Research Article

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Diagnostic values of neutrophil/lymphocyte ratio, platelet/lymphocyte ratio and procalcitonin in early diagnosis of bacteremia**Bakteriyeminin erken teşhisinde Nötrofil/Lenfosit Oranı, Trombosit/Lenfosit Oranı ve Prokalsitonin tanısal değerleri** <https://doi.org/10.1515/tjb-2018-0484>

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Abstract

Objective: The aim of this study is to investigate the diagnostic accuracy of complete blood count (CBC), C-reactive protein (CRP), and procalcitonin (PCT) levels, which can be used as a cultural alternative for the diagnosis of infection faster.

Methods: The patients were divided into two groups as bacteremia (n=220) and nonbacteremia group (n=812). The bacteremia group was divided into two subgroups as Gram-positive bacteria (n=167) and Gram-negative bacteria (n=53).

Results: PCT, CRP, red blood cell distribution width (RDW), platelet distribution width (PDW), neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR), and mean platelet volume (MPV) levels were significantly higher in patients with positive blood culture than non-patients. The serum PCT levels were 3.80 (0.83–37.68) and 0.43 (0.16–2.61) ng/mL, respectively (p<0.001) in the patients with Gram-negative and Gram-positive bacterium. PCT at a cut-off value of

0.45 ng/mL for Gram-negative bacterium; sensitivity of 90% and specificity of 64%.

Conclusions: It is important that RDW, PDW, NLR, PLR, MPV values can be measured quickly, easily and cheaply by automatic hematological analysis. However, among the markers tested, PCT has the best diagnostic performance for Gram-negative bacteremia.

Keywords: Procalcitonin; Blood cultures; Bacteremia; Complete blood count; C-reactive protein.

Öz

Amaç: Bu çalışmanın amacı, enfeksiyonun daha hızlı tanısında kültüre alternatif olarak kullanılabilecek tam kan sayımı, C reaktif protein (CRP) ve prokalsitonin (PCT) düzeylerinin tanısal doğruluğunu araştırmaktır.

Yöntem: Hastalar bakteriyemi (n=220) ve bakteriyemi olmayan grup (n=812) olarak iki gruba ayrıldı. Bakteriyemi grubu Gram pozitif bakteri (n=167) ve Gram negatif bakteri (n=53) olmak üzere iki alt gruba ayrıldı.

Bulgular: Kan kültürü pozitif olan hastalarda olmayanlara göre PCT, CRP, eritrosit dağılım genişliği (RDW), trombosit dağılım genişliği (PDW), nötrofil lenfosit oranı (NLR), trombosit lenfosit oranı (PLR) ve ortalama trombosit hacmi (MPV) düzeyleri anlamlı olarak yüksek bulundu. Gram -negatif ve Gram- pozitif bakteriyemili hastalarda serum PCT düzeyleri sırasıyla 3.80 (0.83–37.68) ve 0.43 (0.16–2.61) ng/mL idi (p<0.001). Gram negatif bakteri için PCT 0.45 ng/mL’lik bir kesme değerinde; % 90 duyarlılık ve % 64 özgüllüğe sahipti.

Sonuç: RDW, PDW, NLR, PLR, MPV değerlerinin otomatik hematolojik analizlerle hızlı, kolay ve ucuz bir şekilde ölçülebilmesi önemlidir. Bununla birlikte, test edilen belirteçler arasında PCT, gram negatif bakteremi için en iyi teşhis performansına sahiptir.

Anahtar Sözcükler: Prokalsitonin; Kan kültürü; Bakteriyemi; Tam kan sayımı; C-reaktif protein.

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Introduction

Early diagnosis of bacteremia in the emergency department affects the success of the treatment. Biological biomarkers have important roles in facilitating rapid diagnosis of sepsis. Complete blood count (CBC) which is useful in the diagnosis, follow-up, and investigation of many systemic inflammatory processes, is cheap and easy to implement in clinical laboratories. Recently, the neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) received from routine CBC are being investigated as useful biomarkers to recommend systemic inflammation. Many studies have shown that these parameters are positively associated with inflammation, cancer, cardiovascular disease, and diabetic nephropathy [1–5].

It has been suggested that NLR a better marker compared to routine parameters such as C-reactive protein (CRP), white blood cell count and neutrophil count for identification of bacteremia [6]. Studies have shown that red blood cell distribution width (RDW) and platelet distribution width (PDW) are associated with Gram-negative bacteremia diseases [6]. Mean platelet volume (MPV) and PLR have been rarely studied in systemic inflammation [7]. Recently, CRP and procalcitonin (PCT) are widely used as rapid, sensitive and specific biomarkers to identify bacteremia. CRP is synthesized in the liver by IL-6 stimulation in cases such as infection, surgery, injury, trauma, tumor, tissue necrosis and similar inflammatory and fever conditions [8]. PCT is produced by proinflammatory stimulation in various cells such as monocyte and hepatocyte, especially in bacterial infections [9]. Increases in PCT levels in bacterial infections occur faster than CRP. While CRP increases in viral infections, PCT increases in bacterial infections [10]. PCT has higher diagnostic accuracy than commonly used laboratory parameters [11–13]. The blood

culture is the gold standard in the diagnosis of infectious diseases, its procedures are slow, and the isolation of the pathogen with the antibiogram is only possible after 48 h of blood culture withdrawal [2, 11, 14–16]. Early initiation of the appropriate antibiotic is critical for positive results in the treatment of infections.

The aim of this study is to investigate the diagnostic accuracy of PCT, CRP and CBC parameters, such as RDW, PDW, NLR, PLR, MPV which results faster and can be used as an alternative to the blood culture for the diagnosis of infection in the patients with suspected bacteremia in emergency department.

Materials and methods

Study design and patient selection

Totally 1264 patients admitted to Tepecik Training and Research Hospital Emergency Department between 2011 and 2016 and had an order for blood culture due to the suspected bacteremia were analyzed retrospectively. One thousand one hundred and thirty samples taken simultaneously with blood culture were included in the study. In addition, when more than one sample was taken from the same patient, the first sample was included in the study. Ninety-eight patients with contamination were not included in the study. A total of 1032 patients from all groups underwent statistical analysis (Figure 1). The patients were divided into two groups as bacteremia ($n=220$) and nonbacteremia group ($n=812$). The bacteremia group was divided into two subgroups as Gram-positive bacteria ($n=167$) and Gram-negative bacteria ($n=53$) (Table 1). The study was approved by the Ethics

Figure 1: Selection of blood culture samples.

Table 1: The demographic and clinical characteristics of the patients.

Characteristics	Pediatric patients	Adult patients
The number of the patients	795	237
The median ages of the patients (years)	1 (0–18)	68 (21–93)
The mean ages of the patients (years)	2.29±3.79	64.01±16.71
The number of nonbacteremic patients	718	94
The number of bacteremic patients	77	143
Gram-positives	68	99
Gram-negatives	9	44

Committee of the Izmir Tepecik Training and Research Hospital.

Blood culture

Blood cultures drawn during the febrile period of the patients were incubated in the BacT/Alert 3D automated blood culture system (BioMerieux, France) in a Medical Microbiology laboratory. Five percentage sheep blood agar and eosin-methylene blue broths were cultured from the bottles giving positive reproductive signals, and the microorganisms were identified in the Vitec-2 fully automatic identification device (BioMerieux, France) as well as conventional methods. The result of a single blood culture from the same patient in the produced isolates was included in the study.

PCT, CRP and CBC analyses

CBC samples were taken into tubes containing ethylenediaminetetraacetic acid (EDTA) as anticoagulants and immediately studied. Samples were taken to a gel clot activator tube for CRP, PCT testing and centrifuged at 1300 g for 10 min to separate serum samples from blood cells.

The serum concentration of PCT was analyzed using a chemiluminescence immunoassay on the Cobas E 411 autoanalyser (Roche Diagnostics GmbH, Mannheim, Germany), CRP level was analyzed by the immunoturbidimetric assay on Beckman Coulter AU5800 autoanalyzer (Beckman Coulter Inc., Brea, CA, USA) and total blood count measurement was performed by impedance method on the Beckman Coulter LH780 autoanalyzer (Beckman Coulter Inc., Brea, CA, USA).

While daily and total variation coefficients (CV) obtained by measuring the three-level controls of CRP 20

times were $\leq 3.2\%$ and $\leq 3.8\%$, respectively, the mean intra-day and inter-day CVs of the PCT kit were 2.1% and 4.5%, respectively.

Statistical analysis

The nonparametric Mann-Whitney U test was used for statistical analysis because the data were not normally distributed. Logistic regression analysis was performed for relation between biochemical variables and blood culture positivity. The diagnostic performance of inflammatory markers was calculated via receiver operating characteristic (ROC) curves. The area under the ROC curve (AUC) was calculated for inflammatory markers, and 95% confidence interval (95% CI) were determined. Significance was defined as p values less than 0.05. The data was analyzed using IBM SPSS Statistics 20 program and MedCalc software.

Results

The mean age was 64.01 ± 16.71 years ($n = 237$) in the adult age group and the mean age was 2.29 ± 3.79 years in the pediatric patients ($n = 795$).

Demographic and clinical data of pediatric and adult patients are demonstrated in Table 1. The PCT, CRP, RDW, PDW, NLR and PLR values were significantly higher in patients with positive blood culture compared with those in negative group. There was a statistically significant difference between Gram-positive and Gram-negative bacteremia in terms of PCT in the bacteremia group ($p < 0.001$) (Table 2).

Based on the logistic regression analysis of risk factors associated with blood culture positivity (Table 3), PCT level was significantly associated with blood culture positivity (Adjusted OR=1.023, $p < 0.001$). Among the tested markers, MPV had the highest sensitivity (71%) and the CRP had the highest specificity (82%) for predicting bacteremia (Table 4). ROC analysis was performed to reveal the diagnostic accuracy of using concentrations of inflammatory markers to distinguish Gram-negative sepsis from Gram-positive sepsis (Figure 2). An optimal PCT cut-off value of 0.445 ng/mL resulted in an area under the curve (AUC) value of 0.840 (0.798–0.882), sensitivity of 90%, specificity of 64%. An optimal CRP cut-off value of 38.3 mg/L resulted in a sensitivity of 84%, specificity of 65%, with an AUC value of 0.796 (0.737–0.856) (Table 5).

Table 2: Comparison of parameters according to culture reproductive status and Gram-staining status.

	Nonbacteremia	Bacteremia	p-Value	Gram-positive	Gram-negative	p-Value
Age (year)	1 (0–5)	54 (2–71)	<0.001	47 (1–69)	59 (39–76)	0.007
PCT (ng/mL)	0.22 (0.12–0.74)	0.73 (0.21–5.30)	<0.001	0.43 (0.16–2.61)	3.80 (0.83–37.68)	<0.001
CRP (mg/L)	12.70 (3.00–60.90)	59.10 (10.95–177.45)	<0.001	38.50 (9.17–143.60)	155 (57.50–253.40)	<0.001
WBC ($\times 10^3/\mu\text{L}$)	11.80 (8.62–16.50)	12.20 (8.55–19.15)	0.332	12.95 (9.40–18.70)	9.30 (5.60–19.60)	0.066
PLT ($\times 10^3/\mu\text{L}$)	319 (243–415)	246 (168–380)	<0.001	262 (185–397)	195 (109–308)	0.006
RDW (%)	15.00 (13.90–16.60)	15.80 (14.15–17.50)	<0.001	15.50 (14.20–17.20)	16.30 (14.40–18.20)	0.163
MPV (fL)	7.90 (7.20–8.60)	8.60 (7.80–9.60)	<0.001	8.50 (7.80–9.50)	8.60 (7.98–9.80)	0.501
PDW (%)	16.80 (16.40–17.37)	17.10 (16.60–17.60)	<0.001	17.10 (16.60–17.60)	17.30 (16.80–17.90)	0.027
NLR	1.74 (0.79–4.84)	6.31 (1.91–13.50)	<0.001	5.79 (1.58–11.73)	10.12 (3.10–22.90)	0.005
PLR	98.1 (59.7–164.4)	164.0 (68.2–356.6)	<0.001	144.9 (65.1–288.9)	270.0 (92.2–581.2)	0.010

Mann-Whitney U test was used. The data are shown as median (25th–75th percent). PCT, Procalcitonin; CRP, C reactive protein; WBC, white blood cell; PLT, platelet; RDW, red blood cell distribution width; MPV, mean platelet volume; PDW, platelet distribution width; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio.

Table 3: Logistic regression analysis for relation between blood culture positivity and other biochemical variables.

	OR (95% CI)	p-Value	Adjusted OR (95% CI)	p-Value
PCT (ng/mL)	1.034 (1.023–1.046)	<0.001	1.023 (1.011–1.035)	<0.001
CRP (mg/L)	1.006 (1.005–1.008)	<0.001	1.002 (1.000–1.004)	0.013
WBC ($\times 10^3/\mu\text{L}$)	1.013 (1.000–1.0026)	0.054	0.996 (0.981–1.011)	0.591
PLT ($\times 10^3/\mu\text{L}$)	0.997 (0.996–0.998)	<0.001	0.999 (0.998–1.000)	0.252
MPV (fL)	1.527 (1.357–1.718)	<0.001	1.192 (1.047–1.356)	0.008
RDW (%)	1.107 (1.052–1.165)	<0.001	1.022 (0.962–1.086)	0.475
PDW (%)	1.455 (1.231–1.719)	<0.001	1.198 (0.994–1.443)	0.057
NLR	1.030 (1.018–0.042)	<0.001	1.001 (0.990–1.012)	0.861
PLR	1.001 (1.000–1.002)	<0.001	1.000 (0.999–1.001)	0.217

OR, Odds ratio, Adjusted OR were corrected for age and gender. PCT, Procalcitonin; CRP, C reactive protein; WBC, white blood cell; PLT, platelet; MPV, mean platelet volume; RDW, red blood cell distribution width; PDW, platelet distribution width; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio.

Table 4: ROC analysis for culture positivity prediction.

	AUC (95% CI)	Cut-off	Sensitivity (%)	Specificity (%)
PCT (ng/mL)	0.664 (0.622–0.707)	0.425	60	66
CRP (mg/L)	0.683 (0.642–0.724)	91.45	46	82
WBC ($\times 10^3/\mu\text{L}$)	0.521 (0.475–0.567)	15.45	37	71
PLT ($\times 10^3/\mu\text{L}$)	0.628 (0.583–0.623)	264	56	68
MPV (fL)	0.664 (0.623–0.705)	7.98	71	53
RDW (%)	0.578 (0.535–0.622)	16.15	44	73
PDW (%)	0.623 (0.592–0.652)	17.01	55	65
NLR	0.691 (0.650–0.733)	3.31	66	67
PLR	0.623 (0.576–0.670)	187.01	46	79

PCT, Procalcitonin; CRP, C reactive protein; WBC, white blood cell; PLT, platelet; MPV, mean platelet volume; RDW, red blood cell distribution width; PDW, platelet distribution width; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio.

Discussion

Focusing on the early diagnosis of sepsis has increased the interest of identifying clinically useful sepsis biomarkers

in Emergency Department [17]. These markers include the fastest, simplest, and cheapest CBC parameters and derivatives, as well as CRP from acute phase proteins and PCT tests being recently more significant. Only a small amount

Figure 2: The ROC curve of procalcitonin (PCT), C reactive protein (CRP), neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) for discriminating between bacteremia group and nonbacteremia group.

of blood cultures requested for suspected bacteremia in the patients of Emergency Department are found to be positive [18].

In our study, 795 (77%) of the patients were children admitted to the Pediatric Emergency Department and only 9.7% of them had culture positivity. Sixty percentage of 237 (23%) patients whom requested a blood culture test in adult emergency department had culture positivity. Despite the low rate of culture positivity in pediatric patient was parallel to the literature, this rate was found to be high in adult patients in our study. In this study where we examined the diagnostic performance of CBC and derivatives (RDW, PDW, NLR, PLR, MPV), CRP and PCT tests of patients with an order for blood culture in the Emergency Department, all values of the patients with positive blood culture were significantly higher than the patients with negative blood culture. As in many studies, PCT showed a better performance compared to the other parameters in our study as well.

For Gram-negative culture positivity, the AUC for PCT, was 0.840 and the cut-off value was 0.45 ng/mL with a

sensitivity of 90.0% and a specificity of 64%. In another study similar to the one we conducted, it has been shown that PCT was a potentially sensitive biomarker for distinguishing Gram-negative sepsis from Gram-positive and fungal sepsis [11].

Loonen et al. have demonstrated that PCT is able to distinguish patients with positive blood cultures from patients with negative blood cultures to a significant extent that CRP levels are similar in both groups and that PCT has a higher performance compared to CRP in terms of discrimination of patients with blood circulation infection [12]. In a retrospective study conducted in China for early diagnosis of sepsis, PCT levels were found to be higher in patients with Gram-negative bacteremia within the first 72 h similar to the results of our study [19]. Despite the fact that there was a significant difference among Gram-negative and positive proliferations in terms of CRP in our study, no difference was found in the study conducted in China. Although the patients coming to the Emergency Department for the first time were examined in our study, samples were also taken from the patients having late admission to the Emergency Department. This may lead to high CRP. Moreover, despite the high number of our pediatric patients, the number of pediatric bacteremia is lower compared to the adult patients and as there may be other diseases in adult patients with bacteremia could explain high CRP. We did not include patients having contamination in their blood culture, thinking that it would affect our evaluation. However, in a study where contamination was also examined in addition to blood culture positivity, PCT has been found to be a better marker compared to CRP [14]. In another study considering PCT, white blood cell (WBC) count, CRP and platelet (PLT) count for blood culture results, it has been shown that PCT is not sufficient and the best result would be presented by the combination of PLT and PCT [20].

NLR and PLR ratio can be easily calculated from the absolute neutrophil and platelet counts. Absolute

Table 5: ROC analysis for Gram-negative reproduction.

	AUC (95% CI)	Cut-off	Sensitivity (%)	Specificity (%)
PCT (ng/mL)	0.840 (0.798–0.882)	0.445	90	64
CRP (mg/L)	0.796 (0.737–0.856)	38.3	84	65
PLT ($\times 10^3/\mu\text{L}$)	0.703 (0.619–0.786)	216	60	78
PDW (%)	0.600 (0.532–0.666)	16.8	74	45
NLR	0.753 (0.684–0.821)	4.68	71	75
PLR	0.679 (0.583–0.776)	199.71	60	81

PCT, Procalcitonin; CRP, C reactive protein; PLT, platelet; PDW, platelet distribution width; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio.

lymphocyte count and absolute platelet count can be obtained from a single CBC test. In chronic inflammatory processes, lymphocyte counts tend to decrease whereas the megakaryocyte is increased. Therefore, markers derived from a total blood count, such as PLR, may be affected by chronic inflammatory diseases [21].

We found that while PCT and NLR are similar in blood culture positivity, PCT had the highest sensitivity (90%) in Gram-negative bacterial growth. Moreover, when we examined the relation between blood culture positivity and other biochemical variables after the adjustment of age and gender, we found that blood culture positivity was only related with CRP, PCT, and MPV in our study. In our study, for prediction of culture positivity PCT showed poor performance with an AUC of 0.664 (0.622–0.707). This performance is not enough for true guidance in clinical practice.

In a study conducted by Zhang et al., the area under ROC curve was found to be 0.624 and 0.718 for RDW and NLR, respectively, and it was emphasized that the combined evaluation of RDW, PDW, and NLR was stronger than the standalone evaluation for prediction of bacteremia [6]. In the study of Oksuz et al. conducted on both pediatric and adult patients in a manner similar to our study, CRP and PCT were found to be significantly higher in the bacteremia group and PCT was found to be a more useful parameter compared to CRP for discriminating bacteremia from contamination in febrile patients [14].

In a similar study, PCT and NLR were found to have a high diagnostic performance for predicting sepsis [2]. In the same study, it was shown that three parameters of CBC, namely the combination of RDW, PDW and NLCR exhibited a high diagnostic performance similar to that of PCT.

In another study PCT was found to be the best marker for sepsis diagnosis and prognosis but CRP was shown to be a marker only in diagnosis [15]. In another study, blood culture positivity was significantly higher in PCT positive patients than PCT negative patients, and sensitivity and specificity of PCT for detecting positive blood cultures were 74.5% and 59.1%, respectively. In addition, similar to our results, PCT levels were higher in Gram-negative patients than Gram-positive patients. With these results, it was concluded that PCT may be a useful marker for sepsis, and can be a strong marker for early diagnosis due to its high sensitivity in Gram-negative bacteremia cases [15]. Guideliness of German Sepsis Society commented that severe sepsis or septic shock are unlikely in the presence of serum PCT concentrations of <0.5 ng/mL and it is highly likely at values

above 2.0 ng/mL [22]. The PCT value of 0.5 is similar to our estimated cut-off value for prediction of blood culture positivity. Despite a decent number of studies examining RDW, PDW, and NLR among CBC parameters for bacteremia, studies on PLR are rare. PLR is a parameter that has recently started to be used as an indicator of inflammation.

In a study comparing all blood count parameters in the diagnosis of acute appendicitis, NLR and leukocyte count were shown to be better inflammatory markers in acute appendicitis and also an important parameter in the diagnosis of acute appendicitis in high PLR levels [23]. In a study, NLR and PLR were found to be significantly high in patients with rheumatoid arthritis, while in another study it was found that PLR was more significant than NLR in terms of indicating inflammation in patients on haemodialysis [2, 3]. PLR has been mostly studied in malignancies and in nonspecific patients [4]. In one study, statistically higher NLR and PLR values were found in patients with Crohn's disease [5]. We did not find a significant superiority of this ratio to other parameters when considering the diagnostic performance of bacteremia prediction in our patients.

In a study comparing lactate, white blood cell (WBC) and neutrophil counts, PCT and immature granulocytes (IG) in predicting sepsis and severe sepsis or septic shock in patients admitted to the emergency department, all biological indicators were found to have AUC <0.70, and sensitivity and specificity <70%. It was proposed that these markers provide a limited benefit for predicting sepsis [17].

In another empirical cohort study, multiple clinical scores and biomarkers were examined in terms of their ability to predict bacteremia in patients with suspected infection and whose blood cultures were requested during ED admission, and five clinical scores and PCT, CRP, lymphocyte and white blood cell counts, NLR and RDW were evaluated. Among the clinical scores, Shapiro score showed the best performance (AUC 0.729), and the best biological markers were found to be PCT (AUC 0.803) and NLR (AUC 0.700). It was concluded that the combination of the admission levels of PCT and the Shapiro score could help reducing minimal false negative blood cultures [18]. In another study, it was shown that a PCT cutoff value of 10.3 ng/mL in patients with sepsis can detect infection caused by GNB with 80.2% specificity. In this study, it was emphasized that sepsis could not be ignored clinically even if the PCT value was normal, and that the measurement of PCT level could increase the suspicion index for GNB [16]. The results of our study are consistent with similar studies.

Limitations

Our study has the following limitations. First of all, we have limited access to the patient information because this is a retrospective study. Comorbid diseases, previous abdominal surgery and drugs used in patients cannot be identified. Information on the use of antibiotics is incomplete before applying to the emergency service. Since the study is based on the referral of patients to the emergency department, the time of onset of the disease is not fully known; therefore the levels of CRP and PCT are assessed accordingly. Moreover, these parameters are evaluated with a single measurement. Blood culture positive cases were separated only as Gram-positive and negative but not according to bacterial type. Positive aspects of our study include the large patient population that was examined, and the population covered all age groups including children and adults. In addition, platelet larger cell ratio count, one of CBC parameters that we did not encounter in other studies on bacteremia prediction was also examined in this study.

Conclusions

In conclusion, early initiation of the appropriate antibiotic is important for effective treatment of severe infections. For this reason, early and accurate diagnosis of blood circulation infections should not be delayed until blood culture is concluded. Therefore, in patients admitted to the emergency department with suspected bacteremia, checking routine blood count parameters and derivatives, as well as PCT and CRP, before blood culture results may be helpful in predicting bacteremia. Especially, high diagnostic accuracy of PCT was observed for the prediction of Gram-negative bacteremia. Physicians could choose adequate antibiotics covering Gram-negative pathogens according to PCT levels.

Conflict of interest statement: The authors declare that there is no conflict of interests regarding the publication of this article.

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