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Can high procalcitonin levels be a biomarker for detecting multidrug-resistant Gram-negative bacteremia?

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ABSTRACT

Aims: Clinicians prefer broad-spectrum empirical antibiotic therapy in patients with suspected bloodstream infection (BSI) due to long test turnaround times of conventional methods. We aimed to assess the contribution of procalcitonin (PCT) to the selection of antibiotics to be used in empirical treatment.

Methods: The results of inpatients whose blood cultures and samples for PCT tests had been sent simultaneously between 2018 and 2022 were analyzed retrospectively. Antibiotic susceptibility results of *Enterobacteriaceae*, *Acinetobacter baumannii* complex and *Pseudomonas aeruginosa*, were evaluated for multidrug-resistance (MDR).

Results: Results of 1206 patients who met the inclusion criteria were included in the study. The PCT median value in BSIs caused by the Gram-negative bacteria found to be statistically significantly higher than those caused by the Gram-positive bacteria, fungal and polymicrobial infections ($p<0.05$). The best cutoff value of ROC, with an AUC value of 0.607 (CI: 95%: 0.578-0.635, $p< .0001$), a sensitivity of 72.1%, and a specificity of 55.4%, for distinguishing GN BSIs from other BSIs was determined as 2.5 ng/ml. The PCT median value of MDR pathogens was found to be statistically significantly higher than that of non-MDR pathogens ($p < 0.05$). A ROC analysis was performed, and the AUC distinguishing MDR pathogens from non-MDR was found as 0.633(CI: 95%, 0.586-0.681; $p <0.0001$), with a best PCT cutoff of 11.4 ng/mL, a sensitivity of 54.8%, and a specificity of 66.3%

Conclusion: High levels of PCT can guide empirical antibiotic treatments, with its property to predict GN bacteria and that they might be MDR GN BSIs.

Keywords: Procalcitonin, bloodstream infection, Gram negative bacteriae, multidrug resistance

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INTRODUCTION

Bloodstream infections (BSIs) are one of the most important causes of morbidity and mortality in hospitalized patients.[1] Rapid diagnosis and timely administration of appropriate antibiotics for the causative agent are very critical for increasing patients' survival chances, but rapid identification of pathogens is often delayed due to the current standard microbiological tests. This situation creates problems in daily practice, and antibacterial treatment is often started empirically.[2] On the other hand, fever, which is the main symptom and sign of bacterial infections, can also be seen in many viral infections and non-infectious conditions. Due to the non-specificity of clinical symptoms and the limitations of diagnostic tests, biomarkers are biological molecules that are increasingly popular and used in diagnosis, monitoring of response to treatment, and determination of prognosis.[3-5] There has been an ongoing pursuit of the ideal biomarker in bacteremia/sepsis in the past 30 years. Important data that procalcitonin (PCT) can help the diagnosis and treatment of patients when used alone or in combination with other biomarkers have been obtained.[6]

PCT is a molecule that is encoded by the calcitonin-1 (CALC-1) gene on the first chromosome and is the precursor of calcitonin.[7] It is a precursor acute phase protein that is normally <0.1ng/ml in plasma and has no hormonal effects. The plasma level starts to increase from the fourth hour following acute inflammation.[8] PCT is a preferred biomarker since it has high sensitivity and specificity, has a short half-life (<24 hours), and is easily measurable and inexpensive.[9]

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Although there are many studies on the use of PCT in the diagnosis of bacteremia/sepsis, prediction of the etiologic agent, and early initiation, follow-up, and termination of antibiotic therapy, research into the relationship between PCT and antibiotic resistance is limited. These few studies have been done in specific patient groups, and there have been a lot of recommendations that results need to be tested in more general patient groups and larger populations.[10,11]

In our study, we aimed to contribute to empirical bacteria-targeted antimicrobial therapy by investigating the value of PCT as a biomarker in predicting Gram-negative bacteria and multi-drug resistant Gram-negative (MDRGN) BSIs and using the data we obtained.

METHODS

This retrospective descriptive study was carried out by collecting usage data in compliance with the principles outlined in the Declaration of Helsinki. The study was carried out with the permission of Haydarpaşa Numune Training and Research Hospital Clinical Researches Ethics Committee (Date: 28.08.2023, Decision No: HNEAH-KAEK 2023/160/4257).

Patients and samples: All blood cultures and PCT results sent from inpatients to our laboratory between 2018 and 2022 were retrospectively reviewed on the laboratory information management system

Inclusion Criteria

- Patients 18 years and older,
- Results of patients whose blood cultures and PCT tests were requested simultaneously and whose blood cultures were positive,
- Blood culture and PCT results taken at the time of the first bacteremia attack when the patient had more than one blood culture and PCT result

Exclusion Criteria

- Commonly considered contaminants (except for *Corynebacterium* spp. *C. jeikeium*), *Bacillus* spp. (except for *B. anthracis*), coagulase-negative staphylococci, and other skin flora member microorganisms only if grown in a blood culture set
- Patients with a medical history of immune system disease or a history of malignant tumors (thyroid carcinoma/lung cancer)[12]

Quantitative identification of procalcitonin: Serum PCT level was studied using the VIDAS BRAHMS Procalcitonin kit on the VIDAS 3 (bioMérieux, Marcy l'Etoile, France) instrument operating with the automated Enzyme-linked fluorescent immunoassay (ELFA) method according to the manufacturer's instructions. The lower detection limit of the assay was 0.05 ng/ml and assay sensitivity was 0.09 ng/ml.[12]

Blood culture: Blood samples taken in accordance with the blood culture sampling rules were inoculated into aerobic and anaerobic bottles.[13] Blood culture bottles were incubated in the automated blood culture system (BacT/Alert (bioMérieux, Marcy l'Etoile, France) for 5 days. Vials with a positive signal were Gram-stained and inoculated for subculture on standard solid media. Gram stain results were reported to the clinician as preliminary information.

Identification and detection of multiple drug resistance (MDR): Identification of bacteria was performed on the MALTI-TOF MS system (bioMérieux, Marcy l'Etoile, France), and antibiotic susceptibility tests were performed on the VITEK 2 Compact (bioMérieux, Marcy l'Etoile, France). Antibiotic susceptibility results were evaluated according to EUCAST guidelines.[14]

In the antibiotic susceptibility results, the results of patients with acquired resistance to at least one antibiotic in three or more antimicrobial categories were classified as MDR.[15] The antibiotic susceptibility results of *Enterobacteriaceae*, *Acinetobacter baumannii* complex, and *Pseudomonas aeruginosa* were evaluated in terms of MDR.

Statistical Analysis

All study data were analyzed on the SPSS 26.0 software package (SPSS, Chicago, IL, USA). Values were presented using numbers and percentages. Variables with a normal distribution were presented using mean ± standard deviation values (SD). Variables with a non-normal distribution were represented by medians and interquantile range values (IQR). To analyze each group, the Mann-Whitney U test was applied to two independent samples and the Kruskal Wallis H test to multiple independent samples. Statistical significance was accepted as $p<0.05$. The receiver operating characteristic (ROC) curve analysis was employed to determine cutoff values. The Uden index was used to define the sensitivity and specificity of these cutoff values (Uden index = sensitivity + specificity - 1) and the best cutoff value was determined .

RESULTS

A sample of 1206 patients whose blood culture and PCT tests had been requested simultaneously and who had pathogenic microorganism growth as a result of blood culture were included in the study. While 1,102 patients had been detected to have a single pathogen, polymicrobial pathogens had been detected in 104 patients. Of the patients with a single pathogen, 562 (50.9%) had Gram-negative bacteria, 446 (40.4%) had Gram-positive bacteria, and 94 (8.5%) had fungi.

PCT levels for infections caused by different microbial species: Median PCT levels corresponding to microbial species isolated in six or more patients with monomicrobial bacteremias are shown in Table 1. *Escherichia coli* (n:216, 38.4%) and *Staphylococcus aureus* (n:195, 43.7%) were the most frequently isolated Gram-negative bacteria and Gram-positive bacteria, respectively. *Candida albicans* (n:42, 44.6%) was the fungal species that had been the most commonly detected agent. To assess whether different microbial groups could be distinguished by PCT levels, median values for monomicrobial bloodstream infections caused by different species were compared (Table 1).

Table1. Median PCT levels corresponding to pathogens isolated from six or more BCs with monomicrobial infection

Pathogen	Number of BCs	Median PCT level (IQR) (ng/ml)
GNB*		
Escherichia coli	216	9.59 (2.60-38.30)
Klebsiella pneumoniae	135	9.11 (2.14-30.03)
Acinetobacter baumannii complex	54	10.62 (2.27-55.2)
Pseudomonas aeruginosa	50	5.74 (1.66-33.10)
Enterobacter cloacae	24	5.04 (1.77-30.54)
Serratia marcescens	16	10.67 (1.20-36.40)
Enterobacter aerogenes	12	7.74 (1.28-41.44)
Proteus mirabilis	9	4.65 (1.55-13.95)
Klebsiella oxytoca	6	19.5 (7.41-63.90)
Stenotrophomonas maltophilia	9	8.47 (2.58-69.41)
Ralstonia pickettii	6	0.63 (0.24-12.88)
GPB**		
Staphylococcus aureus	195	2.13 (0.69-8.40)
Enterococcus faecalis	73	1.22 (0.18-4.01)
Enterococcus faecium	45	1.41 (0.51-5.32)
Staphylococcus epidermidis	39	0.70 (0.15-2.47)
Staphylococcus hominis	33	0.49 (0.18-1.76)
Streptococcus mitis/Streptococcus oralis	11	3.08 (0.22-15.9)
Streptococcus pneumoniae	9	7.73 (0.40-22.33)
Staphylococcus haemolyticus	7	0.27 (0.18-30.7)
Streptococcus parasanguinis	6	0.06 (0.44-0.77)
FUNGUS***		
Candida albicans	42	1.63 (0.64-3.87)
Candida parapsilosis	33	1.78 (0.58-7.52)
Candida tropicalis	14	6.5 (036-22.34)

BC, blood culture; GNB, Gram-negative bacteria; GPB, Gram-positive bacteria; IQR, inter quartile range; PCT, procalcitonin
*GNB that were isolated less than six: *Aeromonas salmonicida, Burkholderia cepacia, Citrobacter koseri, Enterobacter hormaechei, Hafnia alvei, Morganella morganii, Providencia stuartii, Pantoea agglomerans, Pseudomonas putida, Salmonella* spp
**GPB that were isolated less than six*: *Enterococcus gallinarum, Enterococcus avium, Enterococcus hirae, Staphylococcus capitis, Staphylococcus cohnii* ssp, *Staphylococcus lugdunensis, Staphylococcus pettenkoferi, Streptococcus dysgalactiae, Streptococcus gordonii, Streptococcus mutans, Streptococcus parasanguinis*
***Fungus that were isolated less than six: *Candida glabrata, Candida kefyr, Candida krusei*

The PCT median caused by *Klebsiella oxytoca*, one of the Gram-negative bacteria, was found at the highest level. This was followed by *Serratia marcescens*, *Acinetobacter baumannii* complex, *Escherichia coli*, and *Klebsiella pneumoniae*. *Streptococcus mitis/Streptococcus oralis*, one of the Gram-positive bacteria, caused the highest PCT median level, and this was followed by *Staphylococcus aureus*. In fungi, the highest PCT median value belonged to *Candida parapsilosis*.

PCT levels in Gram-negative and Gram-positive BSIs: According to analysis results, the PCT median level in BSIs caused by the Gram-negative bacteria (8.45ng/ml; IQR: 2.12-34.35), was found to be statistically significantly higher than the BSIs caused by the Gram-positive bacteria (1.49.ng/ml; IQR: 0.33-6.15), fungal (1.87.ng/ml; IQR: 0.57-7.45), and polymicrobial infections (4.70.ng/ml; IQR: 0.75-18.02) ($p<0.05$). There was no statistically significant difference between the PCT median levels of Gram-positive, fungal, and polymicrobial BSIs ($p>0.05$). The PCT levels in the different groups of microorganisms in the study are shown in Figure 1.

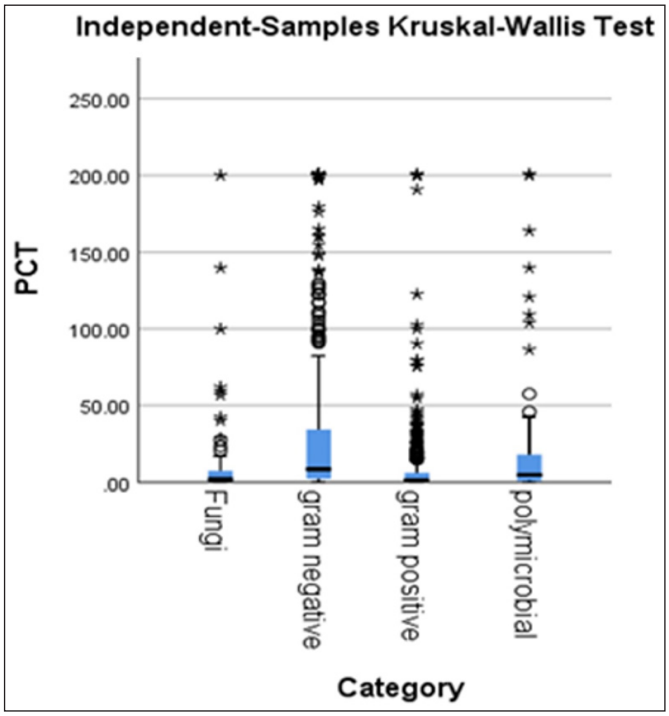

Figure 1. Comparison of PCT levels of microorganisms

A ROC analysis was performed to evaluate the diagnostic accuracy of PCT in predicting Gram-negative BSI. The best cutoff value of ROC, with an AUC value of 0.607 (95% confidence interval: 0.578-0.635, p< 0001), a sensitivity of 72.1%, and a specificity of 55.4%, for distinguishing Gram-negative BSIs from other BSIs was determined as 2.5 ng/ml (Figure 2). Polymicrobial BSIs were not included in the study.

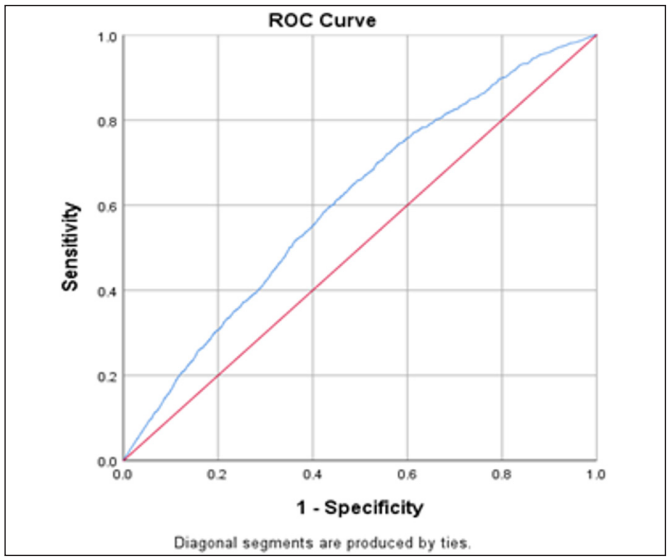

Figure 2. The ROC curve of PCT: Gram-negative bloodstream infections and other blood culture-positive bloodstream infections except for polymicrobial bloodstream

Serum procalcitonin level of multidrug-resistant pathogens and non-multidrug-resistant (nonMDR) pathogens among Gram-negative bloodstream infections: The antibiotic susceptibility results of *Enterobacteriaceae* (n:421), *Acinetobacter baumannii* complex (n:54), and *Pseudomonas aeruginosa* (n:50), which frequently cause Gram-negative BSI, were examined. Of the 277 isolates detected to be MDR, 228 were *Enterobacteriaceae*, 39 were *Acinetobacter baumannii* complex, and 10 were *Pseudomonas aeruginosa*. Polymicrobial BSIs were not included in the study.

In some studies, the PCT median value (12.94 ng/mL; IQR: 3.59-47.08) of MDR pathogens was found to be statistically significantly higher than that of non-MDR pathogens (5.90 ng/mL; IQR: 1.27-18.60) ($p < 0.05$) (Figure 3).

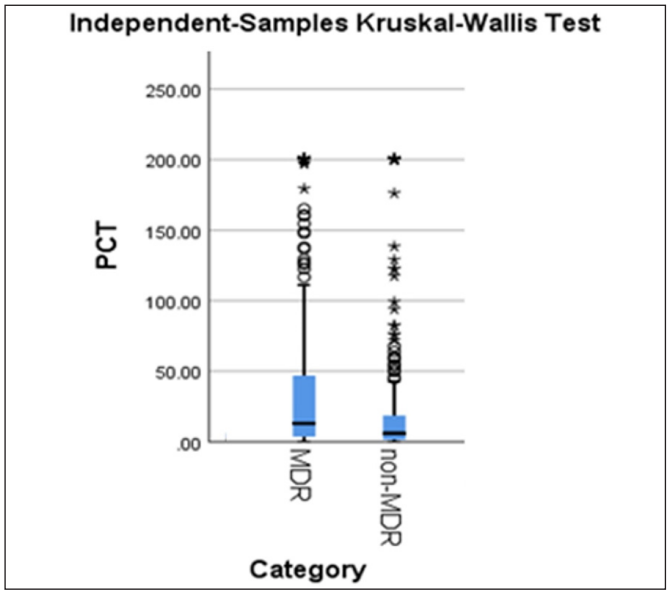

Figure 3. The procalcitonin level of multidrug-resistant Gram negative bacilli (*Enterobacteriaceae*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii* complex) was higher than that of non-multidrug-resistant Gram-negative bacilli (*Enterobacteriaceae*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii* complex)

A ROC analysis was performed, and the AUC distinguishing MDR pathogens from nonMDR was 0.633 (95% confidence interval, 0.586-0.681; $p < 0.001$), with a best PCT cutoff value of 11.4 ng/mL, a sensitivity of 54.8%, and a specificity of 66.3% (Figure 4).

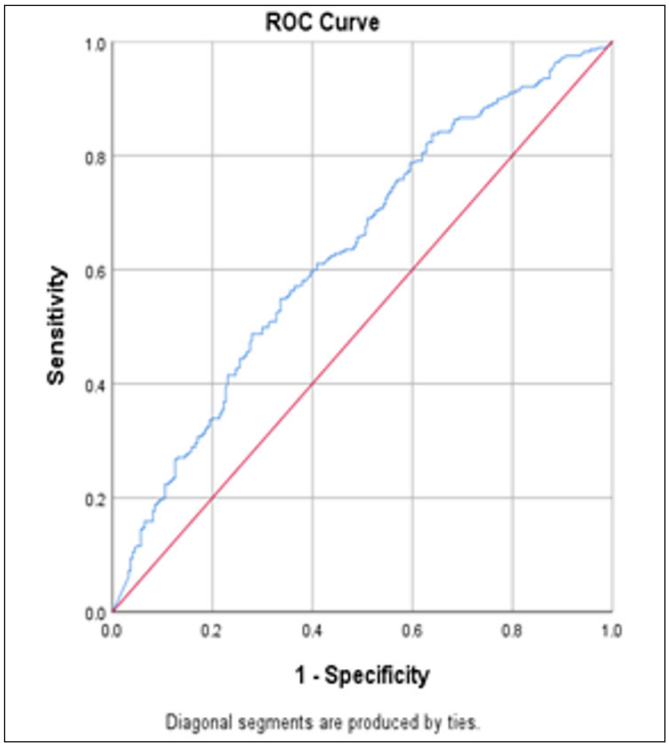

Figure 4. The ROC curve of procalcitonin: procalcitonin ROC curves for multidrug-resistant and non-multidrug-resistant Gram-negative bacilli (*Enterobacteriaceae*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii* complex) bloodstream infections

DISCUSSION

In its report published in 2017, the World Health Organization drew attention to Gram-negative MDR and classified *Enterobacteriaceae*, *Acinetobacter baumannii* complex, and *Pseudomonas aeruginosa* as high-priority pathogens requiring urgent development of new antibiotics.[16] They also warned Türkiye in their 2020 report about taking precautions against resistance, especially in Gram-negative bacteria.[17] Although the principles of rational antibiotic use should be followed to avoid the development of resistance, a significant proportion of antibiotics are prescribed empirically, that is, without culture results to guide antibiotic selection, and even before the confirmation of a bacterial infection.[18]

In the recent literature, PCT has been recommended to be used in clinical diagnosis/treatment algorithms as a diagnostic test for early identification of bacterial infections, guide antibiotic selection, and monitor response to treatment.[9,19,20]

It is known to have a good negative prediction for bacterial infections, especially bacteremia, and guide

a more appropriate empirical antibiotic therapy while waiting for definitive microbiological results.[21-24]

Our main findings indicated that the PCT level in Gram-negative BSIs in inpatients was statistically significantly higher than the PCT level in Gram-positive bacteria- and fungi-caused BSIs. We found that a PCT value of ≥2.5 ng/ml could be helpful in predicting patient with a Gram-negative agent-caused BSI, with a sensitivity of 72.1% and a specificity of 55.4%. In addition, PCT levels were found to be statistically significantly higher in MDRGN BSIs (*Enterobacteriaceae*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* complex) than in non-MDR pathogens. ($p<0.05$). We found that a PCT value of ≥11.4 ng/ml could be helpful in predicting patients with a Gram-negative agent-caused BSI, with a sensitivity of 54.8% and a specificity of 66.3% (*Enterobacteriaceae*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* complex). Although the predictive power of PCT on discriminating bacterial infections was not evaluated in our study, many studies indicated that it could help clinicians to decide whether the suspected infection was truly bacterial.[9,25,26] PCT is more specific for bacterial infections since interferon (INF)-g released in response to viral infections inhibits it.[27]

When a patient with suspected infection presents, there are two key questions: Should antibiotics be started? If yes, which ones? The answers to these questions are not simple because a single parameter is not specific or sensitive enough to support the diagnosis.[28]

The review of various studies on the assessment of the diagnostic accuracy of PCT in predicting Gram-negative BSI and a meta-analysis in which 13 studies had been evaluated indicated that there was no single fixed threshold value at which the best performance was achieved and that PCT varied from 1.3 to 16 ng/ml, AUC values from 0.581 to 0.944, sensitivity from 56 to 77%, and specificity from 68 to 87%.[6,12,29-31] We think that differences arise from patients' demographic characteristics, background diseases, comorbidities, the effects of the drugs they use on PCT, criteria for acceptance and rejection of the study, the time when PCT and blood culture have been taken, the difference between the methods/devices used for measurement, cut-off values, and sensitivity and specificity ratios.[6,32]

PCT is not only a better predictor of bacterial infection and sepsis than others but also has some specificity for the type of bacterial infection that causes symptoms. The PCT differences between Gram-negative and Gram-positive bacteria are thought to be due to differences in the cell wall component of bacteria. Lipopolysaccharides found in the cell wall of Gram-negative bacteria are recognized by toll-like receptor 4 (TLR4), while lipoteichoic acid found in the cell wall of Gram-positive bacteria is recognized by toll-like receptor 2 (TLR2). Activation of different receptors causes different gene expression in leukocytes, and as a result, different cytokines are released. In addition, endotoxins released by Gram-negative bacteria are strong inducers of PCT, and higher IL-6 and IL-8 levels in patients infected with Gram-negative bacteria cause these differences in PCT response.[9,33]

Although the guidance of PCT for antibiotic therapy has been evaluated in detail, little is known about whether it can play a role in determining antibiotic susceptibility. Two studies, one conducted on burn patients (*Pseudomonas aeruginosa* and *Acinetobacter baumannii*, *Klebsiella pneumoniae*) and the other on hematology patients with febrile neutropenia (*Enterobacteriaceae*, *Pseudomonas aeruginosa* and *Acinetobacter baumannii* complex), the PCT values of MDR BSIs were statistically significantly higher than those of non-MDR BSIs in both studies. In the ROC analyses, the best PCT cutoff point was determined as 1.42 ng/mL with 90.9% sensitivity and 88.9% specificity in burn patients and 0.45 ng/mL with 72.6% sensitivity and 51.1% specificity in hematology patients with febrile neutropenia.[10,11]

Watanabe et al.[34] determined that PCT was decisive in GN BSIs and that patients who tested positive for *Escherichia coli* and *Proteus mirabilis*, producing extended-spectrum β-lactamase (ESBL) had statistically significantly higher PCT concentrations than ESBL-negative patients. They stated that distinguishing between ESBL-producing and non-ESBL-producing bacteria according to PCT concentrations could be very helpful in facilitating rapid and appropriate antibiotic therapy, including the use of carbapenems.

In a study on the evaluation of the correlation between MDRGN BSIs (*Acinetobacter baumannii*, *Klebsiella pneumoniae*) developing in COVID-19 patients and inflammatory parameters, the PCT results (0.99; IQR: 0.29-3.83) obtained on the day of hospitalization of patients with MDRGN BSI were significantly higher than the results (0.29; IQR: 0.13-2.59) of control patients with COVID-19 who had not develop bacteremia ($p<0.05$). Except for the PCT value, there was no statistical difference between MDRGN BSI cases and control cases on the day of admission to the COVID-19 ICU in terms of their inflammatory parameters, such as leukocytes, lymphocytes, neutrophils, neutrophil/lymphocyte ratio, platelets, and CRP ($p>0.05$). It was also found that most of the patients admitted to the COVID-19 ICU were prescribed meropenem and piperacillin/tazobactam, most commonly ceftriaxone, and empirical unnecessary antimicrobial therapy was thought to be a risk factor for the development of MDRGN BSIs.[35]

Contrary to all these studies, in a study on the evaluation of hematological and biochemical markers for the early diagnosis of bacteremia caused by *Enterobacteriaceae* bacteria resistant to carbapenems, it was determined that PCT values would not be a predictor of carbapenem resistance.[36]

The examination of approximately 8 million patient data in the USA in 2019 indicated that 37% of inpatients were given empirical antibiotic treatment for Gram-negative bacteria in the first two days of hospitalization and that 22% of all admissions and 61% of presentations receiving empirical treatment for Gram-negative bacteria received broad-spectrum gram-negative antibiotics. In other words, empirical broad-spectrum antibiotic treatment was started for one out of every five hospitalized patients. It was determined that approximately 30% of the patients who received broad-spectrum empirical treatment were not in the intensive care unit, had not undergone surgery, or had not been diagnosed with one of the common infectious syndromes (pneumonia, UTI, sepsis, or bacteremia) described in this study. This group of patients was unnecessarily exposed to broad-spectrum empirical therapy and associated subsequent consequences.[37]

It was shown that recommending antibiotic treatment based on PCT values, developing an institution-specific algorithm considering institutional threshold values, and adding it to antibiotic management algorithms improved antibiotic use.[38]

Considering the results of our study and those of other published studies, the diagnostic algorithm in **Figure 5** was created to distinguish PCT bacterial infections from non-bacterial causes and to identify Gram-negative BSIs and MDRGN BSIs.[39,40]

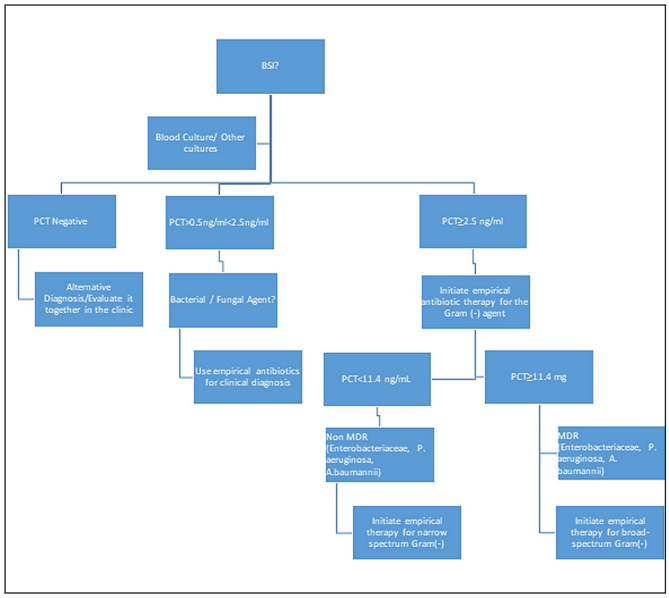

Figure 5. PCT algorithm in suspected bloodstream infection

PCT will help clinicians select the most appropriate empirical therapy in BSIs.[9,20] If the PCT is ≥2.5 ng/ml in cases with suspected infection, it can be assumed that the causative infection agent is Gram-negative bacteria and empirical treatment can be planned accordingly, and unnecessary use of drugs against Gram-positive bacteria and fungi can be avoided. Even if PCT is ≥11.6 ng/ml, MDR Gram-negative bacteria may be the causative agent in patients, and a treatment plan including broad-spectrum antibiotics can be applied. Although broadening the antibiotic spectrum without specific microbial evidence is often criticized for causing antibiotic overuse, considering the high prevalence of MDR in the intensive care unit, PCT-guided broadening of the antibiotic spectrum may be a solution for patients at a high risk of mortality.[41,42]

Although the AUC, sensitivity, and specificity for distinguishing MDRGN BSIs from non-MDR BSIs appear to be relatively poor, it can be tolerated until a definitive diagnosis is made for critically ill patients, as it is preliminary information on how to start antibiotic therapy as soon as possible.[34] In addition, it should not be forgotten that in emergency rooms and ICUs, where rapid decision-making is of critical significance, the time to get the PCT test result is approximately one hour and that it is a test that allows rapid decision-making at the bedside.

In studies in which various algorithms regarding the use of PCT in bacteremia/sepsis are created, the use of different cutoff values and making different recommendations according to the patient population and the clinic where the patient is treated (emergency department, ICU) makes interpretation difficult; however, it is an undeniable fact that PCT guidance also provides benefits such as treatment planning, lower antibiotic exposure, reduced antibiotic-related side effects, reduced risk of antibiotic resistance, shortened hospital stay, and reduced treatment costs.[9,20,28,38,43-45] However, the procalcitonin algorithm is not a stand-alone diagnostic tool, and it is important to use it in conjunction with clinical evaluation. This algorithm provides an additional way for physicians to identify the origin of the infection, but it should be noted that other tests and evaluations are required to make a definitive diagnosis.

To our knowledge, this is the largest study to date on the examination of the clinical utility of PCT for MDR in an unselected patient population with suspected bloodstream infection, but we have several limitations. First, this was a retrospective study and had the inherent limitations of retrospective studies. We did not have detailed information about whether patients had received antibiotic treatment before blood culture sampling, the clinical diagnosis and comorbid conditions of the patients, and whether they had used drugs that may have affected the PCT level.[46]

CONCLUSION

Although PCT threshold values in the management of empirical antibiotic therapy differ in published studies, it is important to adapt and develop an institution-specific algorithm. As with any other antimicrobial management intervention implemented in an institution, the appropriate use of PCT has the potential to improve antibiotic management..

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Haydarpaşa Numune Training and Research Hospital Clinical Researches Ethics Committee (Date: 28.08.2023, Decision No: HNEAH-KAEK 2023/160/4257).

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 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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