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Values of serum PCT, suPAR combined with severity scores for evaluating prognosis of septic shock patients

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Abstract

***Background**: To explore the values of serum procalcitonin (PCT), soluble urokinase-type plasminogen activator receptor (suPAR) combined with APACHE II and SOFA scores for evaluating the prognosis of septic shock patients.* ***Materials and Methods**: A total of 118 eligible patients admitted from August 2017 to January 2021 were divided into survival and death groups. Serum PCT and suPAR levels were detected. APACHE II and SOFA scores were evaluated. A combination predictor pre1 was constructed. The predictive efficacy of the indicator alone or in combination was compared using receiver operating characteristic curve. Risk factors leading to death were analyzed, and a predictive model was established.* ***Results**: Serum PCT and suPAR levels as well as APACHE II and SOFA scores of death group significantly exceeded those of the survival group (P<0.05). PCT, suPAR, SOFA and APACHE II scores were valuable for predicting death. The area under curve (AUC) constructed by predictor pre1 for predicting death was largest. PCT, suPAR, APACHE II, and SOFA scores were independent risk factors for death. The model had AUC of 0.828, with the sensitivity of 86.54%, specificity of 89.03%, and accuracy of 82.47%. The death risk predicted by the model had a high concurrence with the actual one.* ***Conclusion**: PCT, suPAR, APACHE II, and SOFA scores are closely related to the prognosis of septic shock patients. The combined predictor pre1 is more effective than a single index for predicting prognosis. The combined prediction model of septic shock based on PCT, suPAR, APACHE II, and SOFA scores has higher predictive efficiency.*

***Keywords**: septic shock; procalcitonin; soluble urokinase-type plasminogen activator receptor; Acute Physiology, Age and Chronic Health Evaluation II score; Sequential Organ Failure Assessment score; prognosis*

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Introduction

Septic shock is a clinical syndrome presenting infection-induced tissue hypoxia and organ dysfunction.[1] It is one of the most frequently-seen diseases in emergency and severe cases, showing a high death rate [2] and poor prognosis. Hence, it is critical to evaluate the severity of patients' diseases and make reasonable interventions for their prognosis. At present, the severity and prognosis of patients with sepsis are assessed in the clinic commonly using Acute Physiology, Age and Chronic Health Evaluation II (APACHE II) score [3], and Sequential Organ Failure Assessment (SOFA) score [4], as well as serum procalcitonin (PCT) [5], and soluble urokinase-type plasminogen activator receptor

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(suPAR).[6] This study aims to explore the prognostic value of PCT and suPAR combined with severity scoring in septic shock patients, which theoretically guides clinical intervention.

Materials and Methods

General data

We selected 118 patients with septic shock admitted to our hospital from August 2017 to January 2021. These subjects consisted of 67 males and 51 females aged 24-79 years old, with a mean age of (65.74±7.91) years old. Of these, there were 55 cases of pulmonary infection, 28 cases of abdominal infection, 10 cases of urinary system infection, and 25 cases of other infections.

Inclusion criteria were set as follows: Patients who were diagnosed according to the diagnostic criteria of sepsis shock in Sepsis 3.0, the International Guidelines for Sepsis and Septic Shock: 2016. Exclusion criteria were set as follows[7]: (1) Patients aged under 18 years old, (2) those with incomplete clinical data, (3) those with acute coronary syndrome, acute cardiac insufficiency or acute active myocarditis, (4) those complicated with previous congenital heart disease, valvular heart disease, hypertrophic cardiomyopathy or arrhythmia, (5) those complicated with tumors, a history of autoimmune diseases, or acute or chronic liver/ kidney failure, (6) pregnant or lactating women, or (7) those who or whose families did not cooperate with the research or were in poor compliance.

Methods

Age, gender, and body mass index (BMI) of septic shock patients were recorded after admission. Afterwards, the patients were scored using APACHE II and SOFA. On admission, 10 mL of elbow venous blood was collected and centrifuged (3000 rpm) to separate the serum. Later, the serum was frozen, and serum PCT and suPAR were examined by electrochemiluminescence and an ELISA kit.

Grouping

The patients were divided into survival group and death group according to 28-day prognosis.

Statistical analysis

SPSS23.0 software was used for statistical analysis of the data. Measurement data were all expressed as mean ± standard deviation ($x \pm s$), and compared by *t*-test between two groups. Numerical data were expressed by percentage (%), and compared by c^2 test between groups. The fitting of multiple prediction indices was performed using the multivariate Logistic regression model to form a new combination predictor,[8,9] and the receiver operating characteristic (ROC) curve was constructed. By comparing the area under curve (AUC) between the combination predictor and each original covariant, the optimal cutoff value was determined, and the performance parameters such as sensitivity and specificity were calculated. The command statement, operation flow and result output of Stata 10.0 was referred to previous literature.[10] $P<0.05$ meant statistically significant differences.

Results

Clinical data and univariate analysis results

No significant differences were found in gender composition ratio, age, BMI, infection site, and basic diseases between the survival group and the death group ($P>0.05$). In comparison with septic shock patients in the survival group, those in the death group had significantly increased PCT, suPAR, APACHE II, and SOFA scores ($P<0.05$) (**Table 1**).

Death rates of patients with different PCT, suPAR, APACHE II, and SOFA scores

The death rate of patients with different PCT, suPAR, APACHE II, and SOFA scores was an-

Table 1. Clinical data and univariate analysis results

Index	Survival group (n=87)	Death group (n=31)	Statistical value	P
Gender (male/female)	50/37	17/14	0.065	0.799
Age (years old)	64.51±6.33	65.52±7.85	0.715[a]	0.476
BMI (kg/m^2)	24.22±2.64	25.03±2.91	1.428[a]	0.156
Infection site n (%)			0.821	0.845
Pulmonary infection (n=55)	42 (48.28)	13 (41.94)		
Abdominal infection (n=28)	21 (24.14)	7 (22.58)		
Urinary system infection (n=10)	8 (9.20)	2 (6.45)		
Other infections (n=25)	16 (18.38)	9 (29.03)		
Basic diseases n (%)			1.915	0.158
Chronic heart failure	22 (25.29)	12 (38.71)		
Hypertension	20 (22.99)	9 (29.03)		
Diabetes mellitus	25 (28.73)	8 (25.81)		
COPD	20 (22.99)	2 (6.45)		
PCT M (P_{25}, P_{75}) (ng/mL)	1.23 (0.64, 2.42)	4.31 (1.40, 21.34)	-3.850[b]	<0.001
SuPAR (ng/mL)	8.65±5.97	15.68±8.24	5.068[a]	<0.001
APACHE II score (points)	10.06±3.68	19.26±5.48	10.423[a]	<0.001
SOFA score (points)	4.29±3.35	9.68±4.28	7.131[a]	<0.001

[a] is the value of t; [b] is the value of Z; the rest is the value of χ^2.

alyzed. It was discovered that with the increase in the levels of serum PCT and suPAR as well as APACHE II and SOFA scores, the death rate of patients rose (P<0.05) (**Table 2**).

Predictive efficiencies of serum PCT, suPAR. APACHE II. and SOFA scores for prognosis

The combination predictor pre1 was obtained by fitting PCT, suPAR, APACHE II, and SOFA

Table 2. Death rates of patients with different PCT, suPAR, APACHE II scores, and SOFA scores

Index	Case (n)	Death n (%)	χ^2	P
PCT (ng/mL)			17.729	0.001
≤0.8	27	2 (7.41)		
>0.8-1.4	32	5 (15.63)		
>1.4-3.6	31	9 (29.03)		
>3.6	28	15 (53.57)		
SuPAR (ng/mL)			18.606	<0.001
≤8.5	25	0 (0.00)		
>8.5-13.5	29	5 (17.24)		
>13.5-18.5	35	14 (40.00)		
>18.5	29	12 (41.38)		
APACHE II score			38.265	<0.001
≤10 points	24	1 (4.17)		
>10-20 points	76	16 (21.05)		
>20 points	18	14 (77.78)		
SOFA score			19.442	<0.001
≤5 points	32	3 (9.38)		
>5-10 points	63	15 (23.80)		
>10 points	23	13 (56.52)		

scores using Stata 10.0 software. According to the ROC curve analysis results, serum PCT and suPAR, as well as APACHE II and SOFA scores were valuable to some extent in predicting the death of septic shock patients (AUC>0.7). Meanwhile, the AUC of the combination predictor pre1 was larger than that of PCT, suPAR, APACHE II, and SOFA scores in predicting the death of septic shock patients (P<0.05). Besides, the combination predictor pre1 had a sensitivity of 94.2% and a specificity of 93.2%, proving a high predictive value (**Table 3** and **Figure 1**).

Multivariate logistic regression analysis results

Multivariate logistic regression analysis was conducted by using prognosis as the dependent variable, and the statistically significant indicators in univariate analysis (i.e., PCT, SuPAR, APACHE II score, and SOFA score) as independent variables. Multivariate logistic analysis showed that PCT odds ratio (*OR*)=3.925, 95% confidence interval (95%*CI):* 1.352-8.330), suPAR (*OR*=4.802*,* 95%*CI:* 1.064-8.869)*,* APACHE II score (*OR*=1.727, 95%*CI*: 1.063-2.804) and SOFA score (*OR*=2.710, 95%*CI:* 1.118-4.400) were independent risk factors for 28-d septic shock patients (P<0.05) (**Table 4**). The prediction model of death of septic shock patients was established with independent risk factors: the predicted value = EXP 5.316-1.527 (PCT) - 1.416 (suPAR) - 0.035 (APACHE II score) - 0.086 (SOFA score)/1 + EXP 5.316-1.527 (PCT) - 1.416 (suPAR) - 0.035 (APACHE II score) - 0.086 (SOFA score).

Model evaluation results

ROC curves were plotted to evaluate the prediction model. The AUC, sensitivity, specificity and accuracy of the prediction model were

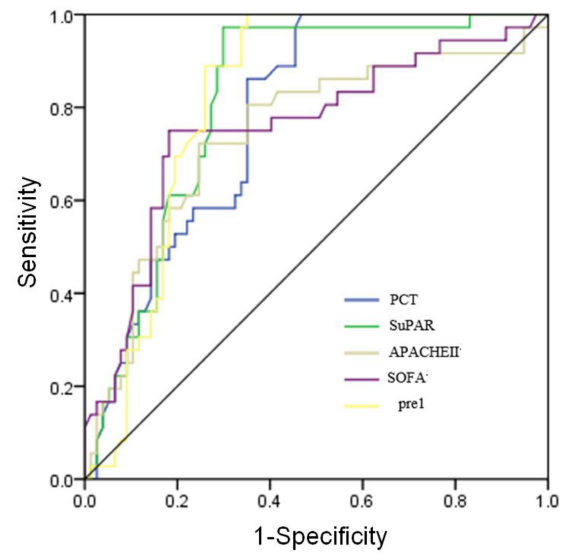

Fig. 1. ROC curves of serum PCT and suPAR, disease severity score and the combination predictor for predicting prognosis.

Table 3. Predictive efficiencies of serum PCT, suPAR, APACHE II, and SOFA scores for prognosis

Index	PCT	SuPAR	APACHE II score	SOFA score	Combination predictor pre1
Sensibility	0.810	0.845	0.810	0.814	0.942
Specificity	0.789	0.914	0.893	0.786	0.932
Positive predictive value	0.725	0.801	0.773	0.756	0.891
Negative predictive value	0.592	0.556	0.557	0.613	0.650
Positive likelihood ratio	1.48	1.81	2.03	1.32	5.10
Negative likelihood ratio	0.62	0.57	0.65	0.44	0.21
Youden index	0.402	0.764	0.703	0.700	0.887
AUC (95%CI)	0.781 (0.743~0.852)	0.805 (0.783~0.864)	0.762 (0.721~0.849)	0.756 (0.736~0.8571)	0.924 (0.854~0.969)

Table 4. Multivariate Logistic regression analysis results

Item	Regression coefficient	Standard error	Wald c^2 value	OR	95%CI	P
PCT	1.874	0.238	3.651	3.925	1.352~8.330	0.022
SuPAR	1.701	0.316	3.675	4.802	1.064~8.869	0.008
APACHE II score	2.203	0.297	5.389	1.727	1.063~2.804	0.004
SOFA score	2.687	0.172	6.835	2.710	1.118~4.400	0.000
Constant	1.784	0.348	76.436	6.053		0.006

PCT (ng/mL): <0.8=0, 0.8~3.6=1, >3.6=2; SuPAR (ng/mL): <8.5=0, 8.5~18.5=1, >18.5=2; APACHE II score: <10=0, 10~20=1, >20=2; SOFA score: <5=0, 5~10=1, >10=2.

0.828 (P=0.018), 86.54%, 89.03%, and 82.47%, respectively. The standard curve of the internal verification calibration chart of the prediction model fitted well with the prediction curve, which indicated a good consistency between the death of septic shock patients predicted by the model and the actually observed condition (**Figure 2 and 3**).

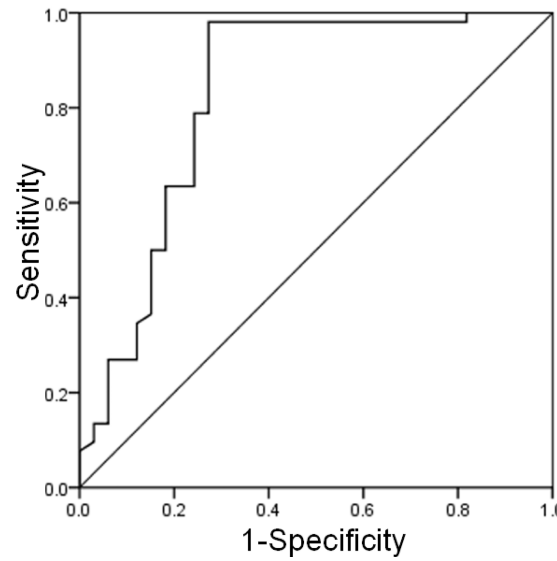

Fig. 2. ROC curve of prediction model.

Discussion

Septic shock, a frequently-seen critical disease in PICU, refers to the most severe stage of sepsis, with a death rate as high as 62-75%.[11] Hence, assessing the severity and prognosis of septic shock patients is of great significance for reducing the death rate.

As the propeptide of calcitonin, PCT is an inflammatory indicator for bacterial infections in

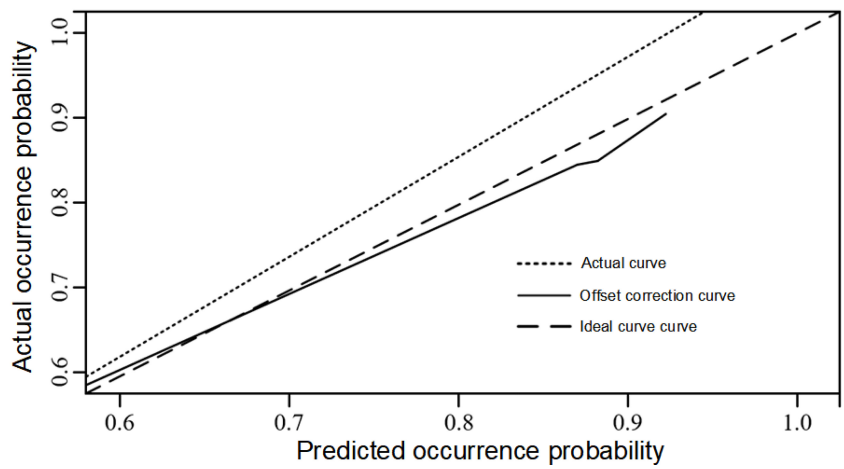

Fig. 3. Calibration curve of internal verification for prediction model.

the body and has a relevance to the severity and prognosis of sepsis.[12] According to the study by Tang et al. [13], PCT acted as a predictor for the prognosis of patients with sepsis, and its predictive value is superior to that of blood lactic acid and CRP. SuPAR, a new inflammatory receptor, is extensively involved in the inflammatory reactions of the body and is a marker effectively predicting the prognosis of patients with sepsis.[14,15] Huttunen et al. [16] detected the level of SuPAR in the peripheral blood of patients with sepsis who survived and died. They found that the level of serum suPAR in patients who died was remarkably increased compared with that in patients who survived. When the cutoff value was 11.0 ng/mL, the AUC for predicting the death of patients was 0.84, and the proportions by subtraction of sensitivity and specificity were 83% and 76%, respectively. Other than serum markers, APACHE II and SOFA scores have also been extensively applied to evaluate the prognosis of patients with septic shock in the clinic. APACHE II score primarily evaluates the patients' acute physiology and chronic health, while SOFA score mainly assesses the patients' multiple organ functions. Studies have proved that[17,18] with the aggravation of patients with sepsis, APACHE II and SOFA scores rise, presenting worse prognosis, and the accuracy of APACHE II score in predicting the death rate of patients is close to that of SOFA score. In this study, the results highlighted that serum PCT and suPAR as well as APACHE II and SOFA scores of the patients in the death group were notably higher than those in the survival group. Meanwhile, the death rate of the patients would be raised with the increases in PCT, SuPAR, APACHE II, and SOFA scores. Moreover, as revealed by ROC curve analysis results, serum PCT and SuPAR as well as APACHE II and SOFA scores were certainly valuable in predicting the death of septic shock patients. Nevertheless, it is difficult to accurately evaluate the prognosis of patients with a single index since sepsis is a complex dynamic process. In 2006, statistician Pepe[19] first reported the method of establishing a new combination predictor by fitting multiple indicators with a Logistic regression model, and since then this method has been widely used in diagnosis in many fields.[20,21] The combination predictor can eliminate the confounding factors among indices and improve the performance of ROC curves in comparison with a single diagnostic or predictive index.[22] In the current research, the combination predictor pre1 was generated with independent risk factors in Logistic regression analysis as covariants. The results illustrated that the AUC of the combination predictor pre1 for predicting the death of patients with sepsis-induced myocardial injury was larger than that of the original covariants. Besides, the combination predictor pre1 had the prediction sensitivity of 94.2% and specificity of 93.2%, which suggested that it is more effective than a single index.

In addition, the factors influencing the prognosis of patients with septic shock were analyzed. It was found that PCT, suPAR, APACHE II, and SOFA scores were independent risk factors leading to the death of patients with septic shock. On the basis of the risk factors affecting the prognosis of patients, a death risk prediction model was established the AUC of which was 0.828, with the prediction sensitivity of 86.54%, specificity of 89.03% and accuracy of 82.47%. Furthermore, the standard curve of the internal verification calibration chart of the prediction model fitted well with the prediction curve, which indicated a good consistency between the death of septic shock patients predicted by the model and the actually observed condition.

To sum up, PCT, suPAR, APACHE II, and SOFA scores exhibit close correlations with the prognosis of septic shock patients. The combination predictor pre1 generated through fitting is more effective than a single index in predicting the prognosis of patients. Besides, the combination

prediction model of septic shock constructed based on PCT, suPAR, APACHE II score, and SOFA score has better predictive efficiency. However, this study still has limitations. This is a single-center study and the sample size is small. The findings will be further validated by performing multi-center prospective studies with larger sizes that are ongoing in our group.

Conflict of interest

There was no conflict in this work.

Acknowledgement

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