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ORIGINAL ARTICLE

Superoxide Dismutase Predicts Persistent Circulation Failure and Mortality in the Early Stage of Acute Pancreatitis

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Abstract

Objectives Oxidative stress is an important event in the pathogenesis of acute pancreatitis. Superoxide dismutase is a major antioxidant enzyme in the body. The aim of this study was to investigate the changes in superoxide dismutase activity early in the onset of acute pancreatitis and its value in predicting the risk of organ failure and mortality.

Methods Data for 2549 patients hospitalized from 2013 to 2017 were extracted from the prospective database, and we selected 854 adult patients who were admitted within 24 h of disease onset with complete data. Serum superoxide dismutase activities on the first, second, and third days of hospital admission for patients with different severities, organ failure, and mortality were compared. The areas under the curve for the prediction of organ failure, pancreatic necrosis, and mortality were estimated using receiver operating characteristic curves.

Results Among the 854 adult patients, superoxide dismutase activities were significantly different among patients with mild acute pancreatitis, moderately severe acute pancreatitis, and severe acute pancreatitis ($P=0.005$). Superoxide dismutase activity was significantly decreased in patients with persistent renal failure (77.8 ± 37.2), persistent circulatory failure (66.2 ± 14.9), and mortality (64.3 ± 16.0). The accuracy of superoxide dismutase with regard to predicting persistent circulatory failure and mortality was high, and the areas under the receiver operating characteristic curves were 0.83 and 0.84, respectively.

Conclusions Superoxide dismutase activity was negatively correlated with the severity and clinical outcome of AP. Superoxide dismutase activity is highly accurate at predicting persistent circulation failure and mortality in the early stage of AP.

Keywords Acute pancreatitis · Superoxide dismutase · Persistent circulation failure · Mortality

Introduction

Acute pancreatitis (AP) is an inflammatory reaction to pancreatic tissue self-digestion and is characterized by edema, hemorrhage, and even necrosis caused by various mechanisms. Sanfey et al. [1] first proposed that oxygen free radicals play an important role in the pathogenesis of AP. In 1995, Kishimoto et al. [2] found that pancreatic tissue from rats with AP produced superoxide free radicals 2–3 h after AP, which proved that AP involved oxidative stress. Many have found that oxidative stress exists in the course of AP, and oxidative stress plays a key role in pancreatic injury and local and systemic complications [3–6]. Reactive oxygen species (ROS) are produced in large quantities during the pathogenesis of AP, and oxidative stress occurs when the body's antioxidant system is unbalanced. In the early stage of AP, due to the failure of the body's antioxidant system, high levels of ROS resulted in damaged capillary endothelial cells, increased vascular permeability, and an aggravated pancreatic microcirculation barrier [7]. Yu [6] showed that ROS can activate the signaling pathways involved in inflammatory responses, promote inflammatory cell aggregation and tissue damage, and increase the severity of the AP course. Oxidative stress is associated with inflammatory processes and AP severity.

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The body's antioxidant system consists of antioxidant enzymes and non-enzymatic antioxidants. Superoxide dismutase (SOD), which is present in the mitochondria or cytoplasm of cells, is the main ROS scavenger in the body. Studies have found that the total antioxidant level in the serum in patients with mild AP (MAP) is significantly reduced [8]. Park et al. [9] reported that patients with severe AP (SAP) had lower SOD activity than MAP patients, and their plasma levels of lipid peroxide and myeloperoxidase were higher than those in MAP patients. Modzelewski et al. [10] found that with improvement in AP, inflammation subsided, and serum SOD and other antioxidant enzyme activities increased. Therefore, we hypothesized that the serum SOD level can be used to dynamically monitor the evolution of AP.

To date, most studies have shown that oxidative stress plays an important role in the pathogenesis of AP [11, 12]. However, there are few studies on the changes in serum SOD activity in the early stage of AP of different severities, and most of these reports were animal studies [13, 14]. A clinical study examined the dynamic changes in SOD during the onset of pancreatitis, but the sample size was small, and the relationship between SOD activity and clinical prognosis in early AP was not determined [15]. At present, there are many biological indicators and scoring systems for predicting AP prognosis [16]. However, the value of the early antioxidant enzyme SOD in predicting organ failure and mortality in AP is still unclear. Therefore, based on prospectively collected AP data, we investigated the changes in SOD activity levels in the early stage of AP, the association with organ failure and mortality, and the predictive value for clinical outcomes.

Methods

Patient Data

This was a large cross-sectional study with patient data from the AP database of the First Affiliated Hospital of Nanchang University, which prospectively collected AP hospitalization data, which was approved by the ethics committee (database approval number: 2011001).We used data from AP patients admitted to the First Affiliated Hospital of Nanchang University from January 1, 2013, to December 31, 2017. Patients younger than 18 years or older than 75 years were excluded from the study, as were those with incomplete data or those admitted more than 24 h after the onset of the disease. Patient demographics and clinical data, including age, sex, etiology, complications, the severity of AP during hospitalization, and death, were collected. Acute Physiology and Chronic Health Evaluation II (APACHE II) scores, Ranson scores, and CT severity index (CTSI) scores were calculated based on patient data.

Diagnosis and Definition

The diagnosis of AP was based on the 2012 revised Atlanta classification criteria [17]. AP severity was classified into MAP, moderately severe AP (MSAP), and SAP according to the 2012 revision of the Atlanta Acute Pancreatitis Diagnostic and Classification Criteria [17]. Organ failure was determined using the modified Marshall Scoring System [17]. Contrast-enhanced computed tomography (CECT) pancreatic necrosis was indicated by diffuse enlargement of the pancreatic or peripancreatic volume, blurred edges, mild enhancement of the edema area after enhanced scanning, and no enhancement of necrotic areas. Mortality rate refers to death during hospitalization. The specific definition is shown in Supplementary Table 1.

SOD Detection

Blood samples obtained from patients at the time of admission (24 h) and the following two days (48 h and 72 h) were tested in our laboratory; we assessed the complete blood count, SOD activity, bilirubin level, C-reactive protein (CRP) level and serum activities of procalcitonin, amylase, lactate dehydrogenase, and aspartate and alanine aminotransferase. The detection of serum SOD activity was performed with a Hitachi 7600 Automatic Biochemical Analyzer (produced in: Chiyoda-ku, Tokyo, Japan). The SOD detection kit (the main component of the reagent is composed of pyrogallol and phosphate buffer) was provided by the Fujian Fuyuan Biotechnology Corporation. The SOD kit was used for the colorimetric analysis. The SOD reference values provided by the manufacturer ranged from 129 U/ml to 216 U/ml.

Statistical Analysis

Continuous data are expressed as the means (standard deviation [SD]) or the medians and interquartile range (IQR). Student's t test was used to compare the means, and multiple groups were compared using one-way ANOVA. For categorical variables, the Chi-square test was used; when the number of observations was fewer than 5, Fisher's exact test was used. The Spearman test was used for nonparametric correlation analysis. ROC curves were used to analyze the predictive value of each index for the clinical prognosis of AP, and the optimal diagnostic threshold was determined by the Youden index method. The difference was statistically significant at $P < 0.05$.

Results

Patient Characteristics

A total of 2549 AP patients were admitted to the First Affiliated Hospital of Nanchang University from January 1, 2013, to December 31, 2017. After the exclusion criteria were applied, 854 eligible AP patients were eventually included (Fig. 1); the population included 514 males (60.2%), and 300 patients (35.1%) had MAP, 387 (45.3%) had MSAP, and 167 (19.6%) had SAP. The causes of disease included biliary causes (55%), hyperlipidemia (29.2%), alcohol (8.4%), idiopathic pancreatitis (4.2%), and other causes (2.5%). There were 145 patients with persistent respiratory failure, 44 patients with persistent renal failure, and 10 patients with persistent circulatory failure, and 8 patients died during hospitalization. Table 1 shows the basic clinical features and clinical outcomes of the AP patients.

SOD Activity Level

Our study found that plasma SOD activity decreased in patients with different levels of AP severity. Compared with MAP (97.75 [SD, 26.81]) and MSAP (95.61 [SD, 27.92]) patients, SAP patients had the lowest serum SOD level (88.96 [SD, 31.12]). Simultaneously, significant differences in plasma SOD activity were detected in the MAP, MSAP, and SAP groups ($P=0.005$). The plasma SOD activity not only decreased with the increase in AP severity but also decreased with the prolongation of time. In AP patients with different severities, the average value of SOD activity decreased the most on the third day (Fig. 2). The SOD decline rates from 24 to 48 h were similar in all three groups. In the 48- to 72-h period, the SOD decline rate in MSAP patients was faster than that in patients with MAP, and the SOD activity of patients with different severity was lower at 72 h than at 48 h; the serum SOD level of patients with SAP was still the lowest (74.81 [SD, 27.38]) (Supplementary Table 2).

There was a difference in plasma SOD activity in patients based on organ failure status. Compared to those with no circulatory failure, patients with persistent circulatory failure had significantly lower SOD levels [(94.1 [SD, 28.2])

Table 1 Baseline characteristics of the patients

Characteristic	$n=854$
Age, median (IQR), y	50 (40–63)
Sex, male, *n* (%)	514 (60.2)
Cause of pancreatitis, *n* (%)	
Biliary	470 (55)
Alcohol abuse	72 (8.4)
Hypertriglyceridemia	255 (29.9)
Idiopathic	36 (4.2)
Other cause	21 (2.5)
Severity *n* (%)	
MAP	300 (35.1)
MSAP	387 (45.3)
SAP	167 (19.6)
Organ failure *n* (%)	
Persistent respiratory failure	145 (17)
Persistent renal failure	44 (5.2)
Persistent circulatory failure	10 (1.2)
Mortality (%)	8 (1)
Length of hospital stay, median (IQR), *d*	8 (6–8)
APACHE II score, median (IQR)	6 (4–8)
Ranson score, median (IQR)	2 (1–3)
CTSI score, median (IQR)	3 (2–4)

APACHE II acute physiology and chronic health evaluation II, *CTSI* Balthazar CT severity index, *IQR* interquartile range

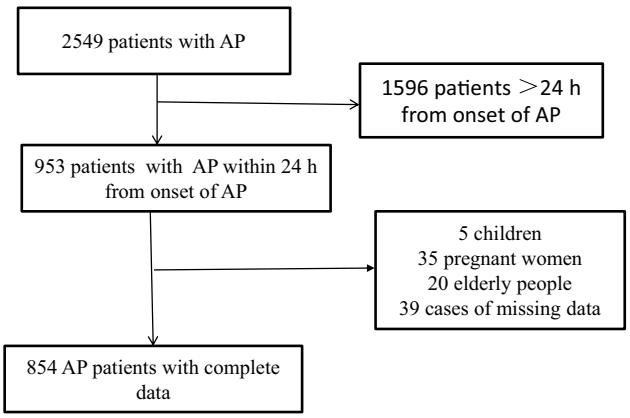

Fig. 1 Study flow chart

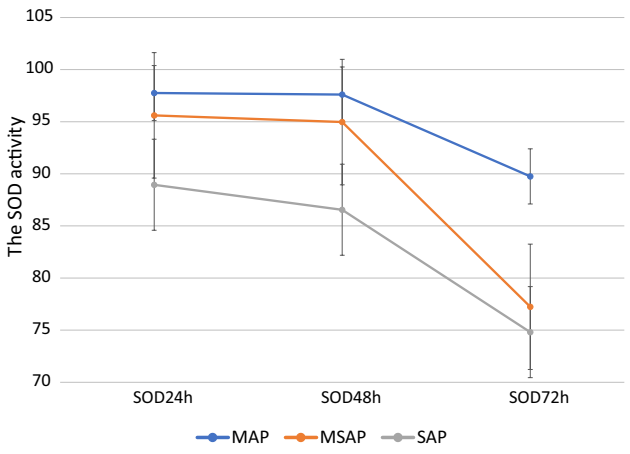

Fig. 2 The SOD activity levels in patients with different severities within 72 h. Blue: MAP, red: MSAP, gray: SAP

vs (66.2 [SD, 14.9]), $P < 0.001$]. Plasma SOD activity in patients with persistent renal failure was significantly lower than that in patients without renal failure [(77.8 [SD, 37.2]) vs (94.6 [SD, 27.5]), $P < 0.001$]. Plasma SOD levels were also reduced in patients with persistent respiratory failure compared to patients without persistent respiratory failure [(94.6 [SD, 27.5]) vs (90.32 [SD, 31.5]), $P = 0.026$]. The SOD level in patients with pancreatic necrosis was significantly lower than that in patients without pancreatic necrosis [(87.0 [SD, 27.5]) vs (94.4 [SD, 27.3]), $P < 0.001$]. The SOD level in surviving patients was lower than that in non-surviving patients [(64.3 [SD, 16.0]) vs (94.0 [SD, 28.2]), $P < 0.001$] (Table 2).

Our subgroup analysis further compared the level of SOD activity in patients diagnosed with SAP within 48 h of onset and in those in whom SAP developed after 48 h. The results showed that there was no significant difference in SOD activity between the two groups. Similarly, in the comparison of different types of organ failure, we found that the level of SOD activity was not significantly different between patients with organ failure within 48 h and after 48 h (Supplementary Table 3).

Correlations Among SOD Activity and Severity, Organ Failure, and Mortality

We explored the associations among SOD activity, organ failure, and mortality. Spearman correlation analysis showed that SOD activity was significantly negatively correlated with AP severity, pancreatic necrosis, persistent respiratory failure, persistent renal failure, persistent circulatory failure, and mortality (Supplementary Table 4).

SOD Activity Predicts Organ Failure, Pancreatic Necrosis, and Mortality

SOD activity was highly accurate at predicting persistent circulatory failure and mortality. When the SOD activity cutoff was 76.5, the AUC for the prediction of continuous circulatory failure was 0.83 (95%CI, 0.74–0.92). The sensitivity, specificity, positive predictive value, and negative predictive value were 90%, 74%, 3.46, and 0.14, respectively. The AUC for the prediction of mortality was 0.84 (95%CI, 0.73–0.95) at a cutoff value of 76.5 (Table 3). SOD has a moderate predictive value for persistent renal failure, with an AUC of 0.72 (95%CI, 0.64–0.80). The predictive value of SOD for SAP, persistent respiratory failure, and pancreatic necrosis was low, with AUCs of 0.64 (95%CI, 0.56–0.71), 0.58 (95%CI, 0.52–0.63), and 0.64 (95%CI, 0.56–0.71), respectively (Table 3).

Comparison of the Predictive Values of SOD, CRP, and APACHE II in Persistent Circulation Failure and Mortality

SOD is a good predictor of persistent circulation failure. The area under the ROC curve for 24-h SOD [AUC = 0.83 (95%CI, 0.74–0.92)] was greater than those of CRP

Table 2 The SOD activity within 24 h in patients with organ failure, pancreatic necrosis, and mortality

Outcome	Number	SOD within 24 h, U/m, mean (SD)		*P*
		No	Yes	
Persistent renal failure	44	94.6 (27.5)	77.8 (37.2)	< 0.001
Persistent circulatory failure	10	94.1 (28.2)	66.2 (14.9)	< 0.001
Pancreatic necrosis	195	94.4 (27.3)	87.0 (27.5)	< 0.001
Persistent respiratory failure	145	94.6 (27.5)	90.32 (31.5)	0.026
Persistent organ failure	167	95.2 (28.11)	88.95 (31.1)	0.024
Multiple organ failure	30	94.3 (27.6)	78.3 (25.0)	< 0.001
Mortality	8	94.0 (28.2)	64.3 (16.0)	< 0.001

Table 3 The SOD predicts SAP, organ failure, pancreatic necrosis, and mortality

	Cutoff	Sensitivity%	Specificity%	Positive predict value, PV+	Negative predict value, PV−	AUC (95%CI)
Persistent circulatory failure	76.5	90.00	74.00	3.46	0.14	0.83 (0.74–0.92)
Mortality	76.5	87.50	74.70	3.46	0.17	0.84 (0.73–0.95)
SAP	87.5	56.29	48.90	1.54	0.44	0.64 (0.56–0.71)
Persistent respiratory failure	93.5	64.83	49.93	1.29	0.70	0.58 (0.52–0.63)
Persistent renal failure	71.5	52.27	83.33	3.14	0.57	0.72 (0.64–0.80)
Pancreatic necrosis	93.5	78.70	48.90	1.54	0.44	0.64 (0.56–0.71)

[AUC = 0.81 (95%CI, 0.70–0.93)] and the APACHE II score [AUC = 0.81 (95%CI, 0.69–0.95)], and the predictive capacity of SOD was higher than those of the other indicators (Supplementary Table 4, Fig. 3a–c). With regard to the prediction of mortality, 24-h SOD activity was superior to the CRP level [AUC = 0.71 (95%CI, 0.50–0.94)] but was weaker than the APACHE II score [AUC = 0.92 (95%CI, 0.85–0.98)] (Supplementary Table 4, Fig. 3d–f).

Discussion

Our study was based on prospectively collected data from patients with AP and showed that the SOD activity level gradually decreased as the severity of AP increased and as the time to onset increased. SOD activity was associated with increased risks of organ failure, pancreatic necrosis, and mortality. SOD can accurately predict the risk of persistent circulation failure and mortality, and its predictive value was higher than that of CRP.

SOD is an important oxygen free radical scavenger in the body and plays a vital role in the oxidant and antioxidant balance [18]. Oxidative stress plays a major role in the occurrence and development of AP, which can reduce the expression of pancreatic SOD and aggravate pancreatic injury [19]. Previous studies have shown significant decreases in SOD activity in AP mice [20] and rats [21], and our clinical studies further validated the above results. SOD activity was significantly decreased in patients with different levels of AP severity, which may be related to oxidative stress in the early stages of AP and excessive ROS to reduce SOD activity. As the onset time was prolonged, SOD showed a decreasing trend, and there was a significant difference in the degree of SOD decline in AP patients with different severities. This result may be because SAP patients have more severe oxidative stress and generate a large amount of ROS, resulting in a more dramatic decrease in SOD activity compared to other patients.

Our study found that a decrease in SOD activity was closely related to pancreatic necrosis and AP severity. The activation of AP results in high levels of ROS and damaged vascular endothelial cells [19], which increase capillary permeability, resulting in massive plasma extravasation, decreased blood volume, slowed blood flow, and circulatory dysfunction. First, we found that the SOD activity in patients with SAP was significantly lower than in patients with MAP and patients with MSAP at 24 h onset of AP, far lower than the baseline value of normal SOD activity (above 129 U/

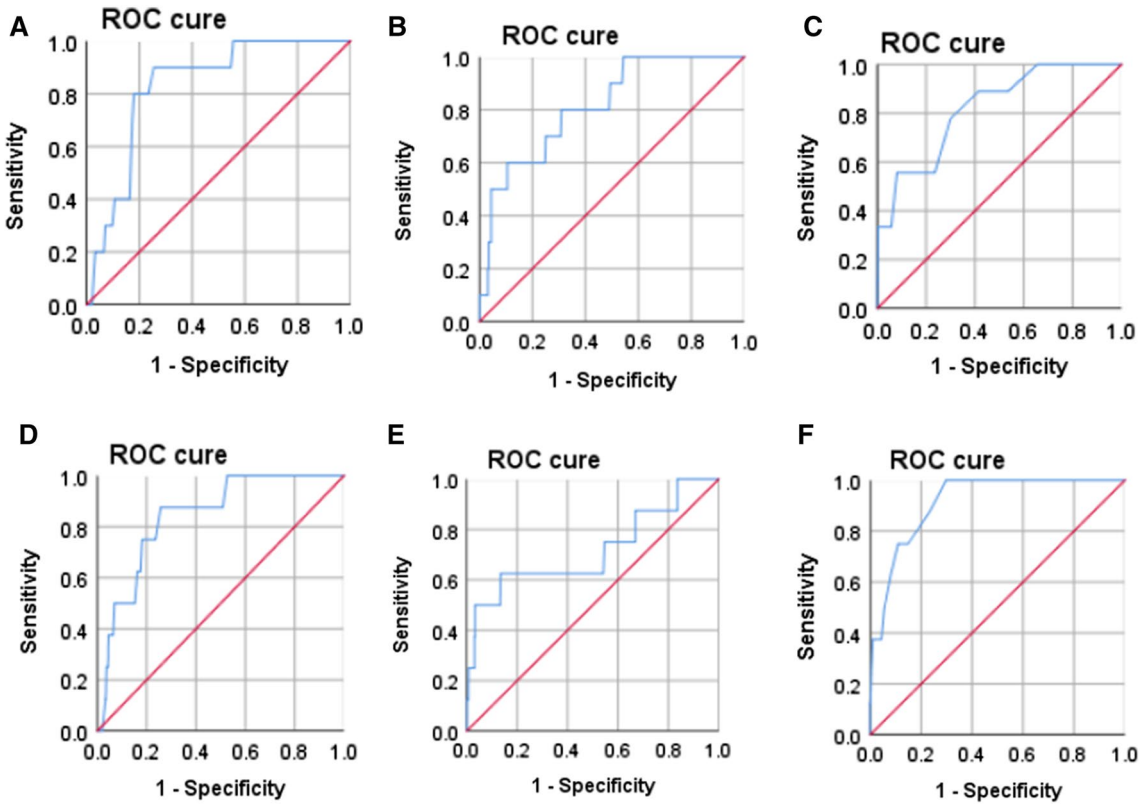

Fig. 3 **a–c** The ROC curve of SOD, CRP and APACHE II as a predictor for persistent circulatory failure in AP, respectively; **d–f** the ROC curve of SOD CRP and APACHE II as a predictor of the mortality in AP

ml). Second, the 48-h period is the initial stage of the systemic inflammatory response. It is possible that the human antioxidant system still has a certain amount of antioxidant capacity to deal with the oxidative stress occurring in AP, and there is limited room for a decline in SOD levels. Therefore, the rates of SOD decline from 24 to 48 h were similar in all three groups. However, from the data, patients with SAP have a greater decreasing slope within 24 to 48 h. In the 48- to 72-h period, the systemic inflammatory response peaked, and severe oxidative stress caused a rapid decline in SOD levels. Among them, the decline rate of SOD levels in MSAP patients was faster than that in MAP, which reflected that the conditions of patients with MSAP were aggravated during the 48- to 72-h period. The SOD levels of patients with SAP were still the lowest at 72 h.

Pancreatic tissue ischemic necrosis promotes the release of inflammatory factors and ROS and an antioxidant imbalance, resulting in reduced antioxidant SOD activity. Our study showed that SOD activity was significantly lower in patients with organ failure than in patients without organ failure ($P < 0.001$); notably, patients with circulatory failure had the lowest 24-h SOD activity (66.2 ± 14.9). Our study found that 24-h SOD activity was significantly different between patients with and without organ failure. The SOD activity levels of patients with SAP were significantly lower than those of patients with MAP and MSAP at 24 h onset. Further subgroup analysis suggested that SOD activity levels in SAP patients at < 48 h or > 48 h were not different, which may indicate that SOD activity is suitable for predicting organ failure at the onset of 24 h, rather than 48 h. The ROC curve analysis showed that SOD can accurately predict circulatory failure, which may be related to increased ROS levels in the body. When the antioxidant enzyme activity is decreased, it will cause inflammatory reactions and microcirculation dysfunction, resulting in apoptosis and tissue damage and eventually leading to pancreatic dysfunction. Necrosis is associated with impairment of circulatory function.

Although oxidative stress is one of the main factors in the pathogenesis of AP, the treatment of AP with antioxidants has not shown encouraging results. At present, in SAP animal experiments, supplemental antioxidants were shown to restore the activity of free radical scavenging enzymes such as SOD, reduce oxygen free radical content in SAP mice, and improve tissue damage caused by oxidative stress [20–22]. Randomized controlled trials (RCTs) performed by Siriwardena et al. [23] did not show efficacy of antioxidants (vitamin C, acetylcysteine, selenium) in the treatment of SAP, and a subsequent RCT [24] also suggested that high doses of vitamin C, an antioxidant, did not result in a significantly improved clinical prognosis of SAP. However, neither of the two RCTs investigated early supplementation with antioxidants, and delayed treatment with antioxidants may affect the results of the study because AP oxidative stress occurs early in the disease. Our study showed that there was a significant difference in the level of SOD activity in AP patients with different severities, and SOD activity decreased significantly within 72 h before the onset of AP. This study examined the time, dose, and duration of AP treatment using antioxidants. For example, 24 h after the onset of the disease, antioxidant supplementation began. Patients with lower SOD levels required a larger amount of antioxidants than MAP patients, and long-term treatment with antioxidants was required due to a further reduction in SOD with the prolonged onset time. Of course, reliable clinical research evidence is needed to support this hypothesis.

Pancreatic necrosis and organ failure in AP are important determinants of AP prognosis, and the mortality rate can reach 30% [25]. Therefore, the accurate prediction of organ failure and mortality in the early stage are critical determinants of the clinical outcome of AP. Some traditional predictive scores, such as the APACHE II score, can be used to assess AP clinical outcomes, but the calculations are complex. CRP is a laboratory indicator for the clinical assessment of the severity and prognosis of AP patients. In our previous studies, CRP was found to have a relatively weak ability to predict death [16]. Our study showed that SOD activity levels were closely associated with AP severity, organ failure, and mortality ($P < 0.001$). SOD predicts the maximum AUC value under the ROC curve for circulatory failure and death; its sensitivity and specificity are high, and its prediction accuracy is greater than that of CRP.

This study has some limitations. First, it is a single-center study. The number of patients admitted to our center for admission and hospitalization is high, and MASP and SAP patients comprised 47.6% and 14.4% of the total, respectively [26]. Second, rhubarb oral laxatives are used in hospitals in China, and this botanical drug has an antioxidant effect. Third, SOD activity levels may be decreased in patients with cardiovascular disease, rheumatic immune disease, and diabetes. We used statistics from large-sample data to minimize the results bias due to comorbidities.

Conclusions

In summary, our study found that serum SOD activity levels gradually decreased with the progression of AP and were negatively correlated with organ failure and mortality. Changes in the SOD activity level have a predictive value for the assessment of persistent circulatory failure and mortality and may also be a reference standard for guiding antioxidant therapy.

Author's contribution W-HH and N-HL co-designed the study. XZ and LL performed all work related to the data processing, statistical analysis, and the drafting of the manuscript. YZ and B-JY participated in the data analysis and interpretation. YZ, XH, W-HH, and N-HL participated in the critical revision and modification of the manuscript. All the authors read and approved the final manuscript.

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Compliance with Ethical Standards

Conflict of interest All authors have read and approved the submitted manuscript, and the manuscript has not been submitted or published elsewhere either in whole or in part, except as an abstract. There are no ethical/legal conflicts associated with this article.

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