Presepsin as a predictor of severe sepsis in urinary tract infection

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Research Article

Keywords: presepsin, urinary tract infection, sepsis, procalcitonin

Posted Date: March 13th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-284985/v1

Abstract

Background Recently, presepsin is reported to be a biomarker for early diagnosis of sepsis and evaluation of prognosis in septic patients, but there are few reports about urinary-tract infections. The objective of this study is to evaluate whether presepsin is a recent marker for detecting severe sepsis, and whether it can predict the therapeutic course in UTI when compared with procalcitonin (PCT) and C-reactive protein (CRP), already used markers.

Methods From April 2014 to December 2016, a total of 50 patients, who were admitted into Gunma university hospital with urinary-tract infections, were enrolled in this study. Vital signs, presepsin, PCT, CRP, white blood cell (WBC), causative diseases of urinary-tract infections and other data were evaluated at the enrollment, third and fifth days. The patients were divided into two groups; with (n=11) or without (n=39) septic shock at the enrollment day, and with (n=7) or without (n=43) sepsis at the fifth day, respectively. Presepsin was evaluated for systemic inflammatory response syndrome (SIRS) or septic shock.

Results Concerning the enrollment day, there was no significant difference of presepsin between SIRS and non-SIRS groups (p=0.276). The median presepsin (pg/mL) was significantly higher in the septic shock group (p<0.001). Multivariate logistic regression analysis showed presepsin (≧ 500 pg/ml) was an independent risk factor associated with septic shock (p=0.007). ROC curve for diagnosing septic shock indicated an area under the curve (AUC) at 0.881 for presepsin (vs. 0.690, 0.583 and 0.527 for PCT, CRP and WBC, respectively). Concerning the 5th day after admission, the median presepsin of the enrollment day was significantly higher in SIRS groups than non-SIRS groups (p=0.006). On the other hand, PCT (≥ 2 ng/ml) of the enrollment day was an independent risk factor associated with SIRS. ROC curve for diagnosing sepsis at the fifth day indicated an AUC at 0.837 for PCT (vs. 0.817, 0.811 and 0.802 for presepsin, CRP and WBC, respectively).

Conclusions This study shows that presepsin may be a good marker for diagnosis of severe patients who need vasopressor therapy at the data of admission, and PCT may be a good marker for predicting hard-to-treat cases in UTI.

Introduction

Urinary tract infections (UTI) are common, and sometimes progresses to sepsis or septic shock, which can be lethal. Mortality from severe sepsis and septic shock is reported to be between 20-50% [1,2], and the ratio of UTI in all-cause of severe sepsis and septic shock is 9-31% [2]. Therefore, the diagnosis and severity of sepsis or septic shock are important at the beginning of treatment in UTI.

Clinically, C-reactive protein (CRP) and procalcitonin (PCT) are used as markers of disease severity in UTI. However, both CRP and PCT have some limitations. The response time after bacterial infections is delayed (CRP; 6hr, PCT; 2-3hr), the trigger for production is not living bacteria (CRP; cytokine, PCT; endotoxin and cytokine), and the serum half-time is long (CRP; 4-6hr, PCT; 20-24hr) [3,4]. Therefore, a new

biomarker of bacterial infection, which reflects the clinical condition at the time of measurement is required.

Presepsin is a 13KDa fragment of the N-terminal of soluble CD14 [5]. Granulated leukocyte phagocytose both bacteria and CD14 and expel presepsin into the blood after enzymatic digestion of bacteria within two hours [5,6]. Recently, presepsin has been reported to have a high sensitivity for detecting sepsis and to be a biomarker for early diagnosis of sepsis [7]. Moreover, elevated presepsin levels on day 1 can evaluate the prognosis of septic patients in intensive-care unit [8,9]. However, there are few reports on the use of presepsin in UTI.

The objective of this study is to evaluate whether presepsin is a useful marker for detecting sepsis or severe sepsis, and whether it can predict the therapeutic courses in UTI compared with other markers, such as PCT and CRP.

Materials And Methods

Patients

We performed a prospective observational study. From April 2014 to December 2016, a total of 57 patients, who were admitted into Gunma university hospital with UTI, were enrolled in this study. Seven patients were excluded from this study due to data unavailability. UTI was diagnosed by a urologist based on urinary sediment (≥ 5 leucocytes/high power field) and symptoms (fever and/or micturition pain and/or flank pain). Patient age, sex, medical history, oral medicine, blood pressure, body temperature, heart rate, respiratory rate, urine and blood culture results, surgical procedure for UTI after admission, causative diseases of UTI, presepsin, PCT, CRP, white blood cell (WBC), Aspartate transaminase (ALT), Alanine transaminase (AST), γ-glutamyl transpeptidase (γGPT) and Creatinine (Cr) were collected. Vital signs and blood data were evaluated at enrollment, and on the 3rd and 5th day after admission. This study was approved by the institutional review board of Gunma University Hospital (No.1650).

Assessment of systemic inflammatory response syndrome (SIRS) and septic shock

The diagnosis of SIRS and septic shock were made according to the criteria set by the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) [10].

Outcomes

Three outcome variables: SIRS on the enrollment day, septic shock on the enrollment day, and SIRS on the 5th day after admission were evaluated by dividing the participants into two groups for each of these variables; with (n=39) or without (n=11) SIRS on the enrollment day, with (n=11) or without (n=39) septic shock on the enrollment day, and with (n=7) or without (n=43) SIRS on the 5th day after admission, respectively.

Statistical Analysis

Mann-Whitney U-test was used for the continuous variables (age, CRP, presepsin, PCT, ALT, AST, γGPT and Cr). We estimated the independence by the chi-squared test or Fisher`s exact test for categorical variables (sex, placement of urinary catheter, urological cancer, urinary calculi, diabetes mellitus and internal use of steroid). Independent predictors were evaluated using logistic regression analysis. The predictive accuracy of presepsin, PCT, CRP and WBC for septic shock or SIRS was evaluated by the area under the curve (AUC) of a receiver operating characteristics (ROC) analysis. The Youden's index (sensitivity + specificity - 1) was used to calculate optimal cutoff values of presepsin. P values ≤ 0.05 were considered evidence of a significant difference. SPSS Statistics Ver. 25 (IBM Corp. IL, USA) was used for statistical analysis.

Results

Patients Characteristic

Table 1 shows the clinical characteristics of the 50 patients. On the enrollment day, septic shock was detected in 22% (n=11) and SIRS in 78% (n=39) of patients. The mean age was 66.5 years, and 33 patients (66%) were male and 17 (34%) were female. Bacterial growth in urine and blood cultures were positive in 90% (n=45) and 48% (n=24) of samples. There were 48% (n=24), 30% (n=15), 24% (n=12), 18% (n=9), 56% (n=28) and 18% (n=9) with placement of urinary catheter, urological cancer, urinary calculi, diabetes mellitus, surgical procedure after admission and internal use of steroid, respectively.

Prediction of SIRS on the enrollment day

The overall median baseline presepsin, PCT, and CRP levels were 483 pg/mL, 0.87 ng/mL, and 10.45 mg/L, respectively, with no significant difference between SIRS and non-SIRS groups (supplemental Table 1).”

Prediction of Septic shock on the enrollment day

The median presepsin level (pg/mL) was significantly higher in the septic shock group (1380 vs. 399, p<0.001). The PCT and CRP levels were not significantly different between septic shock and non-septic shock groups. Other blood investigations that were significantly higher in the septic group included: AST (p=0.003), ALT (p=0.049), γGTP (p=0.002 and Cr (p=0.02), respectively (Table 1a). Logistic regression analysis to evaluate factors associated with septic shock on enrollment day is shown in Table 1b. Factors associated with septic shock on univariate analysis included presepsin (≥ 500 pg/mL), PCT (≥ 2 ng/ml), AST (≥ 34 U/L) and γGTP (≥ 47 U/L). Only presepsin level retained significance after controlling for confounders in multivariate logistic regression analysis (Table 1b). ROC curve for diagnosing septic shock indicated AUC of 0.881 for presepsin, which is larger than other markers (Fig.1). The Cutoff level of presepsin with the optimum diagnostic efficiency by the ROC curves were 492 ng/ml, which was broadly similar to clinical cut off values (500 pg/mL).

Prediction of SIRS on the 5th day after admission

The median presepsin level (pg/mL) was significantly higher in SIRS on the 5th day after admission group (day1; 1167 vs. 419, p<0.001, day3; 633 vs. 311, p=0.027). The PCT (day1; 73.1 vs. 0.55, p=0.003, day3; 20.34 vs. 1.35, p=0.005)) and CRP (day1; 25.63 vs. 8.23, p=0.007, day3; 25.58 vs. 10.71, p<0.001) levels were also significantly different between SIRS and non-SIRS on the 5th day after admission groups. Other blood investigations that were significantly higher in SIRS on the 5th day after admission group included: day1/AST (34 vs. 24, P=0.013), day1/Cr (2.3 vs. 1.05, p=0.007), day1/WBC (18200 vs. 13600, p=0.009) and day3/WBC (11900 vs. 8400, p=0.021) (table 2a). The ratio of positive blood culture (86% vs. 42%, p=0.039) and urinary calculi (57% vs. 19%, p=0.048) significantly differed between SIRS and non-SIRS on the 5th day after admission groups. Logistic regression analysis to evaluate factors associated with SIRS on the 5th day after admission is shown in Table 2b. Factors associated with SIRS on the 5th day after admission in univariate analysis included day1/presepsin (≥ 500 pg/mL), day1/PCT (≥ 2 ng/ml) and urinary calculi. Only day1/PCT level retained significance after controlling for confounders in multivariate logistic regression analysis (Table 2b). ROC curve in patients with definitive prediction of SIRS on the 5th day after admission indicated an AUC at 0.837 for PCT, which is larger than other markers (Fig.1). Concerning presepsin, the cutoff level with the optimum diagnostic efficiency by the ROC curves were 492 ng/ml, which was broadly similar to clinical cut off values (500 pg/mL).

Discussion

In this study, elevated presepsin on admission was an independent risk factor for septic shock, while elevated PCT on admission was an independently associated with SIRS on the 5th day after admission for patients admitted with UTI. Presepsin and PCT have the different origin [3-5]. These results support our hypothesis that presepsin is a useful marker for detecting severe sepsis from UTI. On the other hand, PCT can predict therapeutic courses in UTI better than presepsin.

Presepsin is one of the biomarkers which increases after bacterial infections [11]. The levels are increased in acute pyelonephritis patients with bacteremia [12] and elevation of presepsin levels before treatment might predict the development of sepsis in patients with obstructive acute pyelonephritis [13]. In this study, we evaluated the patients who needed hospitalization due to not only pyelonephritis but also prostatitis, and elevation of presepsin levels on the enrollment day was a predictor of septic shock Therefore, it seems that presepsin is useful for detecting severe urosepsis which need vasopressor therapy.

Sever sepsis and septic shock are fatal, with mortality rates of 28.3%-41.1% [14]. Clinically, it is very useful to predict septic shock at the time of admission. It is, therefore, essential that biomarkers increase immediately after infections and have a high sensitivity for sepsis. Presepsin levels have been shown to increase within 2 hours or later together with blood bacterial counts, and peak at 3 hours [6]. On the other hand, elevated PCT and CRP levels are detected within 3-6 hours and 6 hours, and peak at 6-8 hours and 36-50 hours, respectively [15,16]. It has also been reported that patients with severe sepsis have

significantly higher presepsin levels than those with sepsis, local infection or SIRS [17]. In this study, elevation of presepsin levels on the enrollment day was a predictor of septic shock, but not of SIRS on the day of enrollment. These results suggest that presepsin may be used to identify patients at increased risk of more severe infections at early stages.

One important characteristics of biomarkers is the prognostic value. Presepsin levels on day 1 were reported to be correlated with 60-day in-hospital mortality in patients with sepsis, severe sepsis or septic shock [18], a longer intensive-care unit stay, and a lower degree of resolution of the primary infection [8,9]. Mortality is one of the prognostic variables. Since there were no mortalities in this current study, we used presence or absence of SIRS on day 5 for prognosis. In this study, the levels of presepsin on day1 was significantly higher in SIRS on day 5 groups than non-SIRS on day 5 groups, but the levels of PCT on day1 was only picked up as a predictor of SIRS on day5 by multivariate logistic regression analysis. Concerning PCT, the AUC for PCT to predict 30-day mortality in febrile UTI was reported to be 0.71 (95% CI: 0.56-0.85) [19]. There are few reports about the comparison of presepsin with PCT for evaluating the prognostic value in UTI. Further researches which include a lot of more sever patients of urosepsis than this study are needed to study the availability of each biomarkers to predict treatment outcomes.

This study had some limitations. First, since 2016, sepsis has been defined using the Sequential (Sepsis-Related) Organ Failure Assessment (SOFA) [20]. This study began in 2014, and we did not check conscious level which is a requirement for SOFA scoring. Therefore, instead of SOFA, the SIRS criteria [10] was used for defining sepsis and septic shock. Second, we used a single-center design with a small sample size. Third, we did not consider renal function in setting the reference values of presepsin and PCT. The levels of presepsin and PCT have been reported to be affected by renal function [21,22]. It would be ideal to adjust the reference values depending on renal function. However, these adjustments are yet to be clarified.

Conclusions

This study showed that, in UTI, presepsin may be a good marker for diagnosis of severe patients who need vasopressor therapy at the data of admission, and PCT may be a good marker for predicting hard-to-treat cases.

Abbreviations

ALT: Aspartate transaminase; AST: Alanine transaminase; AUC: The area under the curve; Cr: Creatinine; CRP: C-reactive protein; γGPT: γ-glutamyl transpeptidase; PCT: Procalcitonin; ROC: A receiver operating characteristics; SIRS: Systemic inflammatory response syndrome; SOFA: the Sequential Organ Failure Assessment; UTI: Urinary tract infections; WBC: White blood cell

Declarations

Authors' contributions

YSe perfomed project development, data collection, data analysis and manuscript writing. KK contributed to project development and manuscript editing. DO, HN, YM, TS, SA, MN, HK, HM and YSh contributed to data collection. MM contributed to data analysis. KS contributed to project developments. All authors read and approved the final manuscript.

Funding

No funding sources.

Availability of data and material

The datasets generated during the current study are not publicly available due to ethical restrictions.

Ethical approval and consent to participate

The current study was approved by the Ethical Committee of Gunma University (approval No. 1650), and written consent was obtained from all of the enrolled patients to use their tissues. It was performed in accordance with the principles of the Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Acknowledgments

We thank Ms. Atsuko Oyama, and Ms. Rie Suzuki for their technical assistance.

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Tables

Table 1a. Characteristics of Patients with or without septic shock on the enrollment day

	Total	Septic shock group	Non-septic shock group	
Variable	N=50	N=11	N=39	p-value
Age (years)	66.5 [60.3-75.5]]	64 [49-70]	68 [61-78]	0.055
White blood cell (/mm□)	13600 [10375-18000]	13600 [9900-25600]	13600 [10400-16600]	0.788
C-reactive protein (mg/L)	10.45 [4.26-23.06]	11.47 [6.41-25.63]	10.2 [4.21-22.37]	0.406
Presepsin (pg/mL)	483 [277-1130]	1380 [924-5219]	399 [254-707]	<0.001
Procalcitonin (ng/mL)	0.87[0.20-17.1]	25.06 [0.42-103.73]	0.66 [0.14-2.06]	0.056
Aspartate transaminase (U/L)	24.5 [19.8-35.3]	44 [24-133]	24 [18-29]	0.003
Alanine transaminase (U/L)	17 [11.8-30.0]	19 [15-52]	17 [11-24]	0.049
γ-glutamyl transpeptidase (U/L)	31 [21.0-53.3]	70 [43-74]	26 [20-43]	0.002
Creatinine (mg/dL)	1.24 [0.87-1.99]	1.85 [1.19-3.86]	1.05 [0.85-1.84]	0.020
sex (male/female)	33/17	8/3	25/14	0.440
placement of urinary catheter (Y/N)	24/26	6/5	18/21	0.623
urological cancer (Y/N)	15/35	1/10	14/25	0.085
urinary calculi (Y/N)	12/38	4/7	8/31	0.240
DM (Y/N)	9/41	3/8	6/33	0.308
internal use of steroid (Y/N)	9/41	3/8	6/33	0.308

Values are expressed as number or median [interquartile range, IQR].
DM; diabetes mellitus, Y; yes, N; No,

Table 1b. Prediction of septic shock on the enrollment day by logistic regression analysis

Variable	Univariate analysis			Multivariable analysis		
	P-value	HR	95%CI	P-value	HR	95%CI
sex (male vs female)	0.595					
WBC (4,000-12,000 vs other)	0.497					
CRP (≥ 0.5 vs < 0.5)	0.360					
CRP (≥ 10 vs < 10)	0.848					
Presepsin (≥ 500 vs < 500)	0.007	20.000	2.305-173.553	0.029	12.157	1.298-113.892
PCT (≥ 0.05 vs < 0.05)	0.630					
PCT (≥ 2 vs < 2)	0.025	5.075	1.223-21.065	0.673		
AST (≥ 34 vs < 34)	0.006	8.000	1.829-34.996	0.375		
ALT (≥ 28 vs < 28)	0.105					
γGPT (≥ 47 vs < 47)	0.005	8.889	1.941-40.711	0.081		
Cr (male; ≥ 1.07 vs < 1.07, female; ≥ 0.79 vs < 0.79)	0.095					
placement of urinary catheter (Y vs N)	0.624					
urological cancer (Y vs N)	0.118					
urinary calculi (Y vs N)	0.284					
DM (Y vs N)	0.371					
internal use of steroid (Y vs N)	0.371					

WBC; white blood cell, CRP; C-reactive protein, PCT; procalcitonin, AST; Aspartate transaminase, ALT; Alanine transaminase, γGTP; γ-glutamyl transpeptidase, Cr; creatinine, DM; diabetes mellitus, Y; yes, N; No,

Table2a. Characteristics of Patients with or without SIRS on the 5th day

	SIRS group	Non-SIRS group	
Variable	N=7	N=43	p-value
Age (years)	64 [54-68]	68 [61-77]	0.126
day1/White blood cell (/mm³)	18200 [17200-24900]	13600 [9900-16000]	0.009
day1/C-reactive protein (mg/L)	25.63 [9.58-31.38]	8.23 [4.1-16.6]	0.007
day1/Presepsin (pg/mL)	1167 [878-5129]	419 [277-922]	0.006
day1/Procalcitonin (ng/mL)	73.1 [25.06-103.73]	0.55 [0.14-2.06]	0.003
day1/Aspartate transaminase (U/L)	34 [28-126]	24 [18-33]	0.013
day1/Alanine transaminase (U/L)	23 [18-52]	16 [11-25]	0.056
day1/γ-glutamyl transpeptidase (U/L)	48 [38-72]	28 [21-51]	0.133
day1/Creatinine (mg/dL)	2.30 [1.72-2.71]	1.05 [0.85-1.84]	0.007
day3/White blood cell (/mm³)	11900 [9400-20100]	8400 [5900-10400]	0.021
day3/C-reactive protein (mg/L)	25.58 [16.47-34.54]	10.71 [6.55-15.40]	<0.001
day3/Presepsin (pg/mL)	633 [464-1360]	311 [196-695]	0.027
day3/Procalcitonin (ng/mL)	20.34 [14.23-32.27]	1.35 [0.30-15.09]	0.005
sex (male/female)	4/3	29/14	0.446
urinary culture (P/N)	7/0	38/5	0.454
blood culture (P/N)	6/1	18/25	0.039
placement of urinary catheter (Y/N)	2/5	22/21	0.244
urological cancer (Y/N)	1/6	14/29	0.311
urinary calculi (Y/N)	4/3	8/35	0.048
DM (Y/N)	1/6	8/35	0.630
surgical procedure (Y/N)	6/1	22/21	0.095
internal use of steroid (Y/N)	2/5	7/36	0.370

Values are expressed as number or median [interquartile range, IQR].

DM; diabetes mellitus, P; positive, N; No, Y; yes

Table 2b. Prediction of SIRS on the 5th day by logistic regression analysis

Variable	Univariate analysis			Multivariable analysis		
	P-value	HR	95%CI	P-value	HR	95%CI
day1/WBC (4,000-12,000 or other)	0.19					
day1/CRP (≥ 10 or < 10)	0.280					
day1/Presepsin (≥ 500 or < 500)	0.049	9.176	1.013-83.108	0.366		
day1/PCT (≥ 2 or < 2)	0.012	17.455	1.886-161.528	0.012	17.455	1.886-161.528
day1/AST (≥ 34 or < 34)	0.079					
day1/ALT (≥ 28 or < 28)	0.283					
day1/γGPT (≥ 47 or < 47)	0.177					
day1/Cr (male; ≥ 1.07 or < 1.07, female; ≥ 0.79 or < 0.79)	0.998					
day3/WBC (4,000-12,000 or other)	0.120					
day3/CRP (≥ 10 or < 10)	0.998					
day3/Presepsin (≥ 500 or < 500)	0.067					
day3/PCT (≥ 2 or < 2)	0.998					
sex (male or female)	0.596					
urinary culture (P vs N)	0.999					
blood culture (P vs N)	0.059					
placement of urinary catheter (Y vs N)	0.280					
urological cancer (Y vs N)	0.346					
urinary calculi (Y vs N)	0.040	5.833	1.084-31.377	0.182		
DM (Y vs N)	0.783					
surgical procedure (Y vs N)	0.120					
internal use of steroid (Y vs N)	0.439					

WBC; white blood cell, CRP; C-reactive protein, PCT; procalcitonin, AST; Aspartate transaminase, ALT; Alanine transaminase, γGTP; γ-glutamyl transpeptidase, Cr; creatinine, DM; diabetes mellitus, P; positive, N; No, Y; yes

Figures

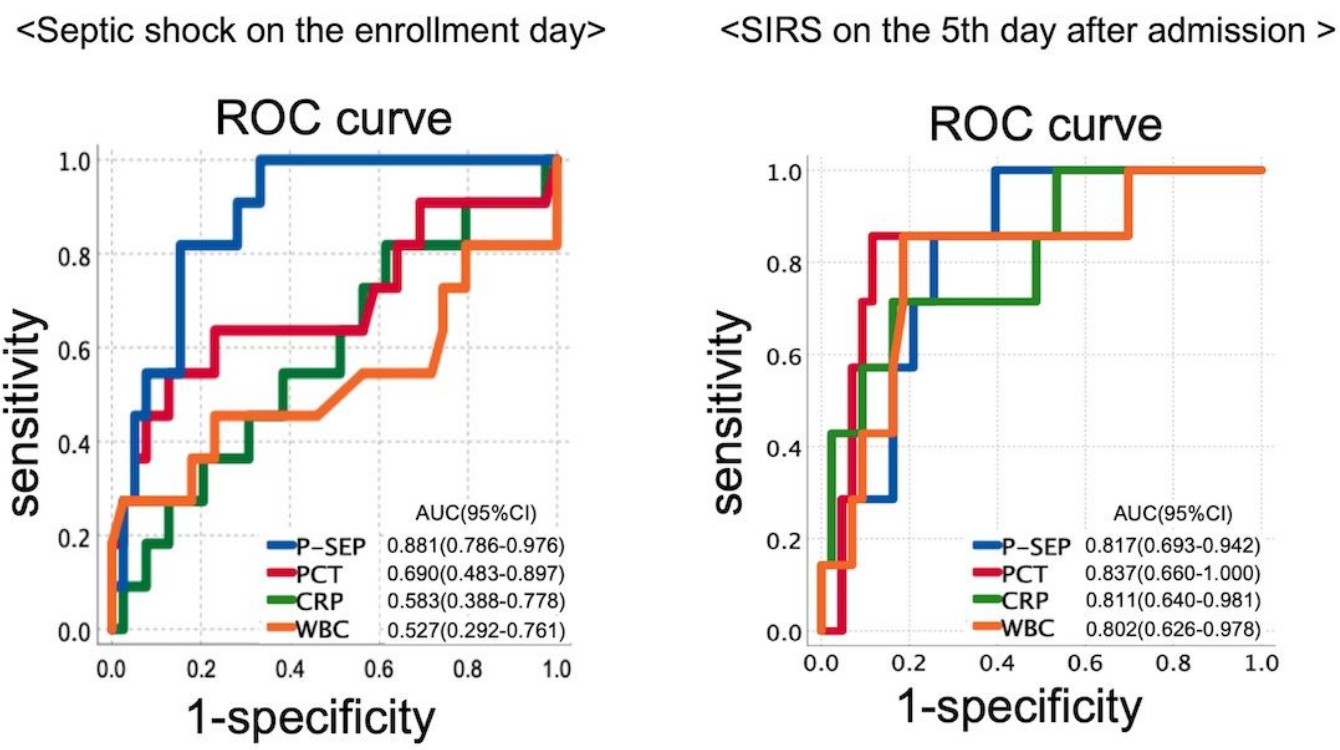

Figure 1

ROC curve for presepsin, procalcitonin, CRP and WBC in patients with definitive prediction of septic shock on the enrollment day and SIRS on the 5th day after admission. P-SEP; presepsin, PCT; procalcitonin, CRP; C-reactive protein, WBC; white blood cell

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- supplementalTable1.docx