compared between the survival group and the death group. The EMP high level group was ≥ 150.00 ng / mL, and the EMP low level group was < 150.00 ng / mL. The sTM high-level group was ≥ 300.00 ng / mL, and the low-level group was < 300.00 ng / mL. The differences in survival curves between different groups were compared by Kaplan-Meier. AUC was used to analyze the prognostic value of EMP and sTM levels alone and in combination in SAP patients.

Results Compared with admission, the levels of EMP, sTM, lactic acid and CVP in 128 SAP patients were all significantly increased at 24 h, 48 h and 72 h after admission, but the MAP was largely decreased ($p<0.05$). EMP and sTM were positively correlated with lactic acid and CVP respectively, but negatively correlated with MAP ($p<0.05$). The death group had much higher levels of EMP and sTM than the survival group ($p<0.05$). From the perspective of 1-year survival rate, the high-level group of EMP was lower than the low-level group ($p<0.05$) and the high-level group of sTM was lower than the low-level group ($p<0.05$). ROC curve analysis confirmed that the sensitivity and specificity of combined detection were 92.39% and 90.54%, respectively, with the AUC of 0.903 (95%CI:0.863–0.928), which was significantly higher than that of single detection ($p<0.05$).

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Conclusion The levels of EMP and sTM were significantly increased in SAP patients, which were closely related to microcirculation disorders and poor prognosis. The combined detection of EMP and sTM has significant prognostic value in SAP.

Keywords Acute pancreatitis, Dynamic monitoring, Endothelial microparticles, Microcirculation disorder, Prognosis, Soluble thrombomodulin

Introduction

As one of the common acute abdominal diseases in the emergency department, severe acute pancreatitis (SAP) has attracted much attention due to its high mortality rate and complex disease course [1]. SAP not only causes severe local inflammation in the pancreas, but also leads to systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndrome (MODS). Microcirculatory disorders are a key pathophysiological process in the progression of SAP to severe complications and even death [2]. Therefore, in-depth exploration of the pathogenesis and dynamic changes of SAP microcirculation disorders is of great significance for early identification of high-risk patients, optimization of treatment plans, and improvement of prognosis.

Endothelial Microparticles (EMP), as a small vesicle released during endothelial cell activation or apoptosis, is considered a sensitive indicator of vascular endothelial injury and dysfunction in terms of its level changes [3]. During the pathogenesis of SAP, vascular endothelial cells are severely damaged due to the release of a large amount of inflammatory factors and self-digestion of pancreatic tissue, further leading to a significant increase in EMP levels. EMP not only participates in the disruption of coagulation fibrinolysis balance, but also exacerbates microcirculatory disorders by promoting inflammatory responses, affecting vascular permeability, and other mechanisms [4]. Therefore, dynamic monitoring of EMP levels is expected to become a new means of evaluating the degree and prognosis of microcirculation disorders in SAP. On the other hand, plasma soluble thrombomodulin (sTM), as an important glycoprotein on the surface of endothelial cells, has multiple functions such as anticoagulation, anti-inflammatory, and protection of endothelial cells [5]. In SAP patients, a large amount of sTM is released into the bloodstream due to extensive damage to endothelial cells. The changes in sTM levels are closely related to the severity and prognosis of SAP [6].

At present, the prognosis evaluation of severe SAP mostly relies on traditional indicators and methods, but these methods have certain limitations and are difficult to achieve accurate prediction [6]. The innovation of this study is that it is the first time to combine the dynamic monitoring of plasma EMP and plasma sTM, two key indicators reflecting vascular endothelial injury. This study tried to construct a more comprehensive and accurate prognosis prediction model by analyzing their dynamic changes in different stages of the disease. We expect to provide clinicians with more targeted prognosis judgment basis and open up new ideas for individualized treatment of SAP, so as to improve the prognosis of patients more effectively. Based on this, the aim of this study is to explore the predictive value of plasma EMP and plasma sTM on the prognosis of SAP.

Materials and methods

General materials

A total of 130 SAP patients admitted to our hospital from May 2021 to April 2023 were chosen as the research subjects. The clinical data of these patients were collected for a retrospective study. To ensure the availability of blood samples, the quality of blood samples collected from patients at 24, 48, and 72 h after admission were promptly sent for testing, and stored under specified conditions to maintain sample stability. Patient data with complete records including blood sample collection and test results at each time point were screened through the medical record system, and were collected and tested by experienced medical staff. At the same time, laboratory equipment was regularly checked to ensure sample quality control. According to previous studies [6–7], after strict screening process, one patient had malignant tumor and another patient received specific anticoagulant therapy during the study, and 128 SAP patients who met the study requirements were finally included (Fig. 1). Inclusion criteria: (1) Patients met the diagnostic criteria for SAP in the revised *2012 Atlanta Classification Criteria* [7]. (2) The patient had microcirculatory disorders, including shock, hypotension, wet and cold hands and feet, fast pulse, wet and cold skin, respiratory failure, increased respiratory rate, hypoxia, elevated lactate levels, as well as symptoms such as reduced urine output, lower limb edema, and systemic edema caused by renal dysfunction. (3) The patient had complete clinical data and follow-up records. (4) All patients' medical records were collected and used in accordance with hospital regulations and complied with relevant privacy protection and ethical review requirements. Exclusion criteria: (1) Patients with malignant tumors, severe cardiovascular diseases, autoimmune diseases, etc.; (2) During the study, patients received treatments that might affect EMP and sTM levels, such as the use of specific anticoagulants, immunomodulators, etc.

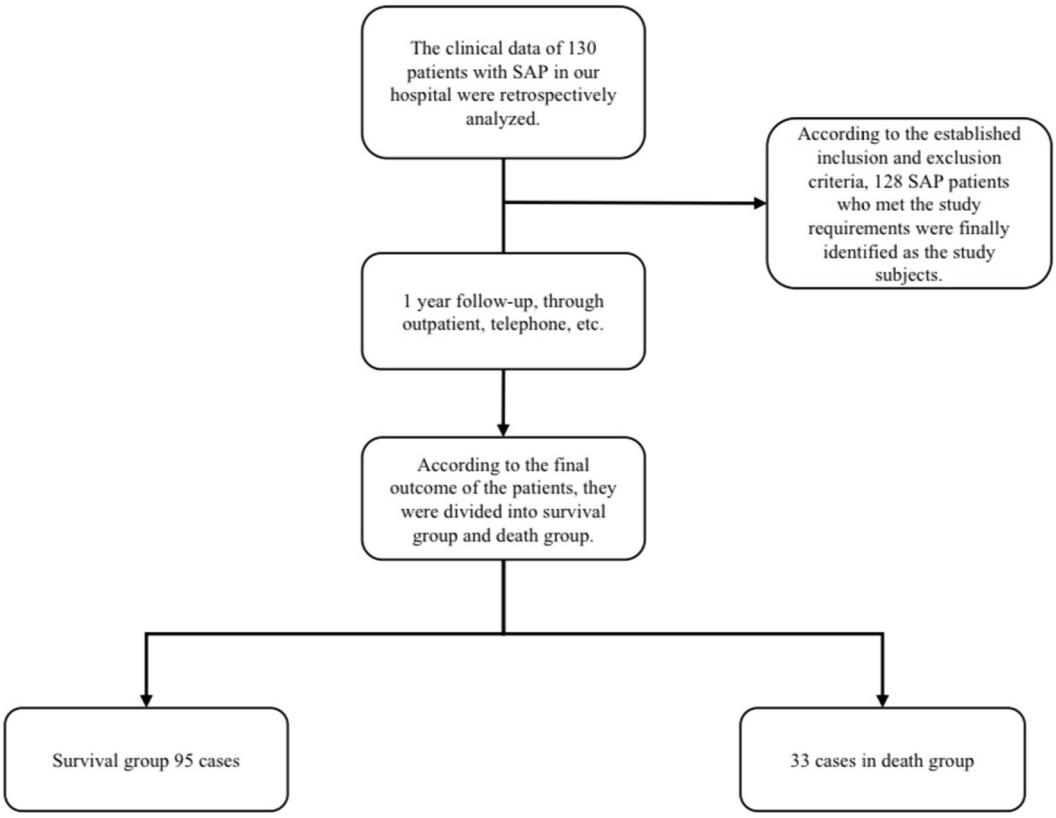

Fig. 1 Inclusion process for 128 SAP patients

Methods

Detection methods of EMP

Upon admission, 24 h, 48 h, and 72 h after admission, 5mL of median cubital vein blood was collected from SAP patients. After allowing the blood sample to stand at room temperature for 30 min, serum and plasma were separated using a centrifuge at a speed of 3000 r/min for 10 min. The plasma was divided into sterile EP tubes and immediately stored at -80 °C. During testing, the sample should be taken out and thawed, followed by pre-processing according to the standard operating procedures of flow cytometry, including antibody labeling and other steps. By using laser excitation fluorescence labeling with flow cytometry, the fluorescence signal intensity and scattered light characteristics were measured. Finally, the quantity or concentration of EMP was analyzed using supporting software.

Detection methods of sTM

Plasma samples were collected upon admission, 24 h, 48 h, and 72 h after admission. After thawing the sample from the − 80 °C freezer, the detection was conducted following the detailed instructions of the ELISA kit. The detection process was listed as follows: sample dilution, adding the sample to a pre-coated microplate with antibodies, incubate to form antigen antibody complexes, washing to remove unbound substances, adding enzyme-linked secondary antibody for incubation, adding substrate for color development after washing, and adding termination solution to terminate the reaction. The absorbance values of each well were measured using an enzyme-linked immunosorbent assay (ELISA) reader. The specific concentration of sTM in the plasma was calculated based on the standard curve provided by the reagent kit.

Detection methods for indicators related to microcirculation disorders

Blood samples were collected from SAP patients upon admission, 24 h, 48 h, and 72 h after admission, and immediately sent to the laboratory. According to the instructions of the lactate detection kit, the sample was processed and tested using a fully automated biochemical analyzer (Model: Roche Cobas c701). The instrument automatically completed sample analysis and directly provided the concentration value of lactic acid. After SAP patients received central venous catheterization, a pressure sensor (Brand: Edwards Lifesciences, Model: TruWave) was used to connect the central venous catheter to the monitoring device. The sensor was adjusted to zero point through non-invasive means, and then the central venous pressure (CVP) value was continuously

monitored and recorded. The non-invasive blood pressure cuff (Brand: Philips, Model: IntelliVue MX550) was tied to the patient's upper arm, and the parameters were set according to the operating instructions of the monitor. The instrument completed blood pressure measurement and calculated the mean arterial pressure (MAP) automatically. Central venous pressure values and MAP equipment were Mairuitong.

Follow-up

SAP patients would be followed up for 1 year through outpatient or telephone visits after discharged, once every 3 months, until April 2024. Survival status verification: The vital status of the patients was confirmed through the hospital information system, community health service centers, or family members. Consult death certificates or other official records when necessary. According to the final outcome of the patients, whether they were alive or not, the patients were divided into a survival group and a death group.

Outcome measures

The EMP, sTM and microcirculation related indexes (lactic acid level, CVP, MAP) of SAP patients at admission, 24 h, 48 h and 72 h after admission were compared. Pearson was adopted to analyze the correlation between EMP and sTM levels with microcirculation disorder related indicators (lactic acid level, CVP, MAP). The levels of EMP and sTM were compared between the survival group and the death group. Based on the previous research results and literature review [5–6], the patients were further grouped according to the thresholds of EMP and sTM level. The EMP ≥ 150.00 ng / mL was considered as the high level group, and EMP < 150.00 ng / mL was the low level group. sTM ≥ 300.00 ng/mL was the high-level group, and sTM < 300.00 ng/mL was the low-level group. The results of EMP and sTM at 72 h after admission were used to draw the survival curve, and the prognostic survival differences of different EMP and sTM levels groups were compared. The receiver operating characteristic (ROC) curve was drawn based on the detection results of EMP and sTM at 72 h after admission, and the AUC value under ROC was used to evaluate the effects of EMP and sTM levels alone and combined monitoring on the prognosis of SAP patients.

Statistical analysis

SPSS 26.0 statistical software was used for data processing and analysis. *Kolmogorov-Smirnov* test was used to test the normality of all measurement data. Measurement data conforming to normal distribution were shown as mean ± standard deviation ($\bar{X} \pm s$), and independent sample t-test was used for inter group comparison. Multiple time point comparisons were performed using repeated measures ANOVA. Enumeration data were expressed using frequency and percentage, and chi square test was used for inter group comparison. Pearson was used for correlation analysis. Kaplan-Meier survival curves were plotted, and log rank tests were used to compare the differences in survival curves between groups. The prognostic value was evaluated using AUC under ROC. DeLong method was used to compare the AUC values of different indicators alone and in combination. All differences were statistically significant with $P < 0.05$

Results

EMP, sTM and microcirculation related indicators of SAP patients at admission 24 h, 48 h, and 72 h after admission

Among the 128 SAP patients, there were 74 males and 54 females, with an age range of 28–76 years (52.37 ± 12.70 years), and a BMI of 18–24 kg/m^2 (23.65 ± 3.84 kg/m^2). Compared with admission, patients had highly increased EMP, sTM, lactate and CVP, and decreased MAP at 24 h, 48 h, and 72 h after admission ($P < 0.001$, Table 1).

The correlation between EMP, sTM and indicators related to microcirculation disorders

EMP and sTM were positively correlated with lactate and CVP, while negatively correlated with MAP ($P < 0.05$, Table 2).

Table 1 EMP, sTM, and microcirculation related indicators of SAP patients at admission, 24 h, 48 h, and 72 h after admission (± *s*)

Time	*n*	EMP (ng/mL)	sTM (ng/mL)	Lactic acid (mmol/L)	CVP (cmH2O)	MAP (mmHg)
At admission	128	120.56 ± 15.63	156.33 ± 17.20	2.56 ± 0.74	10.43 ± 2.56	70.52 ± 7.53
24 h after admission	128	154.22 ± 17.15[a]	188.24 ± 18.61[a]	3.36 ± 1.25[a]	12.89 ± 3.37[a]	64.30 ± 6.77[a]
48 h after admission	128	186.09 ± 18.35[ab]	226.77 ± 20.78[ab]	3.97 ± 1.70[ab]	14.85 ± 3.84[ab]	60.08 ± 6.25[ab]
72 h after admission	128	207.88 ± 20.42[abc]	259.37 ± 21.44[abc]	4.60 ± 2.27[abc]	17.25 ± 4.31[abc]	53.74 ± 5.38[abc]
P	-	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
Cohen's d	-	1.89	1.92	1.23	1.76	1.81
Eta squared (η^2)	-	0.62	0.64	0.45	0.58	0.60

Note: [a]*P*<0.05 compared with at admission; [b]*P*<0.05 compared with 24 h after admission; [c]*P*<0.05 compared with 48 h after admission

Cohen's d was used to compare the difference of means between each time point and admission, and Eta squared (η^2) was used to assess the proportion of variance explained by the overall time effect. Cohen's d effect size interpretation: 0.2 for small effect, 0.5 for medium effect, 0.8 for large effect. Eta squared (η^2) effect size interpretation: 0.01 was small effect, 0.06 was medium effect, and 0.14 was large effect

Table 2 The correlation between EMP, sTM and indicators related to microcirculation disorders

Indicators	EMP		sTM	
	r	*P*	*r*	*P*
Lactate	0.682	< 0.001	0.559	0.002
CVP	0.426	0.017	0.596	< 0.001
MAP	-0.517	0.003	-0.458	0.011

EMP and sTM levels in the survival and death groups

Among 128 SAP patients, there were 95 cases in the survival group and 33 cases in the death group. The levels of EMP and sTM in the death group were much higher than those in the survival group, and the confidence intervals did not overlap ($P < 0.05$, Table 3).

Comparison of prognosis and survival among different EMP and sTM level groups

These 128 SAP patients were divided into a high EMP group of 79 cases and a low EMP group of 49 cases; There were 68 cases in the sTM high-level group and 60 cases in the sTM low-level group. The one-year survival rate of the EMP high-level group was 62.02% (49/79), which was lower than 93.87% (46/49) of the EMP low-level group ($\chi^2 = 16.035$, $P < 0.05$). The one-year survival rate of the sTM high-level group was 60.29%(41/68), which was lower than 90.00% (54/60) of the sTM low-level group ($\chi^2 = 14.700$, $P < 0.05$, Figs. 2 and 3).

The evaluation value of EMP and sTM alone and in combination for monitoring the prognosis of SAP patients

According to the ROC curve, the sensitivity and specificity of EMP in a single detection were 71.53% and 70.05%, respectively, with an AUC of 0.693 (95% CI: 0.572–0.744). The sensitivity and specificity of sTM were 69.65% and 68.22%, respectively, with AUC = 0.682 (95% CI: 0.566–0.738). The sensitivity and specificity of combined EMP and sTM for predicting the prognosis of SAP patients were 92.39% and 90.54%, respectively, with AUC = 0.903 (95% CI: 0.863–0.928), which was much higher than the single detection of both indicator ($P < 0.05$, Table 4; Fig. 4).

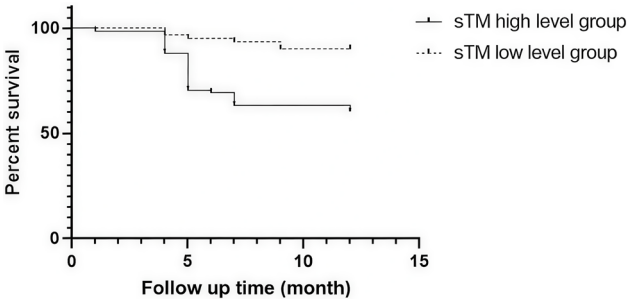

Fig. 2 Progression-free survival (PFS) curves of EMP high and low level groups

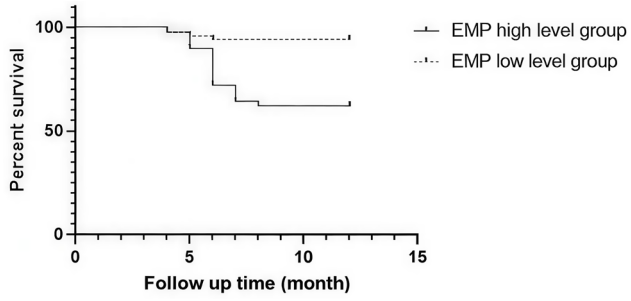

Fig. 3 PFS survival curves of sTM high and low level groups

Table 4 The evaluation value of EMP and sTM alone and in combination for monitoring the prognosis of SAP patients

Indicators	AUC	95% CI	Sensitivity (%)	Specificity (%)	*P* value
EMP	0.693	0.572–0.744	71.53	70.05	< 0.001
sTM	0.682	0.566–0.738	69.65	68.22	< 0.001
Combined detection	0.903	0.863–0.928	92.39	90.54	< 0.001

Discussion

The pathogenesis of SAP is complex, mainly involving multiple aspects such as pancreatic self-digestion, inflammatory response, microcirculation disorders, etc. Among them, microcirculation disorders refer to the dysfunction of the microcirculation system in the pancreas and its surrounding tissues, which is an important pathophysiological change in the pathogenesis of SAP and an

Table 3 EMP and sTM levels in the survival and death groups ($\pm s$)

Groups	*n*	EMP (ng/mL)	95% CI for EMP	sTM (ng/mL)	95% CI for sTM
The survival group	95	114.20 ± 15.83	(110.92- 117.48)	200.53 ± 19.39	(196.62-204.44)
The death group	33	174.23 ± 18.05	(167.87- 180.59)	401.63 ± 25.74	(392.45, 410.81)
t	-	18.090	-	46.980	-
P	-	< 0.001	-	< 0.001	-

Note: EMP and sTM levels in the table are presented as mean ± standard deviation ($\bar{X} \pm s$). Independent sample t test was used for comparison between the survival group and the death group. The t test is suitable for comparing the difference in means between two independent sample populations, so the t test was chosen as the statistical method when comparing EMP and sTM levels between the survival group and the death group. In this study, Table 1 involved the repeated measurement data at different time points, so the repeated measurement ANOVA was used for analysis, while the data in Table 3 are the measurement data of two groups of independent samples, so the independent sample t-test was used. Confidence intervals were calculated using the 95% confidence level as follows: mean ± 1.96 × standard error (SE). Standard error (SE) = standard deviation (SD) /√n, where n was the sample size

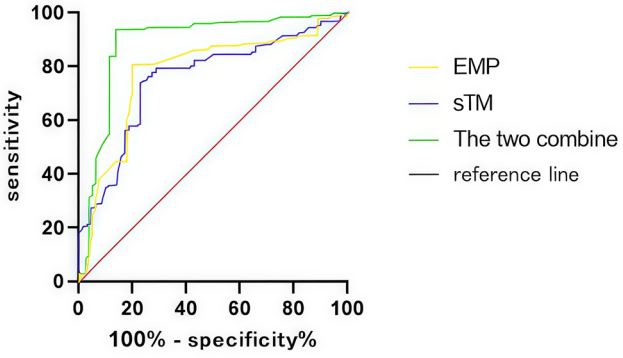

Fig. 4 ROC curves of the evaluation value of EMP and sTM alone and in combination for monitoring the prognosis of SAP patients

important cause of worsening of the condition [8]. Therefore, dynamic monitoring of the process of SAP microcirculation disorders is of great significance for its disease development and outcome. EMP is a small membranous vesicle released by endothelial cells during stress, injury, or apoptosis, rich in various bioactive molecules such as adhesion molecules, cytokines, etc [9]. At present, foreign studies have found increased level of EMP in many diseases, such as cardiovascular diseases, diabetes, inflammatory diseases. Increased EMP is closely related to disease severity and prognosis [10]. In recent years, there has been an increasing amount of research on the changes in EMP levels in SAP patients. There are studies showed higher plasma EMP levels in SAP patients than the healthy control group, and higher plasma EMP levels are positively correlated with the severity of the disease [11]. sTM is a glycoprotein synthesized by endothelial cells, which has multiple functions such as anticoagulant, anti-inflammatory, and endothelial protection. A study has found that plasma sTM levels in SAP patients significantly increase in the early stages and are positively correlated with the severity of the condition and mortality rate [12].

A sample size of 128 patients was selected for this study based on two considerations: First, the study aimed to evaluate the predictive role of plasma EMP and plasma sTM on the prognosis of SAP. A sufficient sample size was needed to cover different conditions, treatment response and prognosis to ensure that the study results were broadly representative and reliable. Insufficient sample size may lead to study bias, which cannot accurately reflect the actual performance of the study factors in multiple samples. Second, the study population was limited to patients admitted to our hospital during a specific period and screened according to strict inclusion and exclusion criteria. The inclusion criteria were the diagnostic criteria for SAP in the revised *2012 Atlanta Classification Criteria* [7], and microcirculation disorders and complete clinical data were required. The exclusion criteria were designed to eliminate disease and treatment factors that could affect the results, ensuring the homogeneity of the study subjects and the completeness of the data. Based on this screening, a sample size of 128 cases was finally determined, which not only met the needs of statistical analysis, but also met the actual research conditions, and provided a scientific and effective basis for subsequent analysis.

This study dynamically monitored EMP, sTM, lactate, CVP, and MAP of SAP patients at admission, 24 h, 48 h, and 72 h after admission. The results showed that EMP, sTM, lactate and CVP all significantly increased, while MAP showed a decreasing trend as time went on. Compared with previous studies [13], our present study has conducted more in-depth exploration in the following aspects: (1) This study focused on the changes in EMP and sTM levels and analyzed the potential association between them and microcirculation disorders in SAP. Although the specific mechanism of its action in microcirculation disturbance in SAP has not been deeply explored, it provides a possible direction for follow-up research. (2) Compared to previous single time point detection, this study provided a more comprehensive reflection of the changes in biomarker levels in SAP patients through dynamic monitoring at multiple time points. (3) Comprehensive evaluation system: This study not only focused on EMP and sTM, but also monitored key physiological parameters such as lactate, CVP, and MAP. In addition, this study also found that EMP and sTM were positively correlated with lactate and CVP, while negatively correlated with MAP, further verifying the important role of EMP and sTM in SAP microcirculation disorders and providing new evidence for SAP disease assessment and prognosis judgment.

There are complex underlying mechanisms behind the above correlations in the pathophysiology of SAP. (1) During SAP, pancreatic tissue autolysis and the release of inflammatory factors cause vascular endothelial injury, leading to increased EMP release. Inflammatory response can stimulate endothelial cells to produce and release EMP [14]. EMP elevation activates inflammatory cells and the coagulation system, promotes microthrombosis, affects blood flow, and leads to tissue hypoxia and lactic acid accumulation [14]. On the other hand, microcirculation disorders reduce the amount of blood returned to the heart, and the heart increases myocardial contractility to maintain circulation, resulting in an increase in central venous pressure [14]. Microthrombosis and increased vascular resistance increased cardiac ejection resistance and decreased mean arterial pressure, thus showing a positive correlation between EMP and lactate, central venous pressure, and a negative correlation between EMP and mean arterial pressure. For example, in the simulated pathological state of SAP, with the increase of

EMP level, the hemorheological indicators changed, and the microthrombosis increased significantly. At the same time, tissue lactate levels increased significantly, central venous pressure increased, and mean arterial pressure decreased, further confirming the key role of EMP in this process [15]. (2) Correlation mechanism of sTM with lactate, central venous pressure and mean arterial pressure: As a glycoprotein on the surface of endothelial cells, sTM participates in coagulation equilibrium in the physiological state. In SAP, endothelial injury leads to increased release of sTM, and the increase in its level reflects the degree of endothelial injury [16]. Endothelial injury results in decreased vascular barrier function, increased vascular permeability, decreased effective circulating blood volume, and increased central venous pressure in order to maintain blood pressure. Microcirculation disorders and insufficient blood volume aggravate tissue perfusion, enhance anaerobic metabolism, and increase lactate production.

Changes in blood volume and vascular resistance also affect mean arterial pressure. According to the previous study [17], sTM levels were detected to be closely related to endothelial injury markers in SAP patients. In addition, with the increase of sTM level, the patient's microcirculation perfusion indicators deteriorated, the lactate level continued to rise, the central venous pressure increased, and the mean arterial pressure decreased, revealing the close internal relationship between sTM and physiological parameters. EMP, as a biomarker of endothelial cell damage, its elevation reflects extensive microvascular damage and inflammatory response in SAP patients. High levels of EMP not only exacerbate pancreatic tissue damage, but also promote the occurrence and development of SIRS and MODS, thereby affecting the prognosis of SAP patients [16]. On the other hand, increased sTM in SAP patients usually indicates abnormal activation of the coagulation system and impaired endothelial cell function. This study not only observed the overall trend of changes in EMP and sTM in SAP patients, but also further refined the patient grouping into high-risk mortality group and low-risk survival group. Thus, we could more accurately evaluate the differences in EMP and sTM in different prognostic groups, thereby enhancing the clinical practicality and pertinence of the research results.

Unlike previous studies that focused more on short-term prognosis or in-hospital mortality [17], this study specifically focused on the impact of EMP and sTM levels on the 1-year survival rate of SAP patients. The results confirmed that in SAP patients, the EMP and sTM levels in the death group were much higher than those in the survival group, and the 1-year survival rate of patients with high EMP and sTM levels was significantly lower than that of patients with low EMP and sTM levels. Therefore, this study will provide new insights into the value of EMP and sTM in predicting long-term survival in SAP patients, which is of great significance for developing long-term follow-up and treatment strategies. Consistent with multiple studies abroad [18–19], this study further confirmed the value of EMP and sTM in the prognostic evaluation of SAP. However, our present study had a longer follow-up time and a more detailed analysis of the relationship between changes in EMP and sTM levels with the survival of SAP patients, providing a new perspective for understanding the pathophysiological mechanisms of SAP. The significantly increased EMP and sTM levels reflect the complex pathophysiological processes in SAP patients, including microvascular injury, inflammatory response, coagulation system activation, etc. These processes interact with each other and jointly promote the deterioration of SAP [18]. High levels of EMP not only exacerbate damage to pancreatic tissue, but also promote systemic inflammatory response and coagulation abnormalities. As a regulatory factor of coagulation and inflammatory response, the increase in sTM content further exacerbates the abnormal activation of the coagulation system, increasing the risk of thrombosis and organ damage [19].

APACHE II score is a comprehensive scoring system widely used in the prognosis evaluation of critically ill patients, but its calculation is complex and depends on multiple clinical and laboratory indicators [19]. BISAP is a simplified scoring system specifically designed to predict the risk of death in patients with SAP. Although the BISAP score is easy to apply in the clinic, its predictive ability may be limited in complex cases [19]. Compared with the existing scoring systems, the advantage of EMP and sTM lies in their biomarker characteristics, which can directly reflect the pathological process of endothelial injury and coagulation dysfunction, making them unique clinical value in early warning, dynamic monitoring and personalized treatment. In addition, our present study combined EMP and sTM to monitor the prognosis of SAP patients and found that the sensitivity, specificity, and AUC of the combined detection of SAP patients were much higher than those of single detection. The innovation of this study lies in the first joint application of EMP and sTM in the prognostic evaluation of SAP, and the related verification about the accuracy and reliability [20].

In summary, the levels of EMP and sTM were significantly elevated in SAP patients, which were closely related to microcirculation disorders and poor prognosis. Besides, the combined detection had important value in the prognostic evaluation of SAP. There were several limitations in this study. First of all, the sample size of the study was only from a specific medical environment and patient population, which may be relatively limited, leading to certain limitations and biases in the

study results. Therefore, it should be carefully considered when generalizing to a wider patient population. Secondly, although this study carried out dynamic monitoring at multiple time points, the monitoring time span was relatively short, and there was still a lack of sufficient research on the changes of EMP and sTM levels in the long-term development of the disease and their effects on the long-term prognosis of patients. In addition, this study only focused on EMP, sTM and some key physiological parameters, and did not deeply explore other factors that may affect the prognosis of SAP, such as gene polymorphism and intestinal microbiota, which may miss some important information. In addition, potential confounding factors may affect the results of the study. In terms of treatment strategies, there may be differences in treatment protocols between different physicians, such as the timing, speed and amount of fluid resuscitation, as well as the selection of vasoactive drugs and antibiotics, etc. Different treatment strategies will interfere with the changes of EMP, sTM levels and other physiological parameters, thereby affecting the prognosis of SAP. However, this study did not strictly control and analyze the consistency of treatment strategies. At the same time, the changes of patients' comorbidities are also factors that cannot be ignored. The metabolism and inflammatory state of SAP patients with cardiovascular disease, diabetes and other chronic diseases are different from those of patients without comorbidities, which may lead to different change trends of EMP and sTM levels. However, the potential confounding factor of comorbidities was not fully considered in the analysis process of this study, which affects the accuracy and universality of the research results to a certain extent.

Our future study will focus on the intervention experiments to further confirm the relationship between EMP, sTM and SAP progression. For example, reducing the levels of EMP and sTM by drugs or other means, to observe the effect on microcirculation function and patient prognosis. The reduced levels of EMP and sTM may improve microcirculation disorders, alleviate tissue hypoxia, and improve the survival rate of patients. They may serve as new targets and theoretical basis for the treatment of SAP.

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Author contributions
Hu Chen confirmed the authenticity of all the raw data and edited the manuscript, Xiao Yuan collected data and processed the data. Hu Chen and Xiao Yuan conducted the statistics.Xiao Yuan reviewed and revised the article. All authors read and approved the final manuscript.

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

Declarations

Ethics approval and consent to participate
All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was approved by The Ethics Committee of The First Affiliated Hospital of Anhui Medical University. Informed consent was obtained from participants for the participation in the study and all methods were carried out in accordance with relevant guidelines and regulations.

Consent to participate
The patients participating in the study all agree to publish the research results.

Consent for publication
Not Applicable.

Competing interests
The authors declare no competing interests.

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