ORIGINAL RESEARCH

Predictive Value of Combination of Procalcitonin and Predisposition, Infection, Response, and Organ Dysfunction (PIRO) System in Septic Patients with Positive Blood Cultures in the Emergency Department

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Purpose: Procalcitonin and predisposition, infection, response, and organ dysfunction (PIRO) system have high predictive value for the prognosis of critically ill patients. There are few studies on the predictive value of patients with positive blood cultures. The aim of the study was to evaluate risk stratification and sepsis-related mortality in patients with positive blood cultures via procalcitonin (PCT) combined with the PIRO system in emergency departments (ED).

Methods: A total of 1074 patients with positive blood cultures were admitted to Beijing Chao-Yang Hospital ED from December 2017 to October 2020. Their serum PCT was recorded, along with a Sequential Organ Failure Assessment (SOFA) score, Mortality in Emergency Department Sepsis (MEDS) score, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, and PIRO score to predict the prognosis of septic patients with positive blood culture in terms of ICU (intensive care unit) admission, multiple organ dysfunction syndrome (MODS) development, and 28-day mortality. Receiver operating characteristic (ROC) curves and logistic regression analysis were used to assess the prognostic value of the scoring systems.

Results: A total of 978 patients met the inclusion criteria. PCT, MEDS, APACHE II, and PIRO scores were found to independently predict ICU-admission, MODS development, and 28-day mortality (P<0.05), whereas SOFA did not. The AUC values of the PCT, MEDS, APACHE II, and PIRO scores for ICU-admission were 0.620, 0.740, 0.780, and 0.751, respectively. In the prediction of 28-day mortality, the AUC values of PCT, MEDS, APACHE II, and PIRO were 0.782, 0.745, 0.805, and 0.831, respectively. The AUC values combined PCT and PIRO system in predicting MODS and 28-day mortality were better than when predicting ICU-admission.

Conclusion: This study indicates that PCT combined with the PIRO scoring system has a higher predictive value and is superior in predicting MODS and 28-day mortality in septic patients with positive blood cultures.

Keywords: procalcitonin, PIRO scoring system, positive blood culture, 28-day mortality

Introduction

Bacteremia and sepsis are common problems in clinical practice. The term bacteremia denotes the presence of bacteria in the blood.[1] Approximately 200,000 patients are affected by bacteremia each year, with 10 cases per 1000 hospital admissions.[2,3] Bacteremia has high mortality, and due to the obvious dangers of undertreatment, many physicians liberally order cultures.[4] Unlike bacteremia, sepsis is more severe, often involving organ function. Sepsis is a syndrome of systemic inflammation in

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response to infection, traditionally be defined as life-threatening organ failure by a dysregulated host response to infection, which is usually a leading cause of high morbidity and mortality in hospitalized patients.[5] Septic shock remains the dominant cause of death in the United States.[6] Blood cultures are generally considered to be the most sensitive method of detecting bacteremia and are useful in certain diagnoses and critically ill patients.[7,8] The blood culture results can be used to guide the adjustment of antibiotics regimes.[9] Positive blood culture usually indicates a serious infection with fever, chills, leukocytosis, focal infection, sepsis, or suspected endocarditis, and has poor outcome.[4]

The concept of the predisposition, infection, response, and organ dysfunction (PIRO) scoring system was presented at the 2001 International Sepsis Definitions Conference, to improve on traditional sepsis classification.[10] The PIRO system is an ideal staging system that incorporates assessment of premorbid baseline susceptibility, specific disorders responsible for illness, host response to infection, and the resulting degree of organ dysfunction. The four components of the PIRO system cover multiple independent factors that may influence the onset, development, and outcome of sepsis.[11] Since the first PIRO system appeared in 2008, many different PIRO systems have been developed. The PIRO system mainly used to study ICU populations with ICU specific features is not suitable for the ED. A new PIRO system developed by Howell is designed for bedside use and is superior to other PIRO systems.[12] Our study applied the Howell-PIRO scoring system to predict the risk stratification and prognosis of septic patients with positive blood cultures in the ED. PCT, a prohormone of calcitonin, encoded by the calcitonin-I (*CALC-1*) gene on chromosome 11, has successfully detected infection, as well as providing antibiotic management guidance.[13] It is able to predict infectious origin of a shock occurring in an acutely ill patient with reasonable accuracy. The increase of PCT is related to the appearance and severity of bacterial infection in ICU patients.[14] It has been used extensively as a biomarker in sepsis diagnosis, risk stratification, prognosis evaluation, and therapy monitoring in recent years.

However, we found that a large percentage of positive blood culture patients were not admitted to the ICU, and did not develop MODS in clinical practice, instead, following timely, systematic, and effective treatment, they were successfully discharged. Therefore, finding suitable methods for the prognosis of patients with positive blood culture is highly important. Consequently, in view of the strong predictive value of PIRO scoring system and PCT in infectious diseases, we attempted to use PIRO scoring system combined with PCT to evaluate the risk stratification and sepsis-related mortality in patients with positive blood cultures in the ED.

Methods
Patients
The study was conducted in Beijing Chao-Yang Hospital ED, a tertiary teaching hospital of Capital Medical University, and was approved by the human research ethics committee of Beijing Chao-Yang Hospital. A total of 1074 septic patients with positive blood cultures were enrolled in our cohort from 2017 to 2020, and written informed consent upon ED admission was acquired.

Inclusion and Exclusion Criteria
The inclusion criteria were as follows: (1) Patients signed informed consent forms; (2) Age >18 years; (3) Patients with sepsis according to Sepsis-3 (suspected or definite infection with an increase in SOFA score ≥2).[15] (4) Positive blood culture results. The exclusion criteria were as follows: (1) Age < 18 years; (2) Terminal stage of disease (malignant cancer with metastases, AIDS, end-stage renal or hepatic disease, chronic heart failure); (3) Viral or fungal infection with positive blood cultures. (4) Refusal to participate in the study by patients or their relatives or transferred to other hospitals.

Data Collection
Patient characteristics were recorded including age, gender, vital signs, and past medical history. Whole blood leukocyte counts, blood gas indexes, and blood biochemistry were identified within 24h. The SOFA, MEDS, APACHE II, and PIRO scores were calculated according to vital signs, and laboratory test results. PCT, CRP (C-reactive protein), Lac (Lactate) and ALB (albumin) were detected by separating blood samples in the laboratory. For PCT, blood samples were collected in serum separating gel tubes and blood culture samples in Bactec bottles. They were centrifuged at 2000 g for

15 min and serum was separated and stored at −20 °C until assayed. Serum PCT was analyzed by Roche Elecsys BRAHMS PCT reagent, on electrochemiluminescence automated immunoassay analyser. NLR (Neutrophil-to-Lymphocyte Ratio) was calculated based on existing data. The Howell-PIRO scoring system[16] was applied in this study, and the criteria (not included malignant cancer with metastases) are shown in Table 1.

Outcome Variables

MODS was defined as the fulfillment of two or more of the severe sepsis criteria at any time within 3 days of enrollment, excluding organ dysfunction, induced by pre-existing disease.[11] Organ function was assessed at enrollment and reassessed when deterioration occurred. All patients were followed up for 28 days through medical records or by telephone. ICU admission during follow-up, development of MODS within 3 days, and 28-day mortality were considered as the outcome criteria.

Statistical Analysis

All data were analyzed by SPSS 25.0 (SPSS Inc., Chicago, IL, USA). Normally distributed data, expressed as the mean ± standard (mean±SD) deviation, was compared using an independent-samples t-test. Data with skewed distribution was expressed as the median and quartiles, and was analyzed via a Mann–Whitney U-test, and a chi-square test was used to compare frequencies. Logistic regression analysis was used to determine the independent outcome predictors. Receiver operating characteristic (ROC) curves were constructed and the area under the curves (AUC) was determined to assess predictive value. Kaplan-Meier 28-day survival curves were constructed, and Log rank tests were used to compare the curves. All statistical tests were two-tailed, and $P < 0.05$ was considered statistically significant.

Results
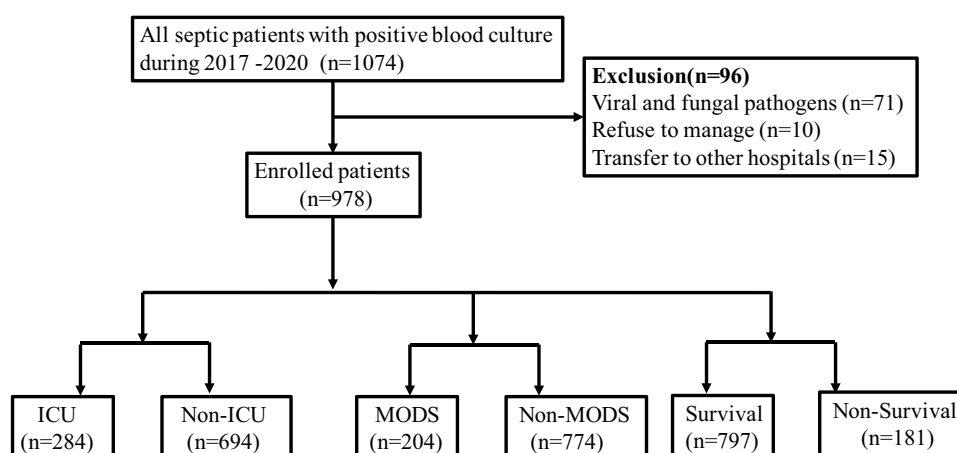## Characteristics of the Study Cohort

As Figure 1 shows, a total of 1074 septic patients with positive blood cultures in the ED between 2017 and 2020 were enrolled in this study. 71 patients had a viral or fungal infection, 10 patients refused to participate, and 15 patients were transferred to other hospitals. Finally, 978 participants completed the 28 follow-up days.

Table 1 Criteria of the Howell-PIRO System (Not Included Malignancy)

Variable	0	1	2	3	4
Predisposition					
Age (years)	<65	65 to 80	>80		
COPD		Yes			
Liver disease			Yes		
Nursing home resident			Yes		
Infection					
Skin/soft tissue infection					
Any other infection			Yes		
Pneumonia					Yes
Response					
Respiratory rate (bpm)				>20	
Bands		>5%			
Heart rate (bpm)			>120		
Organ dysfunction					
SBP (mmHg)	>90		70 to 90		<70
BUN (mmol/l)			>7.1		
Respiratory failure/ hypoxemia				Yes	
Lactate (mmol/l)				>4.0	
Platelet count (x10^9/l)			<150		

Abbreviations: COPD, chronic obstructive pulmonary disease; SBP, systolic blood pressure; BUN, blood urea nitrogen.

Figure 1 Flowchart of the study population.

In our study, 978 septic patients with positive blood cultures were divided into ICU (n=284) and non-ICU (n=694) admission groups. When comparing the characteristics of these patients, we found that there were significant differences in age (P=0.040), chronic obstructive pulmonary disease (COPD) (P<0.001), hypertension (P=0.001), chronic heart failure (CHF) (P=0.007), mean arterial pressure (MAP) (P<0.001), heart rate (HR) (P<0.001), white blood cells (WBC) (P<0.001), Lac (P<0.001), PCT (P<0.001), CRP (P<0.001), ALB (P<0.001), SOFA (P<0.001), MEDS (P<0.001), APACHE II (P<0.001), and PIRO (P<0.001) between ICU and non-ICU admission groups (Table 2, Figure 1).

In addition, we also divided the participants into two other categories, MODS (n=204) and non-MODS (n=774) according to the development of MODS within 3 days. There were obvious differences in age (P=0.001), MAP (P<0.001), HR (P<0.001), respiratory rate (RR) (P<0.001), WBC (P=0.001), Lac (P=0.040), PCT (P<0.001), CRP (P<0.001), ALB (P<0.001), NLR (P<0.001), SOFA (P<0.001), MEDS (P<0.001), APACHE II (P<0.001), and PIRO (P<0.001) between these two groups (Table 2, Figure 1).

After 28 days follow-up, statistical differences were evident in age (P=0.001), chronic heart failure (CHF) (P=0.001), MAP (P<0.001), HR (P<0.001), RR (P<0.001), WBC (P<0.001), Lac (P=0.040), PCT (P<0.001), CRP (P<0.001), ALB (P<0.001), NLR (P<0.001), SOFA (P<0.001), MEDS (P<0.001), APACHE II (P<0.001), and PIRO (P<0.001) between survivor (n=797) and non-survivor (n=181) groups (Table 2, Figure 1).

The median of the SOFA, MEDS, and PIRO scores, and mean of the APACHE II score in ICU-admission, MODS development, and 28-day mortality groups are shown in Table 2, Figure 2. The average SOFA, MEDS, APACHE II, and PIRO scores differed significantly between patients who did, and did not, meet the outcome criteria (P<0.001).

Spearman Correlations Between 28-Day Mortality and SOFA, MEDS, APACHE II or PIRO Score

To investigate the correlations between 28-day mortality and SOFA, MEDS, APACHE II or PIRO score, Spearman correlation analysis was performed. Significant negative linear correlations of 28-day mortality with SOFA, MEDS, APACHE II or PIRO score were presented in Figure 3A–D (r values were −0.62, −0.75, −0.64, −0.49 respectively, and all P<0.001).

Binary Logistic Regression Analysis of the Prognostic Outcome of Septic Patients with Positive Blood Cultures in the ED

Binary logistic regression was used to analyze the independent predictors in our study cohort. The results showed that WBC (β=0.176, odds ratio (OR) (95% CI) =1.192 (1.031–1.379), P=0.018), PCT (β=0.241, OR (95% CI) =1.273 (1.037–1.563), P=0.021), Lac (β=1.261, OR (95% CI) =3.530 (1.867–6.676), P<0.001), ALB (β=−0.142, OR (95% CI) =0.867 (0.792–0.949), P=0.002), NLR (β=0.077, OR (95% CI) =1.080 (1.011–1.155), P=0.023), MEDS score (β=0.895, OR (95% CI)

Table 2 Characteristics of the Study Cohort

Characteristics	ICU (n = 284)	Non-ICU (n = 694)	P	MODS (n = 204)	Non-MODS (n =774)	P	Survivor (n =797)	Non-Survivors (n =181)	P
Age, years	78 (69,84)	70 (59,78)	0.040	82 (78,85)	66 (55,75)	0.001	66 (59,73)	84 (80,86)	0.001
Male, %	161 (56.7)	401 (57.8)	0.754	119 (58.3)	445 (57.5)	0.829	460 (57.7)	105 (58.0)	0.942
COPD, %	90 (31.7)	133 (19.2)	<0.001	57 (27.9)	178 (23.0)	0.142	151 (18.9)	42 (23.2)	0.194
Hypertension, %	147 (51.8)	278 (40.1)	0.001	103 (50.5)	342 (44.2)	0.108	372 (46.7)	80 (44.2)	0.546
CVD, %	63 (22.2)	117 (16.9)	0.051	46 (22.5)	134 (17.3)	0.086	141 (17.7)	34 (18.8)	0.729
CHF, %	137 (48.2)	270 (38.9)	0.007	89 (44.0)	336 (43.4)	0.956	299 (37.5)	93 (51.4)	0.001
CRD, %	40 (14.1)	68 (9.8)	0.052	24 (11.8)	85 (11.0)	0.752	78 (9.8)	20 (11.0)	0.609
DM, %	114 (40.1)	229 (33.0)	0.264	76 (37.3)	249 (32.2)	0.170	235 (29.5)	55 (30.4)	0.811
MAP, mmHg	77 (72,81)	85 (77,93)	<0.001	79 (75,83)	84 (76,92)	<0.001	87 (79,90)	82 (71,91)	<0.001
Temperature, °C	38.51±0.46	38.46±0.52	0.359	38.57±0.41	38.43±0.55	0.075	38.43±0.51	38.61±0.46	0.080
Heart rate, beats/min	102 (90,115)	98 (80,112)	<0.001	116 (104, 134)	90 (78,101)	<0.001	90 (80,100)	119 (107,126)	<0.001
Respiratory rate, bpm	24 (20,28)	24 (23,30)	0.555	30 (29,33)	23 (20,24)	<0.001	23 (20,25)	30 (29,34)	<0.001
WBC, °¡109/L	14.4 (12,18.8)	12.3 (10.8,14.9)	<0.001	15 (14.5,20.3)	11.2 (10.3,12.6)	<0.001	10.6 (10.2,12.1)	16.8 (14.9,20.3)	<0.001
Lac, mmol/L	3.7±1.4	2.4±1.4	<0.001	3.3±1.5	2.5±1.6	0.040	1.8±0.5	3.7±1.6	<0.001
PCT, ng/mL	8.6 (2.5, 12)	5 (2.2, 10.1)	<0.001	8.6 (2.8, 12.5)	3.5 (1.8, 10)	<0.001	2.4 (1.4, 7)	8.5 (3.6, 12.5)	<0.001
CRP	111±39	73±23	<0.001	115±38	70±21	<0.001	67±22	114±34	<0.001
ALB	29±6	33±7	<0.001	25±4	34±5	<0.001	34±6	25±4	<0.001
NLR	14 (8,24)	12 (8,20)	0.080	19 (10,25)	11 (8,19)	<0.001	9 (7,11)	19 (9,25)	<0.001
SOFA	6 (6,8)	4 (3,7)	<0.001	6 (5,9)	4 (4,7)	<0.001	4 (4,7)	6 (5,9)	<0.001
MEDS	11 (9,14)	8 (7,10)	<0.001	13 (10,16)	10 (8,10)	<0.001	10 (8,10)	12 (10,16)	<0.001
APACHE II	16.3±4.8	11.3±2.6	<0.001	15.6±4.2	12.4±2.5	<0.001	12.5±2.6	15.5±4.3	<0.001
PIRO	16 (12,20)	10 (8,12)	<0.001	16 (12,20)	10 (9,12)	<0.001	10 (9,12)	15 (12,20)	<0.001

Abbreviations: ICU, intensive care unit; MODS, multiple organ dysfunction syndrome; COPD, chronic obstructive pulmonary disease; CVD, cerebrovascular disease; CHF, congestive heart failure; CRD, chronic renal disease; DM, diabetes mellitus; MAP, mean arterial pressure; WBC, white blood cell; PCT, procalcitonin; Lac, lactate; CRP, C-reactive protein; ALB, albumin; NLR, neutrophils and lymphocytes ratio; SOFA, Sequential Organ Failure Assessment; APACHE II, Acute Physiology and Chronic Health Evaluation II; MEDS, Mortality in emergency department sepsis; PIRO, Predisposition, Infection, Response, and Organ dysfunction.
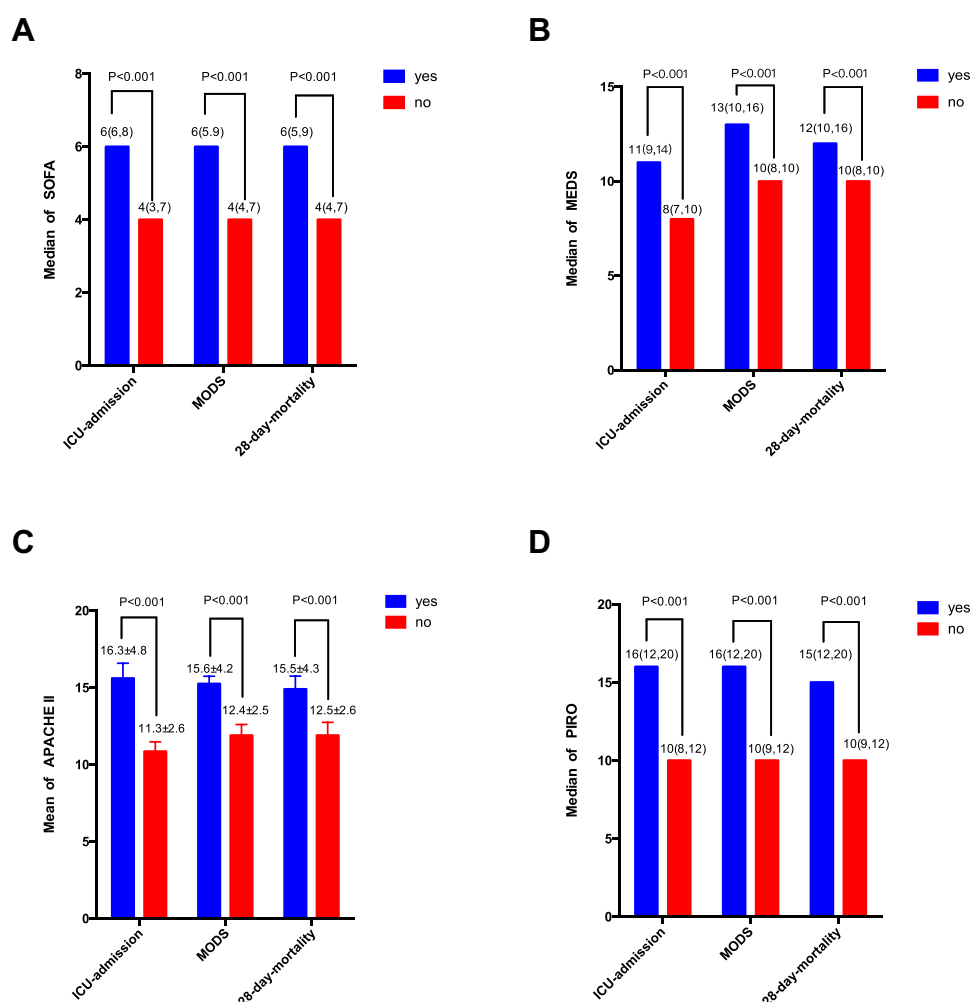
Figure 2 The median levels of SOFA, MEDS and PIRO scores, and mean level of APACHE II score in ICU-admission, developing of MODS and 28-day mortality groups. (**A**) The median level of SOFA score in ICU-admission, developing of MODS and 28-day mortality groups. (**B**) The median level of MEDS score in ICU-admission, developing of MODS and 28-day mortality groups. (**C**) The mean level of APACHE II score in ICU-admission, developing of MODS and 28-day mortality groups. (**D**) The median level of PIRO score in ICU-admission, developing of MODS and 28-day mortality groups.

=2.447 (1.607–3.728), $P<0.001$), APACHE II score (β=0.623, OR (95% CI) =1.864 (1.405–2.474), $P<0.001$) and PIRO score (β=0.328, OR (95% CI) =1.388 (1.118–1.723), P=0.003) were the independent predictors of ICU-admission, but the SOFA score (β=0.220, OR (95% CI) =2.701 (1.548–4.713), P=0.120) was not (Table 3).

In MODS development, WBC (β=0.362, OR (95% CI) =1.436 (1.115–1.849), P=0.005), PCT (β=0.136, OR (95% CI) =1.145 (0.953–1.377), P=0.048), ALB (β=−0.665, OR (95% CI) =0.514 (0.353–0.750), P=0.001), NLR (β=0.270, OR (95% CI) =1.310 (1.092–1.572), P=0.004), MEDS score (β=0.383, OR (95% CI) =1.466 (1.074–2.001), P=0.016), APACHE II score (β=0.372, OR (95% CI)=1.450 (1.056–1.990), P=0.022), and PIRO score (β=0.196, OR (95% CI) =1.216 (1.032–1.434), P=0.019) were the independent predictors of developing MODS, but the SOFA scores (β=0.001, OR (95% CI) =1.001 (0.660–1.518), P=0.995) and Lac (β=0.177, OR (95% CI) =1.194 (0.664–2.145), P=0.554) determined it was not a predictor (Table 3).

In addition, with 28-day mortality, the results showed that WBC (β=0.996, OR (95% CI) =2.707 (1.353–5.417), P=0.005), PCT (β=0.306, OR (95% CI) =1.358 (1.121–1.644), P=0.002), Lac (β=1.822, OR (95% CI) =6.184 (1.565–24.436), P=0.009), MEDS score (β=0.440, OR (95% CI) =1.553 (1.163–2.074), P=0.003), APACHE II score (β=0.484, OR (95% CI) =1.623 (1.179–2.234), P=0.003), and PIRO score (β=0.322, OR (95% CI) =1.380 (1.085–1.754), P=0.009) were the independent predictors of 28-day mortality, but SOFA (β=0.092, OR (95% CI) =1.096 (0.805–1.492), P=0.560),
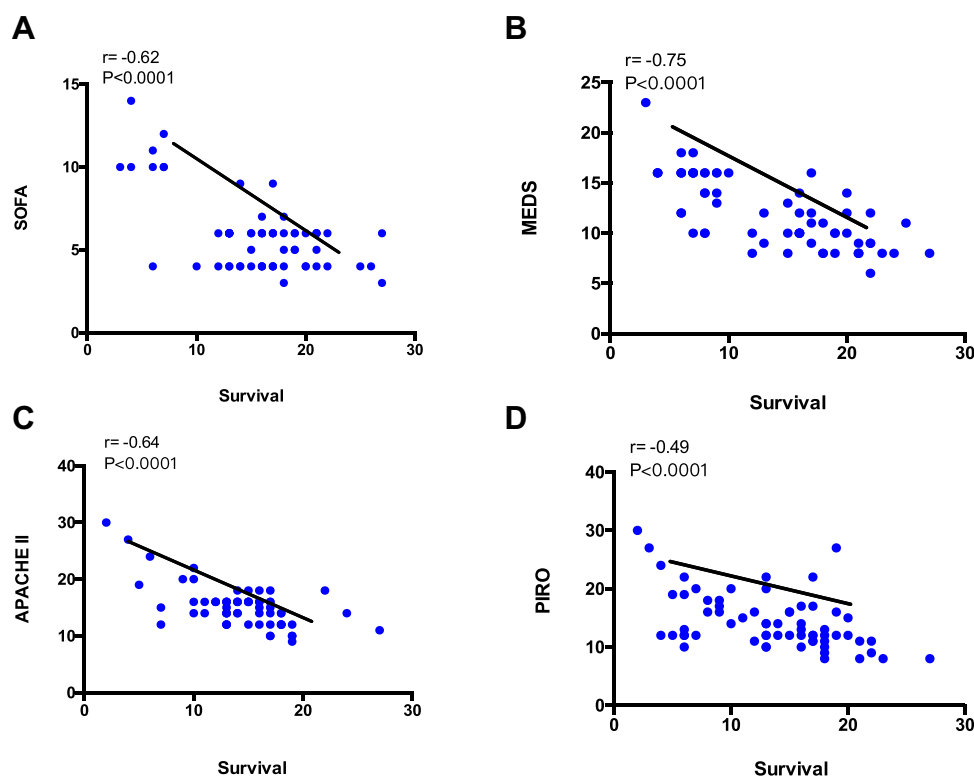
Figure 3 Spearman correlations between 28-day mortality and SOFA score (**A**); MEDS score (**B**); APACHE II score (**C**); PIRO score (**D**) in patients with positive blood cultures.

NLR (β=0.128, OR (95% CI) =1.136 (0.843–1.533), P=0.402), and ALB (β=−0.226, OR (95% CI) =0.798 (0.636–1.001), P=0.051) were not (Table 3).

Prediction of the Prognostic Outcomes of Septic Patients with Positive Blood Cultures

The ROC curves of the PCT, combined with the severe scores for predicting outcomes in septic patients with positive blood cultures, for ICU-admission, MODS development, and 28-day mortality are shown in Figure 4, and the AUCs are presented in Tables 4–6. The AUC values of the PCT, MEDS, APACHE II, and PIRO scores for ICU-admission were 0.620 (95% CI: 0.533–0.706, P=0.009), 0.740 (95% CI: 0.663–0.817, P<0.001), 0.780 (95% CI: 0.709–0.850, P<0.001), 0.751 (95% CI: 0.674–0.828, P<0.001), respectively. The AUC values of a combination of PCT and severe scores for ICU-admission were as follows: PCT+MEDS: 0.772 (95% CI: 0.698–0.846, P<0.001); PCT+APACHE II: 0.821 (95% CI: 0.757–0.885, P<0.001); PCT+PIRO: 0.795 (95% CI: 0.723–0.867, P<0.001). The predictive ability of APACHE II (AUC:0.780) for ICU-admission was slightly better than that of MEDS (AUC: 0.740) and PIRO (AUC:0.751). Consequently, PCT+APACHE II (AUC:0.821) is much better at predicting ICU admission than PCT+MEDS (AUC:0.772) and PCT+PIRO (AUC:0.795) (Figure 4A, Table 4).

Furthermore, for MODS incidence, the AUC values of the PCT, MEDS, APACHE II, and PIRO scores were 0.664 (95% CI: 0.584–0.745, P<0.001), 0.701 (95% CI: 0.622–0.779, P<0.001), 0.761 (95% CI: 0.691–0.832, P<0.001), 0.811 (95% CI: 0.746–0.876, P<0.001), respectively. The AUC values of the combination of PCT and severity scores were as follows: PCT+MEDS: 0.758 (95% CI: 0.685–0.831, P<0.001); PCT+APACHE II: 0.794 (95% CI: 0.727–0.862, P<0.001); PCT+PIRO: 0.837 (95% CI: 0.776–0.898, P<0.001). The ability of PIRO (AUC:0.811) to predict the onset of MODS was much better than that of MEDS (AUC: 0.701) and APACHE II (AUC: 0.761). Therefore, PCT+PIRO (AUC: 0.837) would be better used in predicting the development of MODS than PCT+MEDS (AUC: 0.758) and PCT+APACHE II (AUC: 0.794) (Figure 4B, Table 5).

Table 3 Binary Logistic Regression Analysis of Clinical Outcome for Septic Patients with Positive Blood Culture

| Variables	Predictor	β	SE	Wald	P	OR (95% CI)
ICU-admission	WBC	0.176	1.453	5.632	0.018	1.192 (1.031–1.379)
	PCT	0.241	0.105	5.315	0.021	1.273 (1.037–1.563)
	Lac	1.261	0.325	15.055	<0.001	3.530 (1.867–6.676)
	ALB	−0.142	0.046	9.501	0.002	0.867 (0.792–0.949)
	NLR	0.077	0.034	5.205	0.023	1.080 (1.011–1.155)
	SOFA	0.220	0.142	2.414	0.120	2.701 (1.548–4.713)
	MEDS	0.895	0.215	17.369	<0.001	2.447 (1.607–3.728)
	APACHE II	0.623	0.144	18.644	<0.001	1.864 (1.405–2.474)
	PIRO	0.328	0.110	8.840	0.003	1.388 (1.118–1.723)
	Constant	−13.820	2.939	22.112	<0.001	
MODS	WBC	0.362	0.129	7.861	0.005	1.436 (1.115–1.849)
	PCT	0.136	0.094	2.093	0.048	1.145 (0.953–1.377)
	Lac	0.177	0.299	0.351	0.554	1.194 (0.664–2.145)
	ALB	−0.665	0.192	11.967	0.001	0.514 (0.353–0.750)
	NLR	0.270	0.093	8.452	0.004	1.310 (1.092–1.572)
	SOFA	0.001	0.212	0.000	0.995	1.001 (0.660–1.518)
	MEDS	0.383	0.159	5.808	0.016	1.466 (1.074–2.001)
	APACHE II	0.372	0.162	5.286	0.022	1.450 (1.056–1.990)
	PIRO	0.196	0.084	5.461	0.019	1.216 (1.032–1.434)
	Constant	−18.945	4.468	19.978	<0.001	
28-day-mortality	WBC	0.996	0.354	7.919	0.005	2.707 (1.353–5.417)
	PCT	0.306	0.098	9.764	0.002	1.358 (1.121–1.644)
	Lac	1.822	0.701	6.753	0.009	6.184 (1.565–24.436)
	ALB	−0.226	0.116	3.807	0.051	0.798 (0.636–1.001)
	NLR	0.128	0.153	0.701	0.402	1.136 (0.843–1.533)
	SOFA	0.092	0.157	0.340	0.560	1.096 (0.805–1.492)
	MEDS	0.440	0.147	8.922	0.003	1.553 (1.163–2.074)
	APACHE II	0.484	0.163	8.832	0.003	1.623 (1.179–2.234)
	PIRO	0.322	0.123	6.884	0.009	1.380 (1.085–1.754)
	Constant	−16.492	3.630	20.646	<0.001	

Abbreviations: CI, confidence interval; OR, odds ratio; SE, standard error; WBC, white blood cell; PCT, procalcitonin; Lac, lactate; ALB, albumin; NLR, neutrophils and lymphocytes ratio; SOFA, Sequential Organ Failure Assessment; APACHE II, Acute Physiology and Chronic Health Evaluation II; MEDS, Mortality in emergency department sepsis; PIRO, Predisposition, Infection, Response, and Organ dysfunction.

In addition, after 28-days follow-up, the AUC values of the PCT, MEDS, APACHE II, and PIRO scores for 28-day mortality were 0.782 (95% CI: 0.683–0.882, $P<0.001$), 0.745 (95% CI: 0.627–0.863, $P<0.001$), 0.805 (95% CI: 0.707–0.904, $P<0.001$), 0.831 (95% CI: 0.742–0.920, $P<0.001$), respectively. The AUC values of the combination of PCT and severity scores were as follows: PCT+MEDS: 0.812 (95% CI: 0.705–0.919, $P<0.001$); PCT+APACHE II: 0.866 (95% CI: 0.789–0.943, $P<0.001$); PCT+PIRO: 0.885 (95% CI: 0.810–0.961, $P<0.001$). The ability of the PIRO score (AUC: 0.831) to predict 28-day mortality was better than that of MEDS (AUC: 0.745) and APACHE II (AUC: 0.805). Thus, PCT+PIRO (AUC: 0.885) are slightly better at predicting 28-day mortality than PCT+MEDS (AUC: 0.812) and PCT+APACHE II (AUC: 0.866) (Figure 4C, Table 6).

Patients' 28-Day Survival

As Figure 5 shows, the cumulative survival probability within 28 days was lower in septic patients with a MEDS score>12.5 ($P<0.001$ by the Log rank test), an APACHE II score>15.5 ($P<0.001$ by the Log rank test), a PIRO score>11.5 ($P<0.001$ by the Log rank test), and a combination of PCT+MEDS>0.5 ($P<0.001$ by the Log rank test), PCT+APACHE II>0.23 ($P<0.001$ by the Log rank test), PCT+PIRO>0.39 ($P<0.001$ by the Log rank test), respectively.
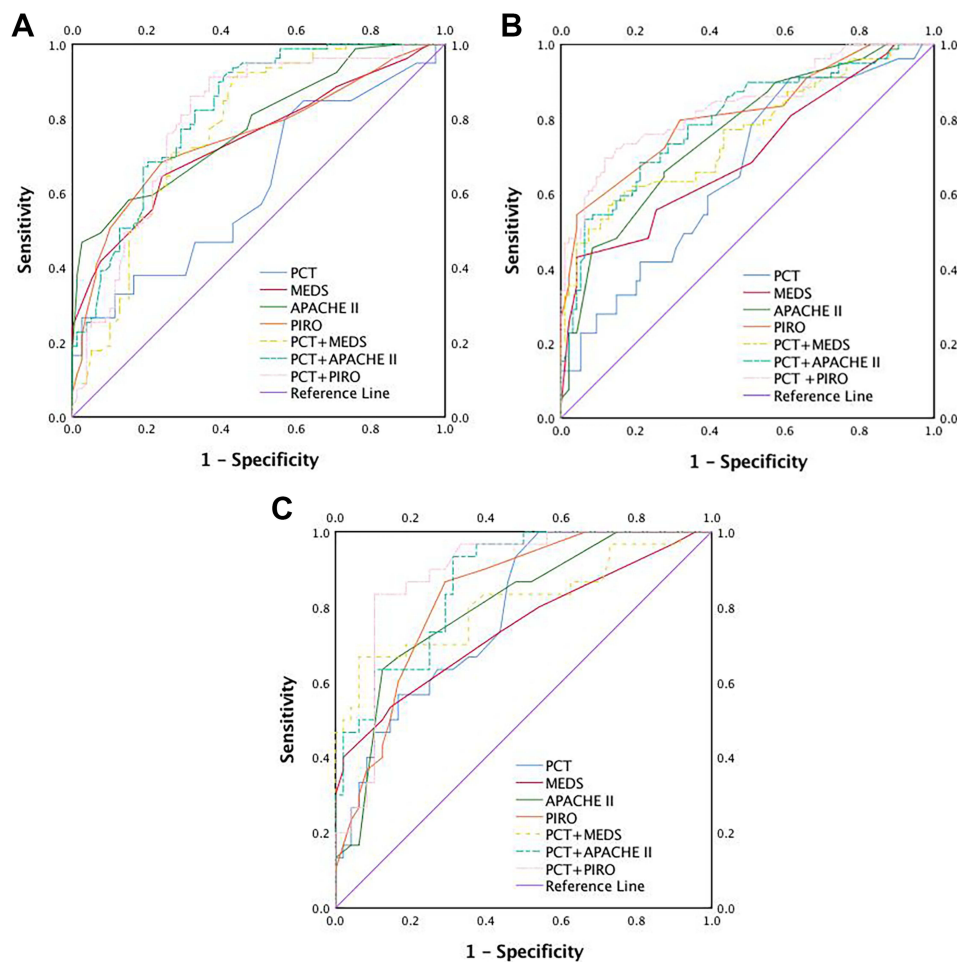
Figure 4 The ROC curves of PCT combined with severe scores for predicting outcomes in septic patients with positive blood cultures for ICU-admission, developing of MODS and 28-day mortality. (**A**) The ROC curves of PCT combined with severe scores in septic patients with positive blood cultures for ICU-admission; (**B**) the ROC curves of PCT combined with severe scores in septic patients with positive blood cultures for developing of MODS; (**C**) the ROC curves of PCT combined with severe scores in septic patients with positive blood cultures for 28-day mortality.

Discussion

Bloodstream infections (BSIs) are commonly considered as being caused by the presence of viable microorganisms in blood,[17] and are often associated with severe infectious diseases with excessively high morbidity and mortality rates.[18–20]

Table 4 Statistical Data of ROC Curve in Predicting ICU-Admission in Patients with Positive Blood Cultures

Variables	AUC (95% CI)	SE	P	Cut Off	Sensitivity	Specificity
WBC	0.725 (0.496–0.954)	0.117	0.075	12.75	0.800	0.750
PCT	0.620 (0.533–0.708)	0.045	0.009	6	0.294	0.977
Lac	0.637 (0.454–0.820)	0.093	0.125	2.25	0.500	0.913
ALB	0.759 (0.574–0.945)	0.095	0.015	26.35	0.875	0.636
NLR	0.615 (0.449–0.782)	0.085	0.225	5.03	0.950	0.353
MEDS	0.740 (0.663–0.817)	0.039	<0.001	8.5	0.646	0.759
APACHE II	0.780 (0.709–0.850)	0.036	<0.001	15.5	0.468	0.975
PIRO	0.751 (0.674–0.828)	0.039	<0.001	11.5	0.684	0.759
PCT+MEDS	0.772 (0.698–0.846)	0.038	<0.001	0.39	0.924	0.557
PCT+APACHE II	0.821 (0.757–0.885)	0.033	<0.001	0.37	0.899	0.608
PCT+PIRO	0.795 (0.723–0.867)	0.037	<0.001	0.45	0.911	0.633

Abbreviations: WBC, white blood cell; PCT, procalcitonin; Lac, lactate; ALB, albumin; NLR, neutrophils and lymphocytes ratio; APACHE II, Acute Physiology and Chronic Health Evaluation II; MEDS, Mortality in emergency department sepsis; PIRO, Predisposition, Infection, Response, and Organ dysfunction.

Table 5 Statistical Data of ROC Curve in Predicting MODS in Patients with Positive Blood Cultures

Variables	AUC (95% CI)	SE	P	Cut Off	Sensitivity	Specificity
WBC	0.879 (0.819–0.938)	0.030	<0.001	12.75	0.911	0.878
PCT	0.664 (0.584–0.745)	0.041	<0.001	1.01	0.911	0.426
ALB	0.789 (0.722–0.856)	0.034	<0.001	28.10	0.851	0.620
NLR	0.727 (0.653–0.801)	0.038	<0.001	7.32	0.873	0.511
MEDS	0.701 (0.622–0.779)	0.040	<0.001	12.5	0.43	0.957
APACHE II	0.761 (0.691–0.832)	0.036	<0.001	12.5	0.658	0.723
PIRO	0.811 (0.746–0.876)	0.033	<0.001	12.5	0.544	0.957
PCT+MEDS	0.758 (0.685–0.831)	0.037	<0.001	0.53	0.582	0.862
PCT+APACHE II	0.794 (0.727–0.862)	0.034	<0.001	0.47	0.684	0.787
PCT+PIRO	0.837 (0.776–0.898)	0.031	<0.001	0.48	0.696	0.883

Abbreviations: WBC, white blood cell; PCT, procalcitonin; Lac, lactate; ALB, albumin; NLR, neutrophils and lymphocytes ratio; APACHE II, Acute Physiology and Chronic Health Evaluation II; MEDS, Mortality in emergency department sepsis; PIRO, Predisposition, Infection, Response, and Organ dysfunction.

Table 6 Statistical Data of ROC Curve in Predicting 28-Day-Mortality in Patients with Positive Blood Cultures

Variables	AUC (95% CI)	SE	P	Cut Off	Sensitivity	Specificity
WBC	0.789 (0.673–0.905)	0.059	<0.001	14.05	0.767	0.896
PCT	0.782 (0.683–0.882)	0.051	<0.001	1.05	0.933	0.521
Lac	0.699 (0.561–0.838)	0.071	0.003	2.25	0.567	0.937
MEDS	0.745 (0.627–0.863)	0.060	<0.001	12.5	0.400	0.979
APACHE II	0.805 (0.707–0.904)	0.050	<0.001	15.5	0.633	0.875
PIRO	0.831 (0.742–0.920)	0.045	<0.001	11.5	0.867	0.708
PCT+MEDS	0.812 (0.705–0.919)	0.055	<0.001	0.50	0.667	0.937
PCT+APACHE II	0.866 (0.789–0.943)	0.039	<0.001	0.23	0.933	0.687
PCT+PIRO	0.885 (0.810–0.961)	0.039	<0.001	0.39	0.833	0.896

Abbreviations: WBC, white blood cell; PCT, procalcitonin; Lac, lactate; APACHE II, Acute Physiology and Chronic Health Evaluation II; MEDS, Mortality in emergency department sepsis; PIRO, Predisposition, Infection, Response, and Organ dysfunction.

Blood cultures are considered to be the reference standard for diagnosing BSIs and are still indispensable in BSI diagnosis.[17] The Surviving Sepsis Campaign guidelines recommend that blood cultures are taken before starting antimicrobial therapy.[21] Blood cultures are straightforward to perform and exhibit high sensitivity to cultivable pathogens.[22] The worldwide increases in incidence have emerged as one of the leading causes of death,[19] particularly in critically ill patients,[20] and the global burden of morbidity and mortality from sepsis is significant.[21] However, improvements in the clinical outcomes of patients with sepsis and septic shock have been made within the last decade, when short-term mortality rates had routinely approached 20%.[22] Delayed, insufficient, or inappropriate anti-infection treatment leads to increased mortality from BSIs.[14,16,23] Prompt initiation of antimicrobial therapies is a critical survival determinant.[24] Currently, the cornerstone of BSI sepsis management continues to be early antimicrobial administration, source control, and supportive care.[25–28] Therefore, early recognition of sepsis criticality, and immediate intervention is significant.

However, there have been very few studies on the criticality and risk structure of septic patients with BSIs. We did find that not all patients with positive blood cultures have a poor prognosis. After timely and effective treatment, many of them were successfully discharged. Therefore, it is necessary to find suitable predictors for the outcomes and prognosis of positive blood culture sepsis. Previous studies showed that SOFA, MEDS, APACHE II and PIRO scores increased with sepsis progression, reaching a maximum limit in septic shock. The PIRO system is an ideal staging system that incorporates assessment of premorbid baseline susceptibility, specific disorders responsible for illness, host response to infection, and the resulting degree of organ dysfunction. Our study applied the Howell-PIRO scoring system to predict
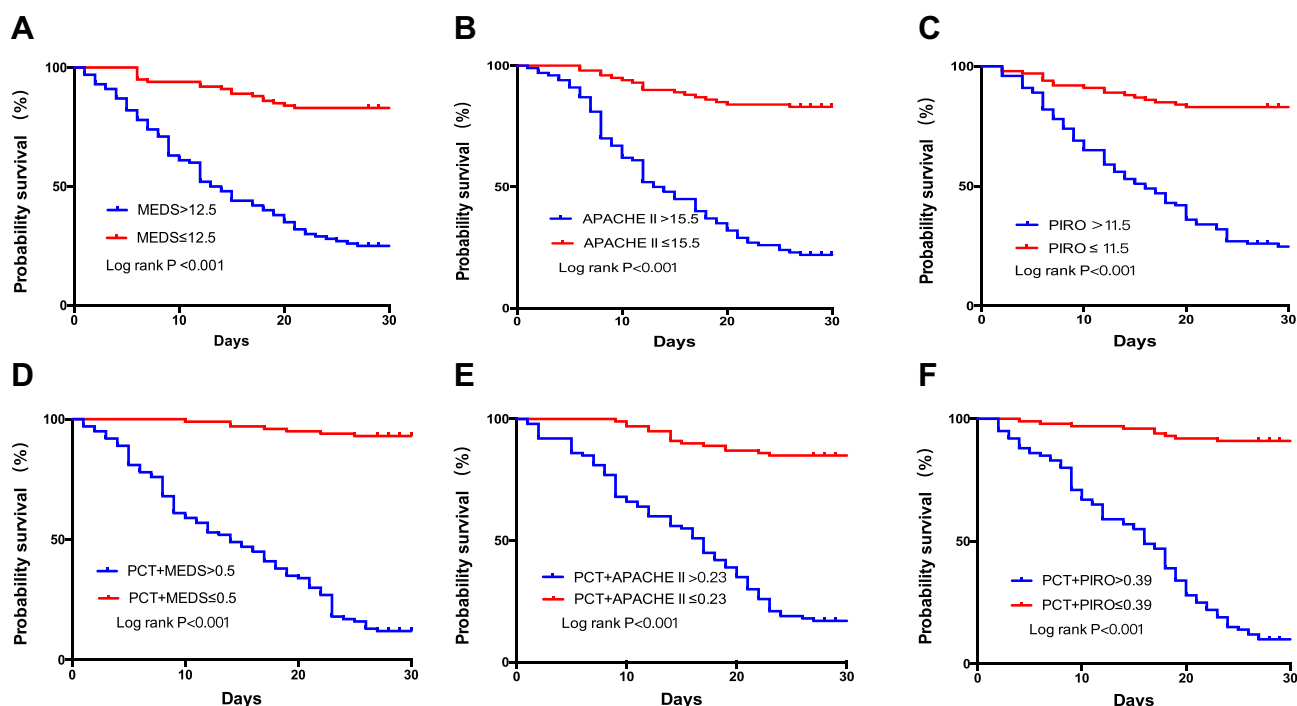
Figure 5 Kaplan-Meier curves for 28-day survival categorized by the MEDS score (**A**), APACHE II score (**B**), PIRO score (**C**), and combination value of PCT+MEDS (**D**), PCT+APACHE II (**E**), and PCT+PIRO (**F**) in septic patients with positive blood cultures.

the risk stratification and prognosis of septic patients with positive BSIs in an ED. The study by Narani et al demonstrated the significant value of PIRO scoring system in assessing risk stratification in emergency department patients with suspected sepsis.[29] The latest study by Vebri et al showed that the modified PIRO severity score could be used as a predictor of mortality in children with pneumonia, as well as be used to select candidates for intensive care.[30] The recent research by Professor T. Cardoso's team had systematically verified the diagnostic and predictive value of the PIRO clinical staging system in ICU and general ward patients, and provided a basis for the decision-making about specific therapeutic interventions and enrollment in clinical trials.[31]

As for PCT, the study of Rao et al showed that PCT was significantly elevated in neonatal sepsis, which was of great significance for the diagnosis of sepsis.[32] PCT was used as predictor of sepsis in obstructive acute pyelonephritis.[33] Zhai et al demonstrated the good diagnostic value of PCT in sepsis closed abdominal injury infection.[34] Thus, PCT was of great significance in sepsis diagnosis and mortality prediction.

In our study, as for ICU-admission, binary logistic regression analysis showed that WBC, PCT, Lac, ALB, NLR, along with the MEDS, APACHE II, and PIRO scores were independent predictors, but the SOFA score was not. The AUC of the APACHE II score was 0.780, which was a little higher than that of PCT (0.620), MEDS (0.740), or PIRO (0.751). In addition, the AUC of PCT in combination with the APACHE II score was significantly higher than that of PCT+MEDS. The AUC of PCT in combination with the APACHE II score was slightly higher than that of PCT+PIRO. The APACHE II score is regularly used to evaluate sepsis severity. For patients admitted to the ICU, their condition is usually critical and they are therefore more likely to develop sepsis or sepsis shock. Our results indicate that the APACHE II score has the highest predictive value for septic patients with positive BSIs. Previous studies have shown that the PIRO scoring system is suitable in assessing ICU patient criticality.[35] This is consistent with our results. The AUC of the PIRO score was comparable with the APACHE II score, and similarly had a high predictive value of ICUadmission. No single biomarker predictions were particularly high, but when combined with other predictors the prediction value increases significantly.

MODS often indicates disease aggravation and deterioration, and is often associated with short-term mortality.[36] In our study, WBC, PCT, NLR, ALB, and the MEDS, APACHE II, and PIRO scores independently predicted MODS

development within three days of ED arrival. However, those of Lac and SOFA did not. The AUC of the PIRO score (0.811) was higher than that of the PCT (0.664), MEDS (0.701), or APACHE II (0.761) scores. Meanwhile, the AUC of PCT combined with the PIRO score was significantly higher than that of any single predictor. The AUC of PCT in combination with the PIRO score was slightly higher than that of PCT+MEDS or PCT+APACHE II score. The PIRO scoring system incorporates the high-risk factors of MODS and variable reflected established organ dysfunction.[11] Therefore, its predictive value was found to be better than both the APACHE II and MEDS scores. These results correspond with the conclusions of previous studies.

In addition, we analyzed the 28-day mortality of positive BSIs. PIRO had a higher predictive value and showed better predictive ability than MEDS or APACHE II scores. In terms of combined prediction, PCT combined with the PIRO score had the highest predictive value for septic patients with positive BSIs. This was consistent with the characteristics of the PIRO scoring system used to assess the severity of critically ill patients. For 28-day mortality, the PIRO scoring system was superior and therefore could be widely used in sepsis prognosis assessment.

The predictive value of the PIRO scoring system and PCT for sepsis is significant. The perfect combination of their advantages has a significant effect on predicting risk stratification and prognosis in septic patients with positive blood cultures. PCT is often used to indicate the severity of bacterial infection. Through the analysis of previous clinical data, it is found that PCT has a high predictive value for ICUadmission, MODS development and 28-day mortality in septic patients with positive blood cultures. After combining it with PIRO scoring system, its predictive value is significantly improved, which has guiding significance for clinical treatment and prognosis. Consulting the literature, there are few studies on blood culture in sepsis, and there is no study on risk stratification and prognosis of patients with positive blood cultures. Our study is the first and of great significance. In future studies, we will further investigate the risk stratification and predictive value of septic patients with negative blood cultures. This will also be a very meaningful study.

Our study had several limitations: It was limited by being a single-center study with a relatively small sample size, and more centers and samples needed to be added to the cohort; some biomarkers had limitations and could not represent all the characteristics of sepsis, and more evaluation biomarkers were needed in the study. Our study also had some positives, in that this was the first time, to our knowledge, that a combination of the PIRO scoring system and PCT has successfully been used to assess the criticality and prognosis of septic patients with positive BSIs.

Conclusions

This study indicates that PCT combined with the PIRO scoring system is superior to that of PCT+MEDS or PCT+APACHE II score in predicting MODS and 28-day mortality in patients with positive blood cultures. The higher predictive value of the PIRO score is therefore essential in assessing the prognosis of sepsis patients with positive BSIs.

Abbreviations

ICU, Intensive care unit; MODS, multiple organ dysfunction syndrome; COPD, chronic obstructive pulmonary disease; CVD, cerebrovascular disease; CHF, congestive heart failure; CRD, chronic renal disease; DM, diabetes mellitus; MAP, mean arterial pressure; WBC, white blood cell; PCT, procalcitonin; Lac, lactate; CRP, C-reactive protein; ALB, albumin; NLR, neutrophils and lymphocytes ratio; SOFA, Sequential Organ Failure Assessment; APACHE II, Acute Physiology and Chronic Health Evaluation II; MEDS, Mortality in emergency department sepsis; PIRO, Predisposition, Infection, Response, and Organ dysfunction.

Data Sharing Statement

The dataset that was used to support the finding of this study will be made available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participant

All procedures performed in studies involving human participant were in accordance with the ethical standards of the institutional and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by Beijing Chao-Yang Hospital Ethics Committee. Written informed consent was obtained from all participants.

Acknowledgments

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that there are no conflicts of interest regarding this work.

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