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ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

The Role of Procalcitonin in Differentiating Between Gram-Negative and Gram-Positive Sepsis

Gram-Negatif Sepsis ve Gram-Pozitif Sepsis Ayrımında Prokalsitoninin Rolü

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ABSTRACT

Aim: Detecting the agent group in sepsis patients with culture positivity is crucial in determining our treatment scheme. We aimed to evaluate the diagnostic accuracy of procalcitonin (PCT) levels in distinguishing between different pathogen groups in sepsis patients with proven bacteremia.

Material and Method: Records of patients hospitalized in ICU were retrospectively investigated over 28 months were retrospectively investigated confirmed microbiologically to have a positive blood culture result. The patients were evaluated in two groups regarding gram-negative (GN) and gram-positive bacteria based on the findings of blood culture and Gram staining. Age, gender, APACHE II score, hospital stay, mortality, and laboratory parameters were compared in both groups. Of 894 patients followed up in ICU during 28 months, 56 sepsis patients confirmed microbiologically to have blood culture positivity were included.

Results: While GN bacteria grew in the blood cultures of 26 (46.4%) patients, 30 (53.6%) patients were found to have GP bacteria. The level of PCT was significantly higher in the GN group, compared to that of the GP group (p=0.003). There were no significant differences in CRP values and APACHE II scores between the GN and GP groups (p=0.147 and p=0.633, respectively). Additionally, no statistically significant difference was determined between the GN and GP groups regarding the mortality rate (p=0.712). Leukocyte, neutrophil, lymphocyte, platelet, and albumin values of both groups were also similar.

Conclusion: PCT was found to be a useful marker in predicting the pathogen groups in early treatment management of patients diagnosed with sepsis.

Keywords: C-reactive protein, Gram-positive bacteria, Gram-negative bacteria, procalcitonin, sepsis

ÖZ

Amaç: Sepsis, yoğun bakım ünitelerindeki hastalarda morbidite ve mortalitenin en önemli nedenlerindendir. Kültür pozitifliği saptanan sepsis hastalarında etken grubunu belirlemek tedavi şemamızı belirlemede önemlidir. Çalışmamızda bakteriyemi kanıtlanmış sepsis tanısı alan hastalarda prokalsitonin (PCT) seviyesinin farklı patojen gruplarını ayırmada tanısal doğruluğunun değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: Yoğun bakım ünitesinde (YBÜ) yatan hastaların kayıtları 28 aylık süreçte retrospektif olarak incelendi. Sepsis tanısı alan, mikrobiyolojik olarak (pozitif kan kültürü sonuçları) doğrulanan tüm hastalar dahil edildi. Hastalar kan kültürü ve Gram boyama sonuçlarına göre Gram negatif (GN) grup ve Gram pozitif (GP) grup olmak üzere iki grupta değerlendirildi. Bu iki grupta yaş, cinsiyet, APACHE II skoru, hastanede kalış süresi, mortalite ve laboratuvar parametleri karşılaştırıldı.

Bulgular: Hastaların 26 (%46,4)'sının kan kültüründe GN, 30 (%53,6) unun kan kültüründe GP bakteri saptandı. PCT düzeyi GN grubunda GP grubuna göre anlamlı derecede yüksekti (p=0,003). GN ve GP grupları arasında CRP değerleri ve APACHE II skorları açısından anlamlı fark yoktu (sırasıyla p=0,147 ve p=0,633). Ayrıca GN ve GP grupları arasında mortalite açısından istatistiksel olarak anlamlı fark saptanmadı (p=0,712). Her iki grubun lökosit, nötrofil, lenfosit, trombosit ve albümin değerleri de benzerdi.

Sonuç: Sepsis tanısı alan hastalarda erken tedavi yönetiminde, patojen gruplarının tahmin edilebilmesinde prokalsitoninin faydalı bir belirteç olduğu saptandı.

Anahtar Kelimeler: C-reaktif protein, Gram-pozitif bakteri, Gram-negatif bakteri, prokalsitonin, sepsis

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INTRODUCTION

Sepsis is among the most important causes of morbidity and mortality in patients admitted to intensive care units (ICU). The rates of mortality can be seen at a rate of 30% in sepsis patients and 50% in septic shock patients (1). It is important to choose appropriate antibiotic therapy and predict the causative pathogen in sepsis in terms of survival (2). It is critical to identify the causative pathogen in blood culture; however, bacteremia is confirmed in only 30% of the patients diagnosed with sepsis (3). When evaluated in terms of Gram-negative (GN) and Gram-positive (GP) bacteria, there are significant differences between the types of sepsis. Such differences arise from the wall structure of the cells of microorganisms (4). While procalcitonin (PCT) is detected at normal levels in patient groups with no infection, PCT appears to be quite reliable, compared to most biomarkers in patients with suspected bacterial infection (5). When the clinical status of the patient suggests the suspicion of sepsis, PCT is a rapid and inexpensive biomarker that can provide insight into the causative pathogen group in indicating the presence of bacteremia. PCT is also significantly elevated in patients with GN bacteremia, demonstrating that PCT can be used to distinguish GN sepsis from GP sepsis (6-8). Therefore, in our study, it was aimed to evaluate the diagnostic accuracy of the PCT level in distinguishing between different pathogen groups in patients diagnosed with sepsis with proven bacteremia.

MATERIAL AND METHOD

Approval was obtained from the local ethics committee of the Faculty of Medicine at Karatay University (Reg. number: 2024/006 and date: 7th June 2024) for our study. The study was conducted in accordance with the principles stated in the Declaration of Helsinki. The medical records of the patients (>18 years of age) hospitalized in the ICU of Meram State Hospital in Konya for 28 months between January 2022 and May 2024 were retrospectively examined. All patients diagnosed with sepsis whose blood culture results were microbiologically confirmed to be positive were included in the study. Coagulase-negative staphylococci, *Corynebacterium* spp., and other skin flora components were considered contaminants when grown in a single bottle. Skin flora pathogens were considered causative pathogens if they grew in blood cultures taken from two different sites. Depending on the pathogen identified in the blood, bacteremia was classified as GP or GN sourced. PCT is examined on every patient with suspected sepsis in the ICU. Non-infectious causes considered to affect the PCT level, such as trauma, surgery, burns, or advanced renal failure, were ruled out from the study. The patients were evaluated in two groups, the GN and GP groups, based on the findings of blood culture and Gram staining. Age, gender, APACHE II score, hospital stay, mortality, and such laboratory parameters as leukocyte, neutrophil, lymphocyte, platelet, PCT, C-reactive protein (CRP), and albumin were recorded in the two groups. In the patients developing sepsis more than once, the first attack of sepsis was recorded. In each patient, the mortality rates within the first 28 days were also recorded. Blood cultures were analyzed using the BACTEC 9240 fully automatic blood culture device (Becton Dickinson, Diagnostic Device System, Spark, USA). The colonies of isolated bacteria were identified through the VITEK 2 Compact® system (BioMérieux, France).

Statistical analysis

Statistical analyses of the study findings were evaluated with the Statistical Package for the Social Sciences software for Windows, version 24.0 (SPSS Inc., Chicago, IL, USA). While the nominal data were described as ratios and percentages, mean and standard deviation (±, SD) were used to describe continuous numerical data. Additionally, median and interquartile ranges were used to describe non-normally distributed continuous numerical data. The presence of normal distribution was evaluated using statistical tests and graphical methods. While the Pearson chi-square test was used to compare the categorical data, the Mann-Witney U test was utilized to compare non-normally distributed numerical data in pairs, and the student's t-test was used in independent groups to compare normally distributed continuous numerical variables. In evaluating the ability of laboratory tests to predict that the sepsis-causing bacterium is a GN bacterium and to predict death, the receiver-operating characteristic (ROC) analysis was applied. A value of $p < 0.05$ was accepted to be statistically significant.

RESULTS

During the study for 28 months, a total of 894 patients were followed up in the ICU. Among 894 patients followed up in ICU, 63 diagnosed with sepsis and confirmed microbiologically to have blood culture positivity were included in the study. Of 63 patients included, two patients seen multiple microorganisms in their blood culture, two diagnosed with chronic kidney failure (CKD), and three where skin flora was detected in their blood culture were determined and excluded from the study. Therefore, a total of 56 patients were included in the study. Of 56 patients, 48.2% (n=27) and 51.8% (n=29) were female and male, respectively. The age of the patients also ranged between 35-97 years (average age, 75.45±11.7 years). Twenty-six (46.4%) patients were found to have GN bacteria in the blood cultures while 30 (53.6%) had GP bacteria in their blood cultures. The level of PCT was significantly higher in the GN group than that in the GP group (p=0.003). Even so, no significant difference was found between the GP and GN groups in terms of the CRP value (p=0.147). There was also no significant difference between the APACHE II scores of

the GN and GP groups (p=0.633). Given the mortality rate, no statistically significant difference was determined between the GN and GP groups (p=0.712). The values of leukocyte, neutrophil, lymphocyte, platelet, and albumin were similar in both groups (**Table 1**).

Table 1. Data for the groups with gram-positive and gram-negative sepsis

	Gram (-)	Gram (+)	p
	Median (Q1-Q3)	Median (Q1-Q3)	
Gender (M/F), n (%)	11 (42.3)/15 (57.7)	12 (40)/18 (60)	[a]0.186
Age (years), mean±SD	79±13	74.5±22	[c]0.464
Leukocyte $\times 10^9$/L	11920±13383	13593±8440	[c]0.755
Neutrophil $\times 10^9$/L	8630±11798	11300±8475	[c]0.588
Lymphocyte $\times 10^9$/L	850±1150	965±1175	[c]1
Platelet $\times 10^9$/L	186±163	187±123	[c]0.475
Albumin	23.8±5.5	25.35±6.5	[c]0.224
PCT (ng/mL)	4.83±15.76	1.25±2.53	[c]0.031*
CRP (mg/L)	126.5±120.5	158.5±113.9	[b]0.633
Apache II score	28±7	28±9	[b]0.147
Hospital stay (days)	46±76	24±37	[c]0.57
Mortality, n (%)	17 (65.4)	21 (70.0)	[a]0.712

[a]Pearson chi-square test, [b]Student's t-test, [c]Mann-Whitney U test, *p <0.05; p <0.001. Q1: First quartile, 25th percentile, Q3: Third quartile, 75th percentile, CRP: C-reactive protein, F: Female, M: Male, PCT: Prokalsitonin

The sensitivity and specificity values were evaluated for PCT at different cut-off levels in distinguishing the cases with the GN and GP origins. The threshold value for PCT was determined as 2.5, with a sensitivity of 61.5% and a specificity of 76.7%. The area under the ROC curve (AUC) for the PCT value was calculated as 0.66 [95% confidence interval (CI): 0.520-0.816, p<0.001] (**Figure 1**), and the AUC obtained for the PCT value was found to be significant. Even so, the AUC for the CRP value was calculated as 0.629 (95% CI: 0.481-0.776, p=0.099) (**Figure 2**). It was determined that the AUC obtained for the CRP value was not significant.

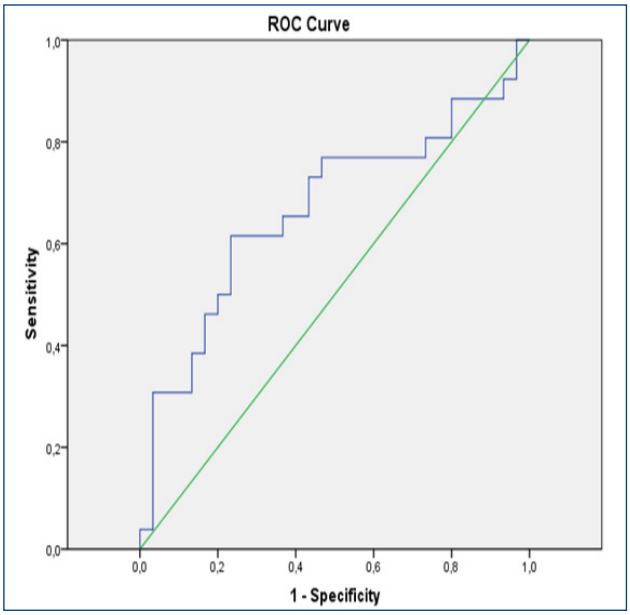

Figure 1. ROC curve for procalcitonin values

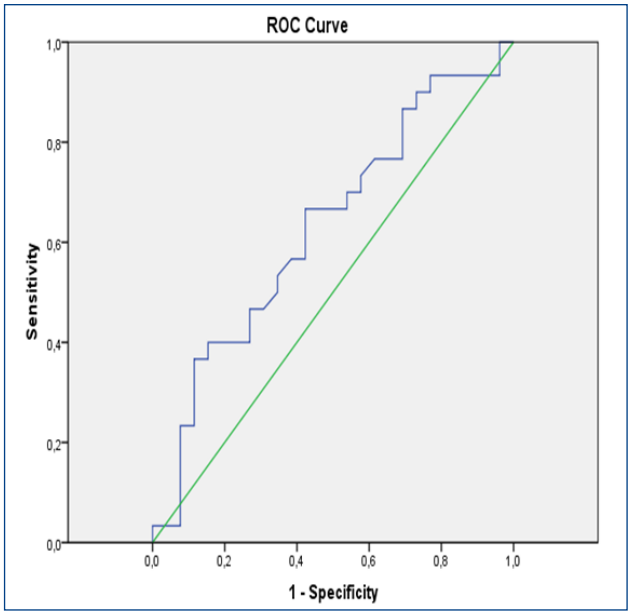

Figure 2. ROC curve for CRP values

DISCUSSION

Early diagnosis is important since sepsis still causes on high morbidity and mortality in ICUs. Among the main pathogens leading to sepsis are bacteria, and there are different mechanisms in the sepsis pathogenesis of GN and GP bacteria. The response given by the host to GN and GP bacteria stems from the structural differences of the pathogens (9). PCT is more significant than other biomarkers of sepsis in predicting whether systemic inflammation is of infectious origin and in evaluating the response to the treatment (10). The inflammatory response has been reported to develop more in the group of patients developing GN sepsis and the issue has been associated with high PCT values (11). In the present study, we evaluated the role of sepsis biomarkers in distinguishing between GN and GP bacterial growths in those diagnosed with sepsis and detected that the PCT value plays a crucial role in differentiating between GN sepsis and GP sepsis.

In our study, the sensitivity and specificity values were calculated at different cut-off levels for PCT in distinguishing between the patients with GN and GP bacterial sepsis. The PCT value was found to be higher in those with GN sepsis [4.8 ng/mL, interquartile range (IQR): 15.76] than in those having GP sepsis (1.25 ng/mL, IQR: 2.53). The threshold value for PCT was determined as 2.5 ng/mL, with a sensitivity of 61.5% and a specificity of 76.7%. The AUC value for PCT was also calculated as 0.66 (95% CI: 0.520-0.816). Positive predictive value (PPV) and negative predictive value (NPV) were found to be 69.5 and 69.70%, respectively.

In the current study where a total of 1.949 samples obtained from those with suspected bloodstream infections were examined, the median PCT values in bacteremia of GN (13.8 ng/mL, IQR: 3.4-44.1) were determined to be higher, compared to the infections GP (2.1 ng/mL, IQR: 0.6-7.6). In the ROC analysis, for a threshold value of 10.8 ng/mL, AUC for PCT in the GN and GP groups was detected to be 0.765 (95% CI: 0.725-0.805) (12).

According to blood culture classifications consisting of a total of 262 cases, the PCT value was found to be higher in the GN sepsis group (26.7 ng/mL, 0.09-188.3) than in the GP bacteria sepsis group (0.84 ng/mL, 0.05-18.79). The threshold value of 3.39 ng/mL for PCT, sensitivity of 80% in identifying GN bacteremia, specificity of 71%, PPV of 35%, NPV of 91%, and 0.73 of AUC were calculated. In 122 cases with blood culture positivity, however, the threshold value of 6.47 ng/mL for PCT, sensitivity of 74% in identifying GN bacteremia, specificity of 81%, NPV of 75%, PPV of 82% and AUC of 0.81 were calculated (13).

In 124 sepsis cases, the threshold value for PCT in differentiating between the cases caused by GN and GP bacteria was determined as 1.3, with a sensitivity and specificity of 70.83% and 84.21%, respectively. The AUC for the PCT value was calculated as 0.80 (95% CI: 0.722-0.887) (14).

In another study including 501 cases and carried out in our country, in which the GN and GP bacteria groups were distinguished, the sensitivity and specificity were calculated at different threshold values for PCT and CRP. In the study, while the optimal threshold value for PCT was found as 1.45 ng/mL, sensitivity as 75%, and specificity as 53%, the AUC was also determined as 0.675 (95% CI: 0.623-0.726) (15).

In another study where 147 patients were evaluated, the PCT value was found to be significantly higher in those in the GP sepsis group, compared to the GN sepsis group; however, no significant increase was detected in the CRP value. In the study, the values of AUC for PCT and AUC for CRP were found as 0.73 (95% CI: 0.65-0.81) and 0.52 (95% CI: 0.43-0.62) respectively, and these findings were different from those in our study; additionally, the serum PCT value was also found to be significantly higher in the GP sepsis group in the study, and no significant difference was found in CRP levels (16).

In the study conducted by Alıcı et al. in our country, the median values of CRP in GN and GP sepsis groups were determined as 167.72 mg/L (94.37-265.81), 145.49 mg/L (81.31-235.23) respectively, and the values were seen to be statistically similar in the GN-GP groups (p=0.73) (15).

In addition to some studies investigating serum PCT levels, there are also others reporting that CRP levels were significantly higher in GN sepsis groups (17,18). In a study, while the PCT values were calculated significantly higher, the values of platelets were reported to be lower in the GN sepsis group, compared to the GP sepsis group (19). In our study, low platelet value was observed to be associated with mortality in sepsis. In a meta-analysis where 45 studies were examined, the levels of CRP, PCT, and TNF-α were found to be higher in the GN sepsis group than those in the GP sepsis group. In our study, while the levels of PCT were observed to be significantly beneficial in the early diagnosis in the GN sepsis group, CRP levels were not helpful in the early diagnosis in the GN sepsis group. In the same study reporting similar findings to those in our study, the researchers stated no significant difference in leukocyte, platelet count, and length of stay in ICU in the GN sepsis group (20). However, it was observed that long hospital stay was associated with higher mortality within all sepsis group patients in our study. In the same meta-analysis, the difference between the GN and GP sepsis groups regarding the APACHE II score was seen not to be significant, similar to our study findings (20).

In our study, while only microbiologically proven cases of sepsis were included, the clinical cases of sepsis were not included, and the retrospective design is among the limitations of our study.

CONCLUSION

PCT was found to be significantly higher in sepsis caused by GN bacteria than in sepsis caused by GP bacteria. PCT was also detected to be a useful marker in predicting pathogen groups in the early management of patients diagnosed with sepsis. However, there was no significant difference between GN and GP groups in terms of the values of hospitalization time, APACHE II score, leukocyte, neutrophil, lymphocyte, platelet, and albumin.

ETHICAL DECLARATIONS

Ethics Committee Approval: Approval was obtained from the local ethics committee of the Faculty of Medicine at Karatay University (Reg. number: 2024/006 and date: 7th June 2024) for our study.

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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