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ORIGINAL RESEARCH

Decreasing Procalcitonin and Its Ratio to Albumin Predict Mortality in Patients with Abdominal Sepsis

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Purpose: Abdominal sepsis may act as a life-threatening disease characterized by a dysregulated inflammatory response and nutritional deficits. Given the complex interplay between inflammation and malnutrition, integrating these biomarkers may provide a more comprehensive understanding of patients' outcomes and improve early prognosis in the intensive care unit (ICU). Herein, we report the predictive value of procalcitonin (PCT) and its ratio to albumin (ALB) for mortality of abdominal sepsis patients, aiming to provide more references for clinical disease management.

Patients and Methods: This is a retrospective study involving one hundred and twenty-four patients diagnosed with abdominal sepsis. Kaplan-Meier survival analysis was utilized to analyze the 30- and 90-day mortality of patients. Univariable and multivariable Cox regression analyses were conducted to confirm the prognostic factors. In addition, ROC analyses were performed to evaluate the diagnostic efficiency.

Results: An 80% decrease of PCT within 4 days was identified as a cutoff to predict the 30-day (P = 0.032) and 90-day mortality (P = 0.030) with the help of Kaplan-Meier analysis. In the multivariate Cox regression analysis, the PCT decrease/ALB was an independent prognostic factor for 30-day mortality (P <0.05) and 90-day mortality (P <0.05) before and after adjustment for age, gender, and BMI. Moreover, ROC analysis revealed the significance of PCT and PCT decrease/ALB in predicting 30-day and 90-day mortality.

Conclusion: In conclusion, the decrease in PCT and the ratio of PCT decrease/ALB are promising biomarkers to predict mortality in patients with abdominal sepsis.

Keywords: PCT, albumin, abdominal sepsis, intensive care unit, mortality prediction

Introduction

Sepsis is a cascade of systemic inflammatory reactions induced by several pathogens, such as bacteria, viruses, or fungi.[1] This complex inflammatory disease can cause severe damage to vital organs such as the heart or kidney and is responsible for approximately 25–50% of deaths in several Western countries.[2,3] Of note, for patients with abdominal sepsis in intensive care units (ICU), the overall mortality rates vary from 7.6% to 36%.[4,5] Blood culture currently is the gold standard for the clinical diagnosis of sepsis but requires a relatively long time, which may lead to a delayed diagnosis.[6,7] Since a timely diagnosis and prompt treatment are required, especially for severely ill patients in ICU. Although great progress has been made in the treatment of sepsis, the overall survival rate remains unsatisfactory. The clinical assessment of patients' prognosis is complex. APACHE II and SOFA scoring are commonly employed indicators, but there are distinct efficiency and accuracy between patients with different severities.[8,9] White blood cell counts and

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body temperature are closely associated with patients' outcomes. However, surgical stress exists in patients undergoing abdominal surgery, simply focusing on the changes in white blood cells and body temperature is not conducive to clinical diagnosis and treatment. Therefore, exploring early and robust predictive biomarkers for sepsis patients is important.

Procalcitonin (PCT) is a biomarker of bacterial infections,[10] as it could respond to several proinflammatory factors, including IL-1β, IL-6, and TNF-α.[11] Due to the dynamic changes of PCT with the development diseases, there are large limitations in utilizing the single and fixed PCT level for sepsis. PCT is rapidly produced during host infection and decreases when the infection is controlled.[12] Hence, the decrease of PCT was considered a potential prognostic factor for sepsis. Recently, a large prospective multicenter clinical study reported that when the PCT level decreased by over 80% for over 96 h, an adverse prognosis of patients in ICU with sepsis was observed,[13] revealing the predictive value of PCT. The employment of PCT decrease could assist the prevention of infection and recurrence and help discriminate infectious and non-infectious inflammation. However, clinical diagnostic methods based on PCT showed significant limitations in sensitivity and specificity. Moreover, the relationship between inflammation and malnutrition is complex and interdependent in pathologically infective status. For example, inflammation may be the cause of malnutrition, and malnutrition can aggravate inflammation.[14] In this situation, a single biomarker related to the inflammatory response or nutritional status can rarely offer a comprehensive mortality prediction. The significance of combined biomarkers has attracted attention from a few studies. Chen et al[15] reported that PCT/albumin (ALB) was an inversely independent prognostic factor for patients with sepsis-induced acute kidney injury. ALB is the most abundant protein in plasma, which could protect the kidney from injury and maintain its perfusion.[16] ALB is associated with inflammation and has also been considered a risk factor for the adverse prognosis of sepsis.[17] PCT and ALB could indicate the inflammation from different perspectives, where PCT could indicate dynamics of infections, and ALB could indicate the function of organs. Hence, combining PCT with ALB could improve the discrimination between infectious and non-infectious inflammation. It could also provide basis for the application of antibiotics and the prediction of patients' outcomes. However, to date, there is a lack of confirmation on the predictive value of combining PCT and ALB in the prognosis of patients with abdominal sepsis. The ratio of PCT decrease/ALB may comprehensively reflect the state of inflammation and malnutrition for sepsis and predict mortality. This study evaluated the significance of PCT decrease and its ratio to ALB in abdominal sepsis, aiming to explore reliable indicators assisting the prognostic prediction of abdominal sepsis.

Material and Methods

Patients

This is a retrospective study performed in the ICU of Shanghai Eastern Hepatobiliary Surgery Hospital from January 2018 to October 2021. A total of 124 patients with abdominal sepsis were enrolled during the study period (Figure S1). The inclusion criteria were: 1) aged ≥16; 2) diagnosed with abdominal sepsis based on the Third International Consensus Diagnostic Criteria for Sepsis and Sepsis Shock (Sepsis-3);[1] 3) patients treated in the ICU or who were admitted to ICU from other wards. The exclusion criteria were: 1) patients who did not have an initial blood draw; 2) patients without complete clinical records (all situations where key information related to diagnosis, treatments, disease history are missing, omitted, or insufficient, such as unknown medical history, incomplete diagnostic information, and missing check items); 3) patients with solid tumor or hematology disease; 4) patients treated with antibiotics before the initial blood draw. The sample size has been evaluated by the G power analysis with the effect size of 0.31, which is sufficient for the following analysis. This study was performed in line with the principles of the Declaration of Helsinki. This study was approved by the ethics committee of the Shanghai Eastern Hepatobiliary Surgery Hospital (approval no. EHBHKY2021-K-011), and written informed consent was waived due to the retrospective study. Patients' data were analyzed anonymously to maintain patient confidentiality.

Data Collection and Follow-Up Assessment

A 90-day follow-up survey was conducted by the treating doctors or via telephone, and mortality was defined as the endpoint event. The baseline data were collected on admission (day 0) from medical records. All clinical records,

including the follow-up information, were collected retrospectively. The prognostic analysis was prospectively performed.

Serum samples were collected from all enrolled patients for PCT assays on admission (day 0) and daily until the 4th day. The decrease in PCT between the two samplings was estimated for its prognostic accuracy. The patients' data were collected from electronic medical records, including (1) baseline demographic data: age, gender, and BMI; (2) admission status data: organ of origin, sequential organ failure assessment (SOFA) score, and acute physiology and chronic health evaluation (APACHE) II score; (3) laboratory data: PCT decrease, white blood cell (WBC), C-reaction protein (CRP), albumin (ALB), and PCT decrease/ALB.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviations (SD) and analyzed by the Mann–Whitney *U*-test. Categorical variables were presented as percentages and compared by the chi-square test or the Fisher exact test. The difference comparison of 30- and 90-day was performed with Kaplan-Meier survival analysis with Log rank tests based on an 80% decrease in PCT. Univariable and multivariable Cox regression analyses were conducted to confirm the prognostic value of related factors, including ALB, CRP, PCT decrease, and PCT decrease/ALB based on the 30-day and 90-day mortality of abdominal sepsis patients. The average values of included indexes were employed as a cutoff. In addition, ROC analyses were performed to evaluate the diagnostic value of these four factors. A P-value<0.05 was deemed statistically significant. IBM SPSS software (version 24.0), GraphPad Prism (version 8.0.2), and MedCalc (version 15.6.1) were applied for statistical analyses.

Results

Baseline Characteristics of Enrolled Patients

This study involved 124 patients, of which 80 were male (64.5%) and 44 were female (35.5%), with a mean age of 67.4 years (range 16–90 years). Thirty patients (24.2%) died within 30 days (Table S1), and 47 deaths occurred within 90 days. Based on the 90-day mortality, patients were grouped into survival and death group. The baseline patients' characteristics are presented in Table 1, showing no significant differences in the distribution of age, gender, or organ of origin between the survival group and the non-survival group. However, the remaining features, including BMI, WBC, CRP, ALB, PCT decrease, PCT decrease/ALB, SOFA scores, and APACHE II scores, were significantly different. The survival cohort showed a dramatical decrease of PCT (26.7±34.0 vs 6.0±26.1, $p = 0.001$), higher ALB levels (24.3±3.7 vs

Table 1 Patient Characteristics Between Survival Group and Non-Survival Group

Variables	Survival Group (n=77)	Death Group (n=47)	P Value
Age (years; mean±SD)	66.1±14.4	69.6±11.2	0.13
Gender (n, %)			0.44
Male	52 (67.5%)	28 (59.6%)	
Female	25 (32.5%)	19 (40.4%)	
BMI (kg/m^2; mean±SD)	23.3±1.5	22.4±1.3	0.001
WBC ($\times 10^9/L$; mean±SD)	10.4±6.6	14.7±10.9	0.018
CRP (mg/l; median (range))	207.9 (154.1–252.2)	225.4 (168.0–276.6)	0.004
Alb (g/l; mean ± SD)	24.3±3.7	22.0±2.9	0.001
PCT decrease (mean ± SD)	26.7±34.0	6.0±26.1	0.001
PCT decrease/ALB (mean ± SD)	1.2±1.5	0.3±1.1	0.001

(*Continued*)

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Table 1 (Continued).

Variables	Survival Group (n=77)	Death Group (n=47)	P Value
Organ of origin (n, %)			0.721
Colon or rectum	18 (23.4%)	12 (25.5%)	
Stomach	11 (14.3%)	8 (17.0%)	
Biliary tract	16 (20.8%)	9 (19.1%)	
Small intestine	10 (13.0%)	7 (14.9%)	
Duodenum	10 (13.0%)	3 (6.4%)	
Liver	3 (3.9%)	3 (6.4%)	
Ileocecum and appendix	3 (3.9%)	4 (8.5%)	
Pancreatitis	6 (7.8%)	1 (2.1%)	
SOFA score (Day 1; mean±SD)	8.3±3.1	12.2±2.2	0.001
APACHE II (Day 1; mean±SD)	19.8±6.4	29.6±4.0	0.001

Abbreviations: BMI, body mass index; WBC, white blood cell; CRP, C-reaction protein; PCT, procalcitonin; ALB, albumin; SOFA, sequential organ failure assessment; APACHE, acute physiology and chronic health evaluation; SD, standard deviation.

22.0±2.9, $p = 0.001$), and a higher ratio of PCT decrease/ALB (1.2±1.5 vs 0.3±1.1, $p = 0.001$) than that of the death cohort. Compared with the survival group, the concentration of CRP [225.4 (168.0–276.6) vs 207.9 (154.1–252.2)] significantly increased in the death group.

Association of PCT Decreases with the Mortality of Patients with Abdominal Sepsis

Patients were grouped based on the level of PCT decrease with 80% as the cutoff. The Kaplan-Meier analysis demonstrated that the 30-day mortality ($P = 0.032$, Figure 1) and 90-day mortality ($P = 0.030$, Figure 2) of patients with PCT decrease of over 80% was significantly higher significantly lower than that of patients with a PCT decrease ≤ 80%.

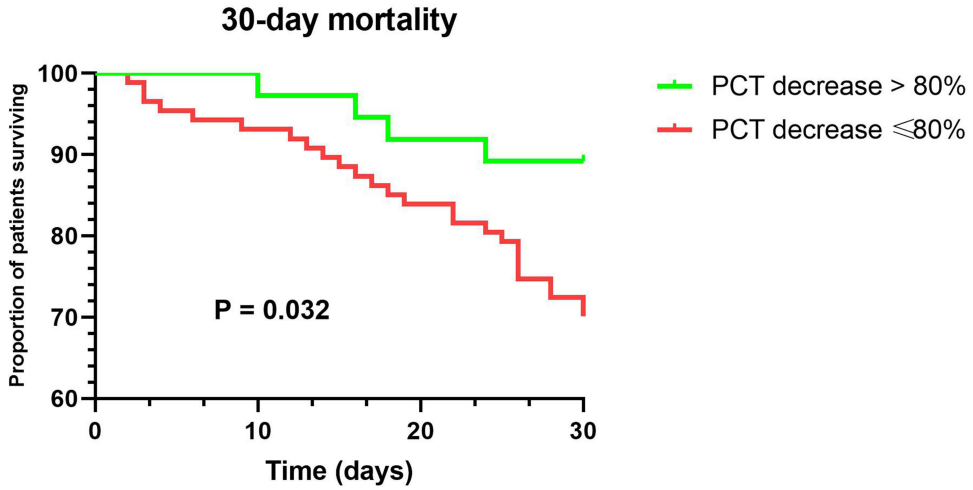

Figure 1 Kaplan-Meier survival curves of 30-day mortality using the cut-off value of 80% PCT decrease from baseline to day 4.
Abbreviation: PCT, procalcitonin.

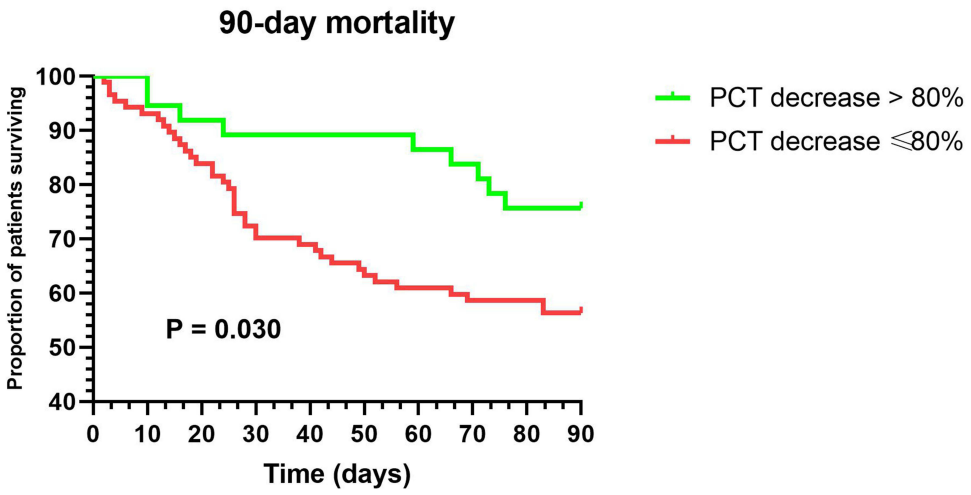

Figure 2 Kaplan-Meier survival curves of 90-day mortality using the cut-off value of 80% PCT decrease from baseline to day 4.
Abbreviation: PCT, procalcitonin.

Univariate And Multivariate Cox Regression Analysis

In the unadjusted analysis, the prognostic significance of PCT decreases (HR = 0.329, 95% CI = 0.115–0.944, $P = 0.039$) and its ratio to ALB was revealed by the univariate Cox regression analysis. In the multivariate Cox regression analysis, only the PCT decrease/ALB was an independent prognostic factor for 30-day mortality [HR 0.285 (95% CI: 0.110–0.739), $P = 0.01$] (Table 2). Regarding the 90-day mortality, ALB [HR 0.255 (95% CI: 0.130–0.501), $P = 0.001$], CRP [HR 1.873 (95% CI: 1.033–3.394), $P = 0.039$], and PCT decrease/ALB [HR 0.505 (95% CI: 0.260–0.981), $P = 0.044$] were identified as independent prognostic factors (Table 3).

After adjustment for age, gender, and BMI (adding age, gender, and BMI into the multivariate Cox model), the multivariate Cox model revealed that PCT decrease/ALB remained the only independent prognostic factor for 30-day mortality [HR 0.299 (95% CI: 0.114–0.784), $P = 0.014$] (Table S1). Furthermore, BMI [HR 0.508 (95% CI: 0.277–0.931), $P = 0.029$], ALB [HR 0.250 (95% CI: 0.127–0.493), $P = 0.001$], CRP [HR 1.748 (95% CI: 0.955–3.199), $P = 0.070$] and PCT decrease/ALB [HR 0.502 (95% CI: 0.255–0.988), $P = 0.046$] were significantly independent prognostic values (Table S2).

ROC Analysis

The diagnostic efficiency of inflammation and nutrition variables to predict 30- and 90-day mortality was evaluated by ROC analysis. PCT and PCT decrease/ALB could significantly predict the 30-day mortality with the AUC of 0.777 (0.693–0.847, $P < 0.001$) and 0.777 (0.694–0.847, $P < 0.001$), respectively, which are significantly higher than that of

Table 2 Results of the Univariate and Multivariate Cox Regression Analysis for 30-Day Mortality of Patients with Abdominal Sepsis from Intensive Care Units

Factor	Univariate		Multivariate	
	HR (95% CI)	P	HR (95% CI)	P
ALB	0.470 (0.220–1.001)	0.051	0.497 (0.230–1.072)	0.075
CRP	1.153 (0.563–2.362)	0.69	1.241 (0.603–2.556)	0.558
PCT decrease	0.329 (0.115–0.944)	0.039	0.538 (0.175–1.652)	0.279
PCT decrease/ALB	0.218 (0.089–0.535)	0.001	0.285 (0.110–0.739)	0.01

Abbreviations: ALB, albumin; CRP, C-reaction protein; PCT, procalcitonin.

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Table 3 Results of the Univariate and Multivariate Cox Regression Analysis for 90-Day Mortality of Patients with Abdominal Sepsis from Intensive Care Units

Factor	Univariate		Multivariate	
	HR (95% CI)	P	HR (95% CI)	P
ALB	0.281 (0.146–0.543)	0.001	0.255 (0.130–0.501)	0.001
CRP	1.577 (0.880–2.825)	0.026	1.873 (1.033–3.394)	0.039
PCT decrease	0.469 (0.227–0.971)	0.041	0.518 (0.234–1.145)	0.104
PCT decrease/ALB	0.367 (0.198–0.680)	0.001	0.505 (0.260–0.981)	0.044

Abbreviations: ALB, albumin; CRP, C-reaction protein; PCT, procalcitonin.

Table 4 ROC Analysis of Inflammation and Nutrition Variables to Predict 30-Day Mortality

	AUC (95% CI)	Sensitivity (%)	Specificity (%)	Youden Index	*P*-Value
ALB	0.593 (0.501–0.680)	76.67	52.13	0.2879	0.088
CRP	0.558 (0.466–0.647)	96.67	21.28	0.1794	0.331
PCT decrease	0.777 (0.693–0.847)	80	74.47	0.5447	< 0.001
PCT decrease/ALB	0.777 (0.694–0.847)	76.67	76.6	0.5326	< 0.001

Abbreviations: ROC, receiver operating characteristic; AUC, area under the curve; ALB, albumin; CRP, C-reaction protein; PCT, procalcitonin.

ALB (AUC = 0.593, $P = 0.088$) and CRP (AUC = 0.558, $P = 0.331$, Table 4 and Figure 3). The sensitivity and specificity of PCT decrease were 80% and 74.47%, respectively, while PCT decrease/ALB showed a sensitivity of 76.67% and a specificity of 76.60%. Moreover, PCT and PCT decrease/ALB were also revealed of the predictive significance for 90-day mortality with the AUC of 0.712 (0.624–0.790, $P < 0.001$) and 0.705 (0.617–0.784, $P < 0.001$), respectively (Figure 4). The sensitivity of PCT decrease and PCT decrease/ALB was 61.70% and 67.70%, and the specificity was 75.32% and 72.73%, respectively (Table 5).

Discussion

Sepsis is a severe inflammatory disease that may cause acute organ dysfunction and even death;[18–20] thus, prognostic biomarkers to perform an early risk assessment of patients with sepsis would help guide treatment, such as the timely use of antibiotics.[21–26] This study involved the retrospective analysis of 124 patients who were diagnosed with abdominal sepsis and treated in the ICU. The analysis revealed that the decrease in PCT and the ratio of PCT decrease to albumin in the survival cohort were significantly higher than in the death cohort. Based on the previous studies,[13,27] a PCT decrease of more than 80% was defined as the best cut-off for predicting mortality. Consistently, significant decreases were observed in abdominal sepsis patients who survived relative to the death group, implying its potential prognostic values. Several studies have discussed the prognostic value of PCT in sepsis. Zhai et al[28] reported that PCT depicted good predictive value in patients with a closed abdominal injury. Additionally, the high PCT level also served as a biomarker for abdominal sepsis, where PCT increased within 3–6 h, peaked after 6–8 h, and then declined to normal during recovery.[29,30] Thus, dynamic changes in PCT or a PCT decrease are of potential in evaluating the process of sepsis and predicting the survival of patients with sepsis.[31,32] A recent multicenter clinical trial reported that the 28-day all-cause mortality in patients with severe sepsis was closely associated with the changes in PCT, confirming its prognostic value.[13] Another study employed 90-day mortality as an indicator and revealed that presepsin could act as a prognostic factor for

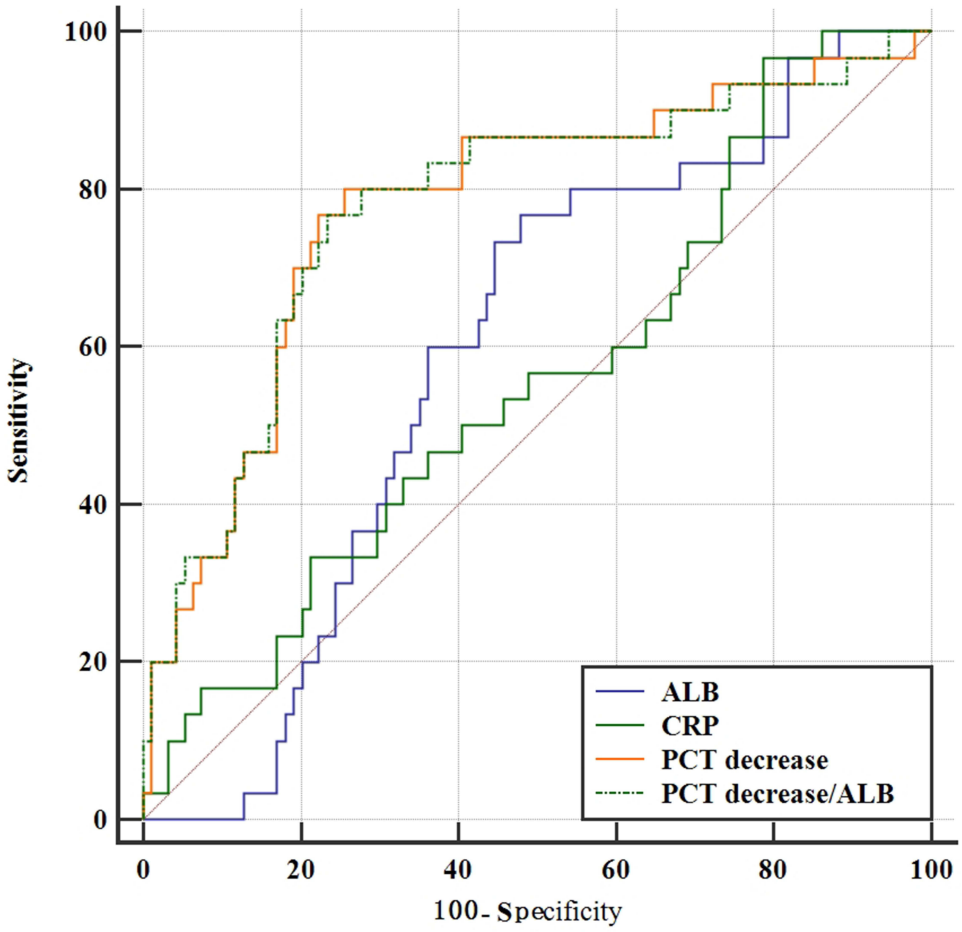

Figure 3 ROC curves of inflammation and nutrition variables to predict 30-day mortality.
Abbreviations: ROC, receiver operating characteristic; ALB, albumin; CRP, C-reaction protein; PCT, procalcitonin.

patients with abdominal sepsis.[33] The 30- and 90-day survival is a critical indicator for evaluating the prognosis of patients with abdominal sepsis.[34–36] Hence, 30- and 90-day mortality were selected as clinical endpoints in the present study, which confirmed that the 80% decrease in PCT can predict 30- (sensitivity of 80% and specificity of 74.47%) and 90-day (sensitivity of 61.70% and specificity of 75.32%) survival of patients with abdominal sepsis.

Nutritional status is an important biomarker for sepsis,[37] and low serum ALB levels may be a detrimental factor for patients with sepsis. The present study found that patients with better prognosis showed higher levels of PCT decrease and ALB than those of patients in the death group, which was in accord with the above-mentioned studies. ALB was demonstrated to show significant predictive value for 90-day mortality of patients with abdominal sepsis. Furthermore, these differences also represented a faster recovery of PCT levels or better nutritional status in the patients who survived.

The relationship between inflammatory level and nutritional status in patients with abdominal sepsis is close and inseparable. A severe inflammatory storm, such as sepsis, can burn off the nutrient reserves and reduce the level of ALB. In addition, poor nutritional status may aggravate inflammation and impair the multi-organ functions in patients with sepsis. In this setting, combining inflammatory and nutritional factors may provide a robust biomarker to comprehensively analyze the prognosis of abdominal sepsis. Previously, ALB has been combined with inflammation-related factors to predict the severity and development of infections. For instance, the ratio of C-reactive protein (CRP)to ALB could predict the prognosis of infectious diseases, especially for sepsis, which could represent both inflammation and nutrient status.[38,39] From this perspective, the ratio of PCT decrease to ALB was focused on abdominal sepsis. Chen et al[15] reported that the ratio of PCT to ALB was an independent predictive biomarker for mortality risk assessment in patients

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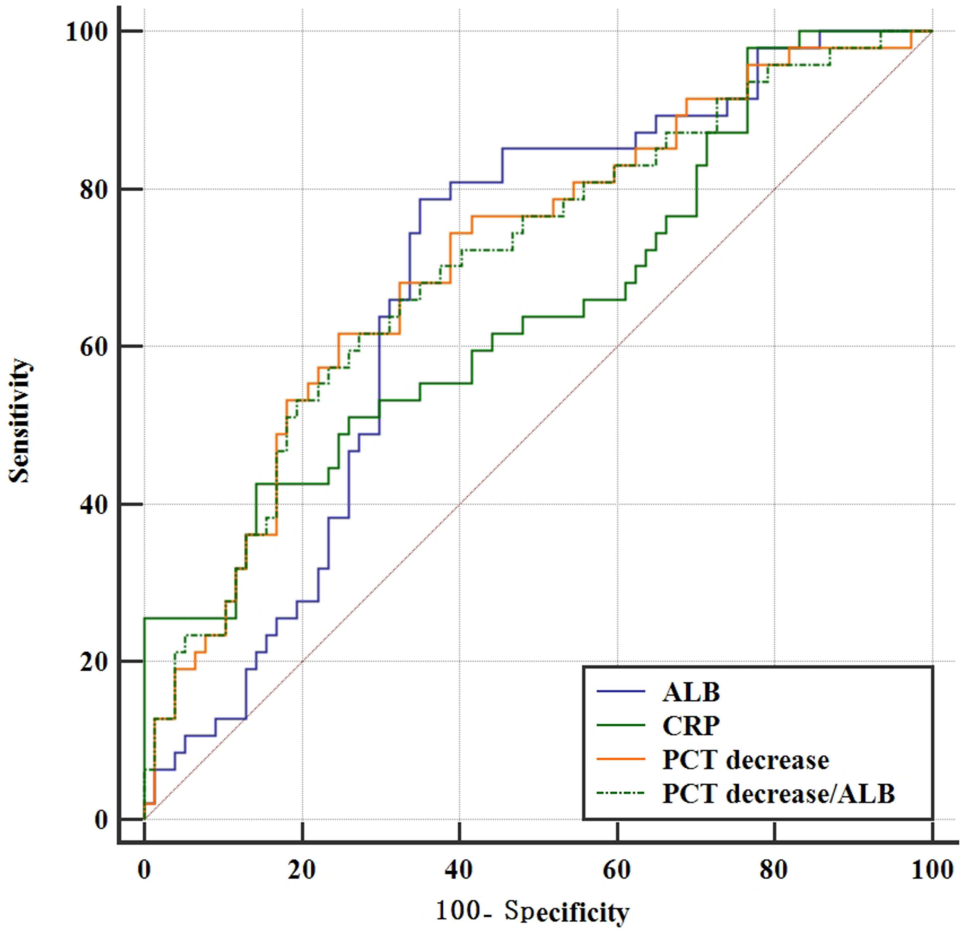

Figure 4 ROC curves of inflammation and nutrition variables to predict 90-day mortality.
Abbreviations: ROC, receiver operating characteristic; ALB, albumin; CRP, C-reaction protein; PCT, procalcitonin.

with sepsis-induced acute kidney injury. To date, the prognostic significance of the ratio between PCT decrease and ALB to predict the prognosis of patients with sepsis remains unclear. The prognostic significance of PCT decrease and ALB separately was not significant in both 30- and 90-day survival of patients with abdominal sepsis. The PCT decrease/ALB was demonstrated to show significance in predicting 30- and 90-day survival rates. The ROC analysis also confirmed that the PCT decrease/ALB had equivalent or even better performance in predicting 30-day mortality (sensitivity of 76.67% and specificity of 76.60%) than ALB (sensitivity of 76.67% and specificity of 52.13%) or PCT decrease (sensitivity of 80% and specificity of 74.47%) alone. The ratio of PCT decrease/ALB increased the diagnostic specificity in patients

Table 5 ROC Analysis of Inflammation and Nutrition Variables to Predict 90-Day Mortality

	AUC (95% CI)	Sensitivity (%)	Specificity (%)	Youden Index	*P*-Value
ALB	0.688 (0.598–0.768)	78.72	64.94	0.4366	< 0.001
CRP	0.652 (0.561–0.735)	42.55	85.71	0.2827	0.003
PCT decrease	0.712 (0.624–0.790)	61.7	75.32	0.3703	< 0.001
PCT decrease/ALB	0.705 (0.617–0.784)	67.7	72.73	0.3443	< 0.001

Abbreviations: ROC, receiver operating characteristic; AUC, area under the curve; ALB, albumin; CRP, C-reaction protein; PCT, procalcitonin.

with abdominal sepsis, thus emphasizing the robust diagnostic efficiency of the integrated marker, indicating the improved prognostic significance by combining PTC decrease and ALB.

The identification of novel biomarkers to dynamically monitor disease progression in patients with abdominal sepsis is the main contribution of this study. Early diagnosis, in-time treatment or control, and close monitoring remain the cornerstone of reducing the mortality of patients with sepsis.[40] Thus, the combination of dynamic inflammatory factors and nutrient factors, the ratio of PCT decrease to ALB here, to predict the mortality of patients with sepsis can guide clinicians to make triage decisions. In addition, it could also provide a reference to determine if patients should be admitted to ICU wards or discharged to normal wards. The present study also helps clinicians perform risk stratification of sepsis and dynamically modify the treatment regimen, such as antibiotic therapy.

However, there are also several limitations in this study. First, this is a single-center study with a relatively small sample size, which might limit clinical significance. Although we have expanded the sample size as large as possible, and the effect size of the sample size has also been validated, larger multicenter studies are still needed to validate the study results. Also, this study may have selection bias due to its retrospective nature, and prospective studies with a comprehensive assessment of the population selection should be performed to further verify the prognosis value of a PCT decrease and the PCT decrease/ALB in patients with abdominal sepsis.

Conclusion

In conclusion, a decrease over 80% in PCT levels was identified as a promising prognostic biomarker in abdominal sepsis, predicting the 30- and 90-day mortality accurately. Additionally, the ratio of PCT decrease to ALB could improve the predictive specificity of PCT and ALB in the prognosis of patients with abdominal sepsis.

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Disclosure

The authors report no conflicts of interest in this work.

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