Research Square

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The C-Reactive Protein to Albumin Ratio as a New Predictor for Bacterial Culture in Patients with Severe Sepsis and Septic Shock: A Single-Center Retrospective Analysis.

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Abstract

Background: Severe sepsis and septic shock with a high mortality rate are common critical illnesses in the emergency department. Early detection and intervention are a key to improve patient outcomes. The CAR is a fresh inflammation-based prognostic score and widely used in clinics. The primary aim of this study was to investigate the relationship between CAR and blood culture.

Methods: 331 adult subjects admitted to the Emergency Intensive care unit via the emergency department from December 1, 2018 to June 30, 2020 were included in this analysis. The study population was divided into positive group and negative group according to the results of blood culture, ROC curves was used to assess the diagnostic performance of CAR, PCT and other risk factors for predicting blood culture, and Youden's index derived cut-offs were calculated.

Results: The patients were subdivided into the positive group and the negative group, 72 cases and 259 cases, respectively. The university analysis indicated that admission PCT, review of PCT, CAR, hepatobiliary system infection, urinary tract infection (relative to lung infection) was significantly corelated with the risk of bloodstream infection. Albumin was negatively correlated with the risk of bloodstream infection. A prediction value of CAR>5 was a significant marker in predicting bloodstream infection (sensitivity:50%; specificity: 71.43%; PPV32.73%; NPV83.71%; P<0.001). Admission PCT and reviewed PCT exhibited greater predictive significance compared with CRP or CAR. At a cut-off of 3.98 ng/ml, reviewed PCT offered the best accuracy in predicting bloodstream infection with the sensitivity, specificity, PPV, and NPV of 84.72%,54.83%, 34.08% and 92.76%; There was no difference in hospital stay and 28-day mortality between the two groups.

Conclusion: A higher CAR is associated with increased incidence of bloodstream infection in patients with severe sepsis and septic shock.

1. Introduction

Sepsis and septic shock remains a major health problem in the intensive care unit(ICU)patients worldwide and is associated with high mortality rates[1, 2]. Recent studies have shown that the mean mortality was 37.3% in the ICU, 39.0% in-hospital and mortality at 28/30 days was estimated at 36.7%[3]. Implementation of sepsis protocols such as early fluid resuscitation, antibiotics and the use of vasopressin has led to a steady decline in mortality, but if the patient is complicated with bloodstream infection (BSI), mortality and hospital stay greatly increased [4, 5]. Because the results of blood culture take anywhere from 24 to 72 hours to obtain, this method is not appropriate for early diagnosis. Therefore, early detection and intervention are critical to improve patient outcomes.

C-reactive protein (CRP) is an acute-phase protein released by hepatocytes and its level in the blood increases within hours in response to inflammation and infection[6]. It can be used for diagnosis, guidance of antibiotic use and mortality prediction, especially in infection cases[7, 8]. Similarly, synthesized exclusively in the liver, albumin plays an important role in several physiological mechanisms

including the regulation of osmotic pressure[9], it was show to be considered as a predictor of severity, prognosis and mortality in patients with sepsis and septic shock.[10, 11]. The CRP to albumin ratio (CAR) is a new inflammation-based prognostic score and widely used in clinics. It can predict the prognosis of patients with acute pancreatitis, acute kidney injury, cancer, critically ill and so on. [12–15] However, there are relatively few studies available which investigates the relationship of this marker with BSI.

In this study, the relationship between the CAR and BSI in patients with sepsis and septic shock was investigated. The predictive value of the CAR for the occurrence of BSI is also evaluated. We reviewed patients with severe sepsis and septic shock who had been processed for the past 2 years. By analyzing the relationship between CAR and blood culture where we hypothesized that CAR could be used as an independent predictor of BSI.

2. Materials And Methods

2.1. Study design and subjects

This retrospective study included patients admitted to a 9-bed Emergency Intensive care unit (EICU) in an 850-bed university-affiliated tertiary care hospital in China. The emergency department (ED) volume of this hospital is approximately 70,000 patients per year. All adult subjects admitted to the EICU via the ED from December 1, 2018 to June 30, 2020 were screened, and subjects diagnosed with sepsis and septic shock were entered in the study. The definitions of sepsis and septic shock were based on sepsis-3 criteria[16]. Patients aged < 18 years and those with pregnancy, undetected CRP and albumin, ICU stay of less than 24 h, severe immunosuppression were excluded. We excluded patients with malignancy, chronic liver disease, liver cirrhosis and infusion of albumin in ED due to a possible effect on albumin levels. Patients for whom blood culture could not be obtained were also excluded from this analysis. Finally, 331 patients were enrolled in the analysis.

2.2 Data collection and definitions

Because of the observational nature of the study, the need for informed consent from enrolled subjects was waived. Case report forms were completed for each included subject and the data were gathered. Missing data could not be addressed due to the characteristic of a retrospective study. Demographic and clinical data were obtained retrospectively from the electronic medical records of each subject. These included baseline characteristics, the source of infection, total hospital length of stay, duration of ICU stay in days and ICU mortality. Initial severity of illness was identified using the Acute Physiology and Chronic Health evaluation score (APACHE II) within the first 24 h of ED admission. The retrospectively identified variables of the initial laboratory examinations at the time of emergency admission were as follows: CRP, Pro-BNP, albumin levels, sodium, potassium, chloride, glucose, lactate, pH, creatinine, white blood cell(WBC), PCT, IL-6, partial pressure of oxygen(pO2), bicarbonate ($HCO3^-$) and blood culture results. PCT and blood culture were reexamined within 24 hours after entering ICU. Normal ranges for CRP and albumin levels respectively were 0 to 4 mg/L and 35 to 50 g/L using an automatic nephelometer

(Johnson, USA). The CAR was calculated by dividing the CRP level by the albumin level. The Cobas 411electrochemiluminescence immunoassay (Roche, Basel, Switzerland) was used to assess blood concentrations of PCT and the normal range was 0 to 0.05ng/ml.

All patients were collected at least two sets of aerobic and anaerobic blood cultures after rigorous skin disinfection. Positive blood culture refers to the isolation of microorganisms from a set of blood cultures collected on the same day. Coagulase-Negative Staphylococci, Micrococcus spp, Bacillus spp, Corynebacterium spp, *Propionibacterium* spp belong to the skin microbiota, which were considered to be contaminants and excluded.[17]

2.3 Study outcomes

The primary outcome was to observe the relationship between CAR and blood culture for admission. Secondary outcomes were risk factors of a positive blood culture, diagnostic efficacy of other inflammatory markers for positive blood culture and all-cause 28-day mortality.

3. statistical Analysis

Statistical Package for Social Sciences (SPSS) for Windows 20 (IBM SPSS Inc., Chicago, USA) and MedCalc 15.1 (MedCalc Software bvba, Ostend, Belgium) were used to perform statistical analysis. According to the results of blood culture, the study population was divided into a positive group and negative group. The normal distribution of the data was evaluated with the Shapiro-Wilk test. Values with normal distribution were presented as mean ± standard deviation, while values without normal distribution were reported as percentages, medians, and interquartile ranges (IQR, 25th to 75th percentile), and analysed using the Student t test or analysis of variance. Categorical variables were expressed as numbers (percentages) and compared using the chi-square or Fisher's exact test. After performing univariate analysis, all significant parameters were further investigated using a multivariate binary logistic analysis with a stepwise backward elimination method to determine the independent risk factors of blood culture. The odds ratio and 95% confidence interval of each independent variable were calculated. The Hosmer-Lemeshow test was used to assess the goodness of fit of the model. We constructed Receiver Operating Characteristic (ROC) curves and computed the area under the Curve (AUC) to assess the diagnostic performance of CAR, PCT and other risk factors for predicting blood culture. Logistic regression model was used to analyse different predictive parameters and calculated the predictive probability that was used to ROC analysis. When a significant cut-off value was observed, the sensitivity, specificity, positive and negative predictive values were presented. A two-sided $P < 0.05$ was considered statistically significant.

4. Results

4.1. Subject characteristics

Demographic characteristics of participants stratified by blood culture are summarized in Table 1. A total of 331 patients were eligible for this analysis. Depending on the results of blood culture, the patients were divided into the positive group and the negative group, 72 cases and 259 cases, respectively. Pulmonary infection in the positive group was less than that in the negative group, while hepatobiliary system infection and urinary tract infection were significantly more than those in the negative group. Patients with positive blood culture were the more likely to have an elevated PCT, lactate, CRP and a lower albumin. There was no difference in hospital stay and 28-day mortality between the two groups.

Table 1
Baseline characteristics of patients in this study according to blood culture results

Characteristic	Overall	Blood culture results		P Value
		negative	positive	
Patients	331(100%)	259(78.2%)	72(21.8%)	
Sex				
Female	114(34.4%)	86(26.0%)	28(8.5%)	0.18
Male	217(65.6%)	173(52.3%)	44(13.3%)	0.37
Age, median (IQR), y	76(64–83)	76(64–83)	77(65–84)	0.24
APACHE-II score median (IQR)	20(15–24)	19(14–24)	20(15–25)	0.37
Source of bacteremia				
Pulmonary	114(34.4%)	110(42.5%)	4(5.6%)	< 0.01
Hepatobiliary system	62(18.7%)	38(14.7%)	24(33.3%)	< 0.01
Abdominal	24(7.3%)	22(8.5%)	2(2.8%)	0.1
Urinary	83(25.1%)	46(17.8%)	37(51.4%)	< 0.01
Skin and soft tissue	22(6.6%)	19(7.3%)	3(4.2%)	0.06
Unknown	26(7.9%)	24(9.3%)	2(2.8%)	0.07
Blood lactate ± SD (mg/dl)	3.80 ± 3.05	3.68 ± 3.12	4.22 ± 2.77	0.18
WBC ± SD (10*9 /L)	12.80 ± 6.91	12.53 ± 6.70	13.74 ± 7.60	0.19
C-reactive protein ± SD (mg/L)	115.6 ± 96.78	108.42 ± 99.79	141.42 ± 80.53	0.01
Admission PCT ± SD (ng/ml)	9.64 ± 17.57	7.82 ± 15.98	16.18 ± 21.22	< 0.01
Reviewed PCT ± SD (ng/ml)	18.08 ± 27.43	14.50 ± 24.86	30.96 ± 32.21	< 0.01
IL-6 ± SD (Pg/ml)	294.80 ± 870.56	265.16 ± 782.45	401.44 ± 1132.72	0.24
Pro-BNP ± SD (Pg/ml)	1450.65 ± 2030.49	1514.07 ± 2163.35	1171.61 ± 1314.49	0.56
Albumin ± SD (g/L)	31.23 ± 5.43	31.86 ± 5.36	29.00 ± 5.14	< 0.01
CRP/ albumin ± SD	4.0 ± 3.57	3.7 ± 3.64	5.06 ± 3.09	0.004
Glycosylated hemoglobin ± SD (%)	6.67 ± 1.91	6.71 ± 1.94	6.54 ± 1.81	0.51
Mean days in ICU (IQR), d	6(3–10)	5(3–10)	6(4–10)	0.89

Characteristic	Overall	Blood culture results		P Value
		negative	positive	
Mean days in hospital (IQR), d	10(7–15)	10(7–15)	11(8–17)	0.35
28-day mortality	81(24.5%)	66(25.5%)	15(20.8%)	0.42

4.2. Blood culture results.

The positive rate of blood culture was 21.8%. Since most of the pathogenic bacteria originate from the urinary tract(51.4%)and hepatobiliary system（33.3%）, the main pathogens cultivated were Escherichia coli (55.6%)and Klebsiella pneumoniae（18.1%）. The rests were Pseudomonas aeruginosa (5.6%), Staphylococcus aureus (4.2%), Enterobacter cloacae (4.2%) and some other pathogens (11.1%), as showed in Table 2. There were 9 cases of Staphylococcus epidermidis and Corynebacterium considered to be contaminants and excluded.

Table 2
Distribution of pathogens with positive blood culture

Organism	Number of isolates (%)
Escherichia coli	40(55.6)
Klebsiella pneumoniae	13(18.1)
Pseudomonas aeruginosa	4(5.6)
Acinetobacter baumannii	1(1.4)
Staphylococcus aureus	3(4.2)
Enterobacter cloacae	3(4.2)
Others	8(11.1)

4.3. Univariate and multivariate analysis for discriminating BSI

Figure 1 showed the univariate logistic regression models between baseline variables and BSI. The univariate analysis indicated that admission PCT (OR = 1.023, 95% CI, 1.009–1.036, P = 0.001), review of PCT (OR = 1.019, 95% CI, 1.010–1.028, P < 0.0001), CAR (OR = 1.08, 95% CI, 1.01–1.16, P = 0.024), hepatobiliary system infection (OR = 17.37, 95% CI, 5.66–53.28, P < 0.001), urinary tract infection (OR = 22.12, 95% CI, 7.46–65.62, P < 0.0001) were positively correlated with the risk of BSI. Albumin (OR = 0.89,95% CI, 0.85–0.95, P < 0.0001) was negatively correlated with the risk of BSI.

Multivariate analysis results were presented in **Fig. 2.**The results also showed that reviewed PCT (OR = 1.01, 95% CI, 1.00-1.03, P = 0.007), hepatobiliary system infection (OR = 15.54, 95% CI, 4.87–49.55, P < 0.001) and urinary tract infection(OR = 19.34, 95% CI, 6.34–59.04, P < 0.001) (relative to lung infection) were independent risk factors for predicting BSI, but CAR and admission PCT were excluded(P > 0.05).

4.4 The ROC curve for BSI

We evaluated the predictive value of admission PCT, reviewed PCT, albumin, CRP and CAR alone using ROC analysis (**Fig. 3**). The area under the ROC curve for BSI was 0.714(0.662–0.762), 0.73(0.679–0.777), 0.669(0.615–0.719),0.6(0.545–0.653) and 0.62(0.565–0.672) for admission PCT, reviewed PCT, albumin, CRP and CAR, respectively. A prediction value of CAR > 5 was considered to a significant marker in predicting BSI (sensitivity:50%; specificity: 71.43%; PPV32.73%; NPV83.71%; P < 0.001).By comparing the AUC, admission PCT and reviewed PCT exhibited greater predictive significance compared with CRP or CAR. At a cut-off of 3.98 ng/ml, reviewed PCT offered the best accuracy in predicting BSI with the sensitivity, specificity, PPV, and NPV of 84.72%,54.83%, 34.08% and 92.76%; 3.97 ng/ml was the optimum cut-off of admission PCT, the sensitivity, specificity, PPV, and NPV were 66.7%, 69.1%,37.5% and 88.18%, respectively.

In order to explore the application value of multi-indicator joint prediction of BSI, We combined PCT with the site of infection and albumin through the Logistic analysis model to establish a regression equation to calculate the BSI probability comprehensively, and then used ROC analysis to calculate AUC. Through calculation, we found that reviewed PCT combined with the site of infection could more effectively predict the occurrence of BSI with AUC of 0.840(95%CI 0.796–0.878; sensitivity:84.72%; specificity:72.59%; PPV46.51%;NPV94.06%)(**Fig. 4A)**. The combination of reviewed PCT, albumin and the site of infection maximally increased the predictive power with the highest AUC of 0.844(95%CI 0.801–0.882; sensitivity:87.50%; specificity:70.27%;PPV45%;NPV95.29%) (**Fig. 4B)**.

5. Discussion

Severe sepsis and septic shock with a high mortality rate are common critical illnesses in the ED, and the mortality rate of patients with BSI is higher. Early recognition and appropriate antibacterial treatment are a key to improving patient outcomes[18]. CAR as a new inflammation-based prognostic score is widely used in clinics and an independent risk factor for 30-day mortality after ICU admission[12–15]. Whether it can predict BSI in patients with sepsis or septic shock does not know. The current study showed that CAR determined from data collected in the ED was another predictor of bacterial culture in patients with severe sepsis and septic shock. However, the predictive power of CAR was lower than albumin alone. Moreover, the sensitivity and specificity for prediction of BSI were not so high compared with the PCT in this single center study. Therefore, clinical usefulness of CAR in predicting BSI in patients with severe sepsis and septic shock is questionable.

Many studies have shown that the PCT can be a useful biomarker to detect bacterial etiology at initial stages of infection and could be helpful also in differentiating bacterial from non-bacterial infections[19, 20].We found that PCT checked in the ED gets a better diagnostic accuracy and higher sensitivity and specificity than IL-6,WBC and CRP. Furthermore, Reviewed PCT concentrations of patients with BSI were significantly higher than those of patients without BSI. PCT reviewed within 24 hours was an independent predictor of BSI after multiple factor regression analysis and its cut-off value was 3.98 ng/ml, NPV was

92.76%. Two concentrations of PCT were similar, which could be a coincidence. But it also indicated that PCT at a cut-off of 3.98 ng/ml could be used for distinguishing BSI and non-BSI. It means that if the value of PCT is not significantly increased, the probability of patients with BSI is very low. Evidence suggests that differences in PCT concentrations during different types of infection and PCT value of patients infected with gram-negative rods is significantly higher than that of patients with gram-positive cocci. The same conclusion in this study, greater than 84.7% of the positive blood culture results were gram- negative rods. Blood cultures are more frequently positive in patients who are PCT positive than PCT negative patients [21, 22]. We found that the diagnostic efficiency of reviewed PCT was higher than that at the beginning, which reminds us that it is important to observe the level of PCT dynamically, especially in the hepatobiliary system and urinary system infection.

Based on the results of this study, albumin level was also an independent predictor of BSI. Albumin has pleiotropic physiological activities including antioxidant effects, maintenance of colloidal osmotic pressure and positive effects on vessel wall integrity[23]. The underlying inflammatory state gives rise to a decrease of albumin production in the liver by increasing inflammatory factors and the concentration of albumin tends to decrease in acute phase of infection. Hypoproteinemia causes the decrease of plasma colloidal osmolality and peripheral edema[24]. Severe sepsis also leads to disruption of the endothelial glycoprotein layer, damage to the microvasculature, resulting in interstitial accumulation of fluid and subsequently edema. Increased vascular permeability and tissue edema are likely to cause bacterial displacement, aggravating the inflammatory response and forming a vicious circle[25, 26]. Therefore, albumin is associated with disease severity and the mortality rate[27]. Whether timely correction of hypoproteinemia can reduce the incidence of BSI is unknown, and further prospective studies are needed to confirm.

To maximize the diagnostic efficiency, we combined PCT with albumin and the site of infection in the logistic analysis model and built the regression equation to calculate BSI probability comprehensively, and subsequently used ROC analysis to calculate the AUC. And in the validation set, the combination of reviewed PCT, albumin and the site of infection maximally increased the predictive power, the AUC in predicting BSI reached 0.844, NPV was 95.29%. It indicated that we could exclude most patients with non-BSI. But biochemical indicators have their limitations. The highest PPV was only 46.51% when the reviewed PCT combined with the site of infection. New technologies can make up for this. PPV was 68% after adjudication of discrepant pathogens detected by A novel multiplex real-time PCR for BSI in critically ill patients with sepsis[28]. The M-PCR provided good overall performances for bacterial identification (sensitivity 80%, 95% CI 71–88%,specificity 99%, 95% CI 99–100% PPV 87% (95% CI, 80–93%), and NPV 99% (95% CI, 99–99%)) and resistance gene detection[29]. Recently, next-generation sequencing (NGS) methods and application of machine-learning methods have showed promising results in the diagnostic of BSI[30]. But they have no advantage in terms of price, further studies are required to assess the cost-efficiency and clinical impact of these determination methods.

Previous studies have demonstrated that BSI and their evolution of severe sepsis and septic shock are one of the most important causes of morbidity and mortality[4, 5, 31]. In our study, we observed no

increase in mortality in patients with BSI(P = 0.42). A possible explanation for this might be that we were more likely to pay more attention to patients with positive blood cultures. Second, 84.7% of BSI were from urinary tract and hepatobiliary system, techniques of biliary and urethral drainage for these patients we actively carried out which is considered the reason for reducing the mortality rate[32, 33]. Otherwise, small sample size could also be one of the reasons.

Limitations

We also required to consider the limitations of this study. First, it was a retrospective design, which may have introduced bias. Second, this study was a single-center retrospective analysis, and the results may differ from those of other centers. Furthermore, the sample was small. Finally, sensitivity and specificity of CAR for prediction of BSI were not so high in this study. Therefore, large, multicenter studies are required to confirm these results and establish CAR as a useful marker for the prediction of BSI in severe sepsis and septic shock patients.

Conclusion

In summary, this study demonstrated that a higher CAR is associated with increased incidence of BSI in patients with severe sepsis and septic shock. However, sensitivity and specificity of CAR for prediction of BSI were not so high compared with PCT. PCT was an independent predictor of BSI and PCT out-performed the CRP and IL-6 in detecting BSI. Dynamic reexamination of the PCT within 24 hours after admission is more significant to exclude BSI. Moreover, the combination of multiple indexes can improve the effectiveness of diagnosis.

Abbreviations

CAR
CRP to albumin ratio
ICU
Intensive care unit
EICU
Emergency intensive care unit
ED
emergency department
PCT
Procalcitonin
APACHE II
Acute Physiology and Chronic Health evaluation score
IQR
Interquartile range
SD

Standard deviation
OR
Odds ratio
BSI
Bloodstream infection
WBC
White blood cell
CRP
C-reactive protein
ROC
Receiver operating characteristic
PPV
Positive Predictive Value
NPV
Negative predictive value
$HCO3^-$
bicarbonate
AUC
Area Under Curve

Declarations

Availability of data and materials

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

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Contributions

LZF and NHB conceived and designed the research and assisted in revision of manuscript; GJS cleared and analyzed research data and wrote the initial paper. SL assisted in the design of the research and interpret research results and revised paper; ZAP collected research data and assisted in interpretation of research results; HZJ collected the research data; ZXZ assisted in interpretation research results. All authors read and approved the final manuscript.

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Ethics declarations

Ethics approval and consent to participant

This study was approved by the Ethical Committee of Hospital in 2020 (2020LWKY005), and the need for patient consent was waived.

Consent for publication

Not applicable.

Competing interests

None of the authors has a competing financial interest regarding this research.

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Figures

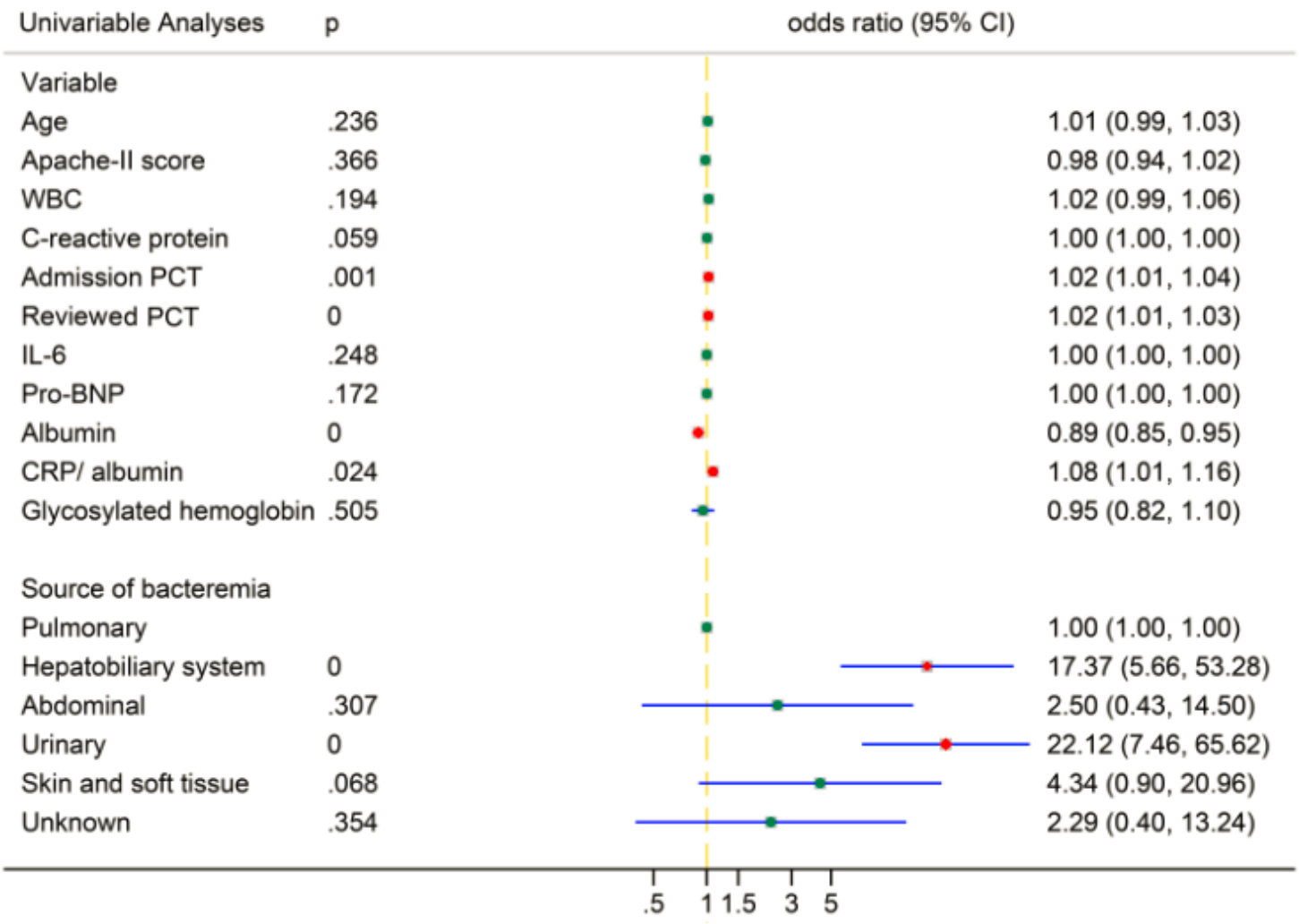


Figure 1

Univariable Logistic Analyses for Discriminating BSI in severe sepsis and septic shock

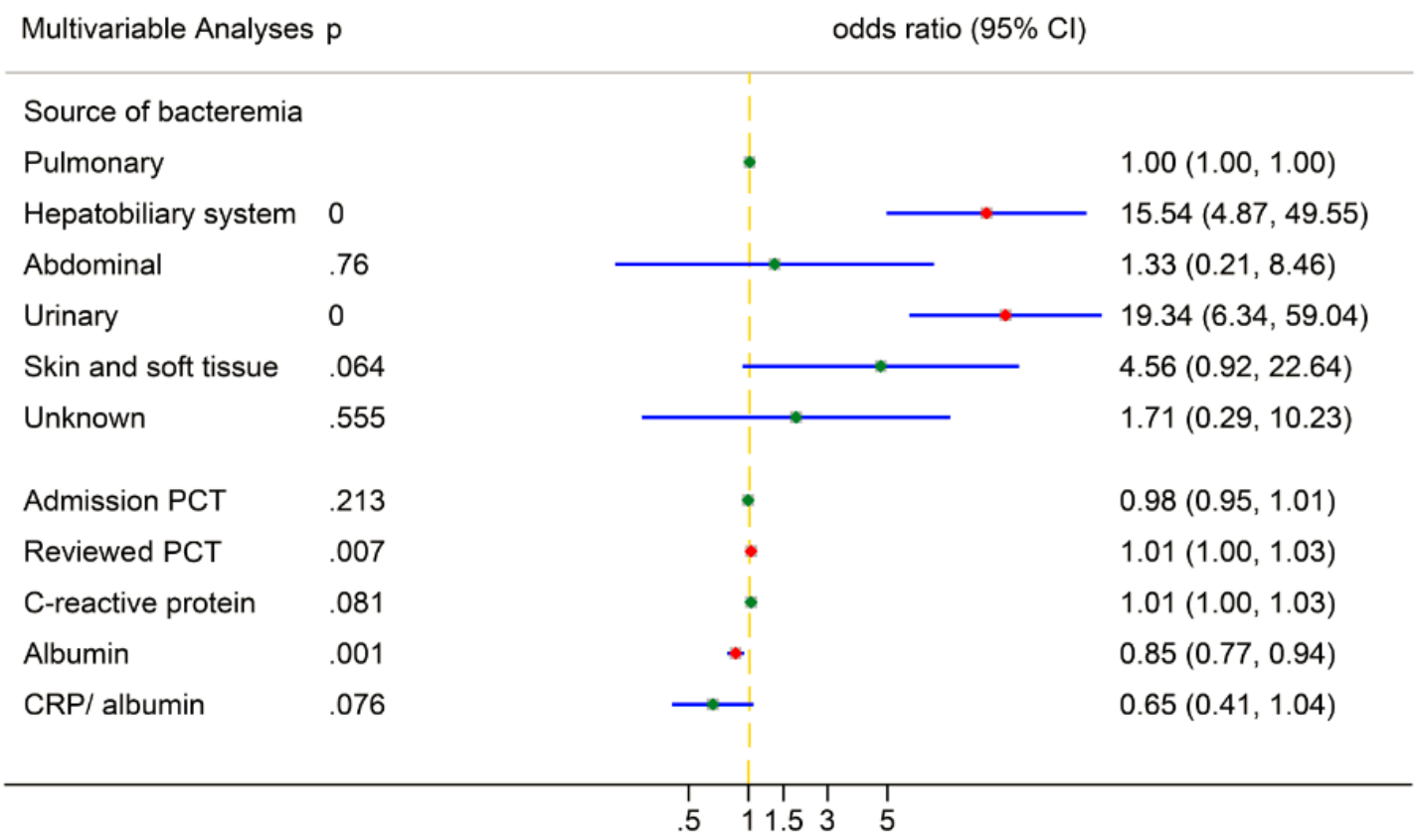
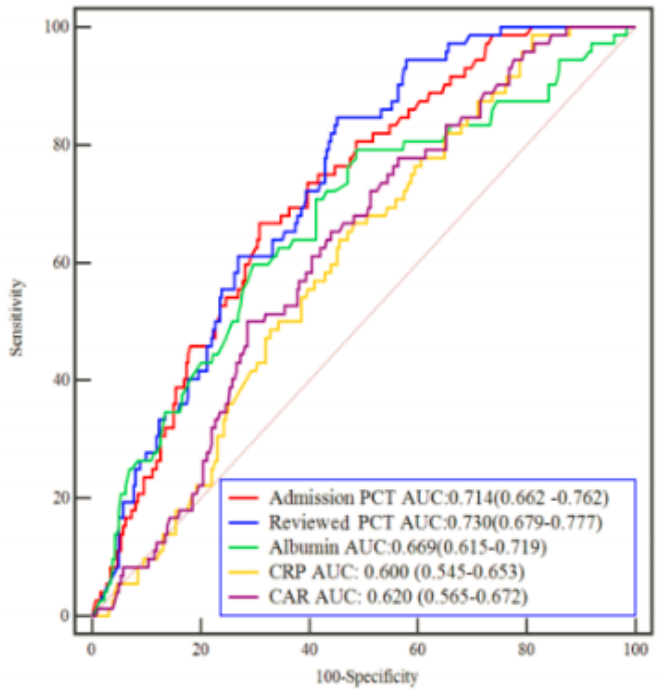


Figure 2

Multivariable Logistic Analyses for Discriminating BSI in severe sepsis and septic shock



Pairwise comparison of ROC curves

Admission PCT ~ Reviewed PCT	
Difference between areas	0.0161
Standard Error [a]	0.0141
95% Confidence Interval	-0.0116 to 0.0438
z statistic	1.142
Significance level	P = 0.2533
Admission PCT ~ Albumin	
Difference between areas	0.0450
Standard Error [a]	0.0471
95% Confidence Interval	-0.0473 to 0.137
z statistic	0.956
Significance level	P = 0.3388
Admission PCT ~ C-reactive protein	
Difference between areas	0.114
Standard Error [a]	0.0437
95% Confidence Interval	0.0279 to 0.199
z statistic	2.598
Significance level	**P = 0.0094**
Admission PCT ~ CAR	
Difference between areas	0.0943
Standard Error [a]	0.0437
95% Confidence Interval	0.00864 to 0.180
z statistic	2.158
Significance level	**P = 0.0310**

[a] DeLong et al., 1988

Figure 3

The ROC curve comparison of admission PCT, reviewed PCT, CRP, albumin, and CAR in the prediction of BSI

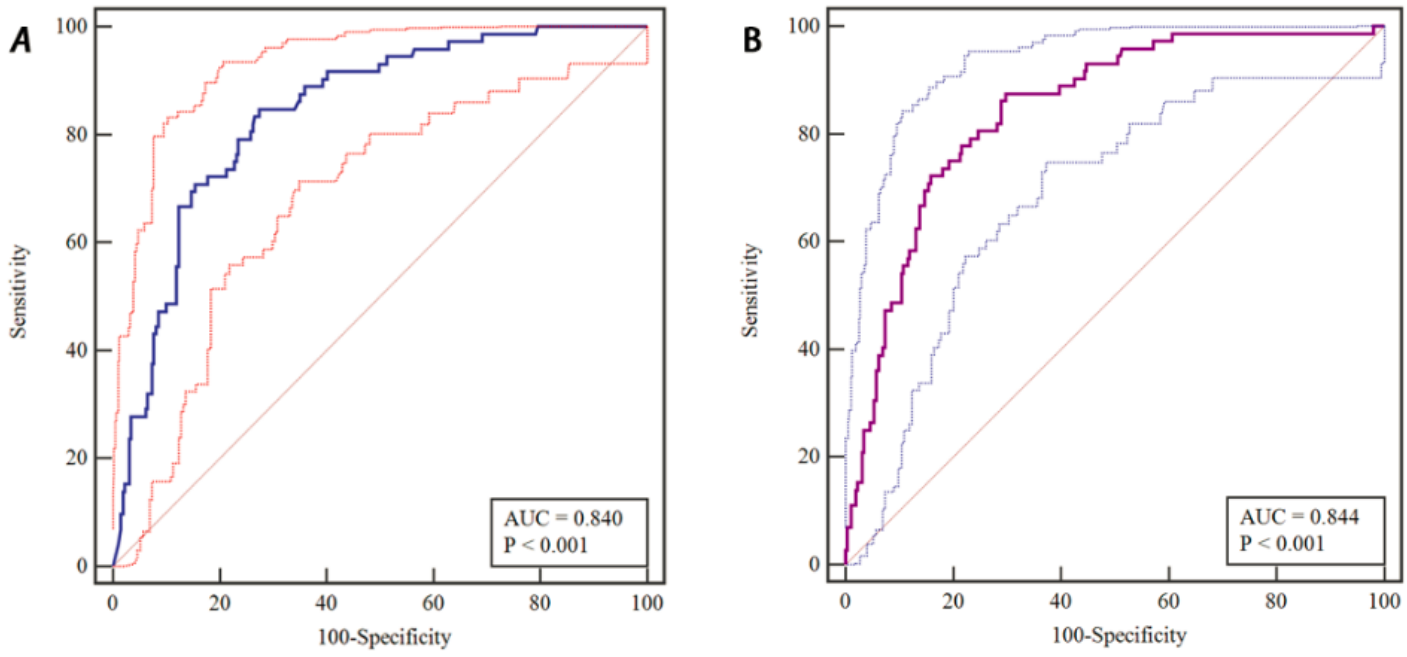


Figure 4

A ROC analysis for combination of reviewed PCT and the site of infection in prediction BSI. B ROC analysis for combination of reviewed PCT, albumin and the site of infection in prediction BSI.