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The utility of procalcitonin in the diagnosis of severe sepsis: a validation study

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ABSTRACT

Background: One of the main causes of morbidity and death is still severe sepsis, particularly in environments with minimal resources when prompt detection is difficult. Early identification of sepsis may be possible with procalcitonin (PCT), a biomarker that is raised in bacterial infections. By contrasting serum PCT with blood culture data, this study sought to assess the diagnostic accuracy of serum PCT in detecting severe sepsis.

Methods: Over the course of six months, from December 1, 2023, to May 1, 2024, this cross-sectional validation study was carried out in the Department of Medicine at Khyber Teaching Hospital in Peshawar. Non-probability consecutive sampling was used to recruit 111 patients with severe sepsis, ages 18 to 60. Blood cultures and serum PCT levels were taken at presentation. All data analysis was performed using SPSS version 25. Patients were determined true positive if both "PCT" (positive procalcitonin) and blood culture were positive; false positive if "PCT" was positive while blood culture was negative; true negative if both "PCT" and blood culture test was negative; and false negative if "PCT" was negative while blood culture was positive.

Results: Of the 111 patients, 60.4% were male; the mean age was 42.6 years, the sensitivity of procalcitonin was 87.3%, specificity was 75.0%, positive predictive value was 82.1%, negative predictive value was 81.8%, and overall diagnostic accuracy was 82.0%. There was a statistically significant association between procalcitonin and blood cultures ($p = 0.0001$).

Conclusion: Serum procalcitonin is a valuable diagnostic tool in the early identification of severe sepsis. Procalcitonin's high sensitivity and strong predictive values lends to a recommendation for the incorporation of serum procalcitonin into clinical practice guidelines for rapid treatment of sepsis.

Keywords: Biomarker, Blood Culture, Procalcitonin, Sepsis

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Introduction

Sepsis continues to be a significant healthcare burden worldwide, with considerable contribution to morbidity and mortality, especially in critically ill patients. Sepsis is defined as a dysregulated host response to infection resulting in life-threatening organ dysfunction for which early recognition and early initiation of therapy are needed to improve outcomes (1). Severe sepsis is the designation of sepsis plus organ dysfunction,

resulting in an increased chance of progression to septic shock and death (2). Routine diagnostics, including clinical scoring systems and non-specific inflammatory markers like C-reactive protein (CRP) and leukocyte count, have inadequate sensitivity and specificity for early detection (3).

In recent years, procalcitonin (PCT) has gained attention as a potential biomarker for diagnosis of sepsis in its early stages. PCT is a prohormone of calcitonin that is synthesized in thyroid C-cells under normal conditions, but during systemic bacterial infection, the production of PCT is increased in various extrathyroidal` tissues, including the liver and lungs (4). While CRP may increase in any inflammatory condition, PCT rises quickly (rather than days) due to bacterial infections, and systemic inflammation correlates with the higher concentration of PCT (5). PCT often remains low in viral infections and in non-infectious inflammatory diseases, making it a more reliable biomarker (6).

Several studies have shown the diagnostic and prognostic role of PCT in patients with suspected sepsis in emergency and critical care settings (7-9). PCT-guided algorithms have also been assessed for their role in informing the initiation of antibiotic therapy, reducing unnecessary antibiotic exposure, and decreasing the potential for resistance development (10). Nevertheless, the diagnostic cut-off values for PCT vary by population, clinical setting, and laboratory, making it difficult to apply uniformly (11).

There remains an ongoing discussion about the correct threshold of procalcitonin (PCT) that best distinguishes systemic inflammatory response syndrome (SIRS) from sepsis and severe sepsis despite its increased use (12). Some studies have reported improvement in the accuracy of assessment and risk assessment by pairing PCT levels with clinical judgment and other markers including lactate and SOFA scores (13). However, even in contexts that have lower resources and where the mortality from sepsis remains disproportionally high, there is limited evidence that supports the validity of PCT to aid in clinical practice (14). With that, implementing PCT into local sepsis pathways will need to be validated in context to clinical effectiveness and cost-effectiveness in clinical practice (15).

As validation studies are need of time as gold standard markers are expensive mostly unavailable in every region as well as require expertise. Accurate and early diagnosis of severe sepsis still presents a challenge in clinical practice, particularly in settings where resources are limited, and where delays in diagnosis can have devastating consequences. Often, diagnostic tests do not possess enough specificity to differentiate systemic inflammatory response and true bacterial sepsis. In these settings, procalcitonin (PCT) has emerged as a new potential biomarker for the rapid rise that occurs in the setting of bacterial infection, as well as its ability to provide information about illness severity. Nevertheless, the diversity in the cut-off values, patient groups, and health setting conditions, requires local validation before the consistency of the PCT injection into sepsis protocols. The current study would have helped to establish the diagnostic accuracy of procalcitonin in the diagnosis of sepsis in our particular clinical environment by considering the blood culture as a gold standard.

Methods

This cross-sectional validation study was conducted in the Department of Medicine, Khyber Teaching Hospital, Peshawar, over six months, i.e., from 1st December 2023 to

1st May 2024, following the approval of the research synopsis. The ethical approval for the study was granted by the Institutional Research and Ethical Review Board Committee (IREB) of Khyber Medical College, Peshawar, under the approval number 732/DME/KMC, dated 16-11-2023.

A total of 111 patients were enrolled using a non-probability consecutive sampling technique. The sample size was calculated using Buderer's formula with the assumptions of a sepsis prevalence of 28.3%, expected sensitivity of 76.0%, specificity of 72.0%, a 15% margin of error, and a 95% confidence interval (16, 17).

The inclusion criteria for the study comprised adult patients aged between 18 to 60 years of either gender who were clinically diagnosed with severe sepsis based on predefined operational definitions. Severe sepsis was diagnosed if the patients had evidence of satisfying the systemic inflammatory response Consortium criteria and proved organ dysfunction. Patients were excluded if they had taken antibiotics in the prior 15 days, as previous antimicrobial treatment could affect procalcitonin levels and culture results. Furthermore, patients with reported chronic kidney disease, liver cirrhosis, or any malignancy were removed to mitigate potential confounding variables that may impact biomarker expression or clinical outcomes when defining severe sepsis.

Patients aged 18 to 60 years in both sexes who met the definition of diagnostic criteria for severe sepsis were included. An individual was defined as having sepsis if they presented with two of the following clinical variables: temperature >38°C or <36°C; a heart rate exceeding 90 beats/minute; respiratory rate >20 breaths/minute, or as the partial pressure of carbon dioxide or $PaCO_2$ <32 mmHg; leukocyte >12 $x10^9$/ L (or <4 $\times 10^9$/L), or >10% immature neutrophils; and severe sepsis was defined if the patient had evidence of organ dysfunction: increase in serum creatinine by >0.5 mg/dl; total bilirubin >2 mg/dl; or any signs of altered level of consciousness.

Patients were excluded if they had received antibiotics in the previous 15 days or had a history of chronic kidney disease, liver cirrhosis, or malignancy.

After obtaining informed written consent, patients meeting the inclusion criteria were recruited from the indoor medical wards. Baseline demographic and clinical data, including age, gender, BMI, socio-economic status, education level, occupation, and area of residence, were recorded on a structured proforma. The antecubital vein was cleansed using an alcohol swab, and 5 cc of venous blood was aseptically collected using a gel tube. This sample was referred to the hospital lab, where serum procalcitonin (PCT) levels were estimated. A PCT of over 0.60 ng/mL was regarded as positive for sepsis. Moreover, a 10-cc of venous blood was taken and placed in a blood culture bottle and also transported to the microbiology lab, where culture media was used to identify the pathogens. The confirmatory evidence of sepsis was a positive blood culture with evidence of the growth of microorganisms.

The data was entered and assessed using IBM SPSS version 25. Frequencies and percentages were calculated under categorical variables, i.e. gender, PCT positive, blood culture results, socioeconomic class, education level, occupation and place of residence. Following the distribution analysis (Shapiro-Wilk test), the quantitative

variables, such as age, BMI, and length of illness, were presented in terms of mean +- standard deviation. The diagnostic accuracy of serum procalcitonin in the diagnosis of severe sepsis was identified and chi-square was used to apply statistical tests. True positives were those patients with a positive PCT and a positive blood culture; false positives were those with a positive PCT and a negative blood culture; true negatives were those with a negative PCT and a negative blood culture; and false negatives were those with a negative PCT and a positive blood culture.

Results

A total of 111 participants participated in the study, whose mean age was 42.6 years (SD +-11.3). Most of the participants were men, with 60.4% of the sample being males, and 39.6 being women. Body mass index (BMI) was 25.1 kg/m2 (SD +-4.6) with an overwhelming majority of the people being overweight. Concerning the socio-economic status, 46.8% of the participants had the middle-income group, 43.2% in the low-income group and only 10.0% in the high-income group. The level of education was diverse with 53.2 per cent having attended primary up to secondary education, 25.2 per cent illiterate, and 21.6 per cent having higher education. On the question of employment, 33.3% of the respondents were employed, whereas the rest (66.7%) were unemployed or housewives. The urban population constituted 55.0 percent of the study population, and the rural population comprised 45.0 percent. (Table 1)

Table 1: Demographic and Clinical Characteristics of Study Participants (n = 111)

Variable	Category	n (%)
Age (years)	Mean ± SD	42.6 ± 11.3
Gender	Male	67 (60.4%)
	Female	44 (39.6%)
BMI (kg/m²)	Mean ± SD	25.1 ± 4.6
Socio-economic Status	Low	48 (43.2%)
	Middle	52 (46.8%)
	High	11 (10.0%)
Education Level	Illiterate	28 (25.2%)
	Primary to Secondary	59 (53.2%)
	Higher Education	24 (21.6%)
Occupation	Employed	37 (33.3%)
	Unemployed/Housewife	74 (66.7%)
Residence	Urban	61 (55.0%)
	Rural	50 (45.0%)

In this study, procalcitonin (PCT) showed a strong diagnostic performance when compared with blood culture results. Of 111 participants, the outcomes showed that PCT identified 55 true positives and 36 true negatives and 12 false positives, and 8 false negatives. The sensitivity of PCT was determined to be 87.3% meaning it has a good capability of identifying true cases of infection, whereas specificity was found to be 75.0, implying that it is a reasonable capacity to exclude non-infected cases. The positive predictive value was 82.09% and the negative predictive value was 81.82%, demonstrating that PCT reliably predicted both presence and absence of infection. The overall diagnostic accuracy was 81.98%, with a highly significant

association between PCT results and blood culture findings (p = 0.0001). (Table 2)

Table 2: Comparison of Procalcitonin with Results of Blood Culture of the Study Participants (N=111)

PCT	Blood Culture Positive	Blood Culture Negative	Total	p-value
Positive	55 (True Positive)	12 (False Positive)	67	0.0001
Negative	8 (False Negative)	36 (True Negative)	44	
Total	63	48	111	
'Sensitivity': 87.3% *'Specificity': 75.0%* *'Positive Predictive Value': 82.09%* *'Negative Predictive Value': 81.82%* *'Overall Diagnostic Accuracy': 81.98%*				

The serum procalcitonin (PCT) diagnostic performance was found to be clinically useful for the identification of severe sepsis. The sensitivity of PCT was 87.3%, which detected most of the true cases of sepsis, and it had a specificity of 75.0%. Sensitivity and specificity values represent a moderate ability to rule out non-septic individuals. Among patients with a positive PCT test, 82.1% (132/161) were confirmed as septic according to blood culture criteria, which suggests a good positive predictive value for this test. Once again, among patients who were negative for PCT, 81.8% (36/44) were culture negative for sepsis, which would again suggest good negative predictive value. (Figure 1)

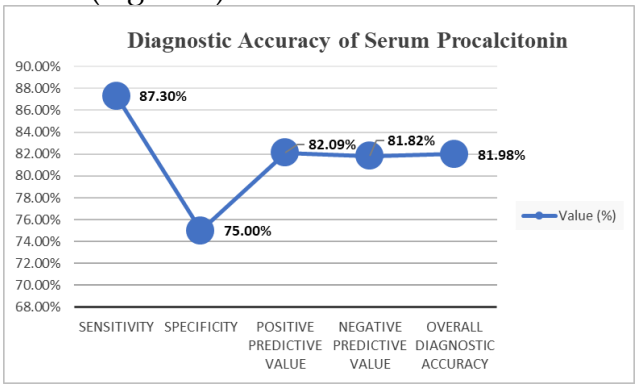

Figure 1: A graph showing the Diagnostic Accuracy of Serum Procalcitonin

Discussion

The current research demonstrated promising findings on the diagnostic performance of serum procalcitonin (PCT) in detecting severe sepsis. With an 87.3% sensitivity, 75.0% specificity, 82.1% positive predictive value, an 81.8% negative predictive value, and an overall diagnostic accuracy of 82.0%, PCT is a consistent diagnostic biomarker to assess early sepsis.

This is in line with the previous research findings. An example was a previous study that concluded that it was sensitive with a specificity of 85.0% and 74.0%respectively, which is similar to this study, particularly in the exclusion of non-sepsis(18). A different study reported slightly better values, a sensitivity of 100% and specificity of 72.0% again underpinning that PCT has high sensitivity to detect true cases of sepsis (19). The sensitivity and specificity were 90% and 80.2%, respectively, in a large-scale analysis, which is very similar to the diagnostic strength that we observed in our data(20). A fourth study reported an accuracy of 83.0% on the diagnostic, which is quite comparable to our report of 82.0% (21).

Similar to the findings, these studies confirmed our findings with one having a sensitivity of 86% and specificity of 76% showing the stability of PCT in various populations of patients (22). A different study established predictive positive and negative values of 79.1% and 84.0%, respectively, and the clinical applicability of PCT as a diagnostic tool was validated (23). Another comparative study also cited PCT sensitivity of 84 percent and specificity of 51 percent, which once again validated our findings and its use as a possible biomarker in the early diagnosis of sepsis (24). Finally, when it comes to a multi-center validation

study, diagnostic accuracy was reported to be 84, which once again supports the claim of reliability of PCT in the classification of septic and non-septic conditions in general clinical practice (25).

The findings of research suggest that serum procalcitonin provides support in diagnosis in the initial stage of severe sepsis. Procalcitonin is suitable because of its high sensitivity and predictive values in fast clinical decision-making in emergency and inpatient patients. If PCT is incorporated into diagnostic pathways, earlier initiation of antimicrobial therapy could take place, thereby speeding up serious infection management and lowering mortality rates. PCT could also be a helpful adjunct to clinical assessment and therapy in low-resource settings where timely blood culture may not always be available.

Limitations of the Study

The single-site, tertiary hospital study limits inferences that may be made to other settings or populations.

Non-probability consecutive sampling design can still achieve reliable findings, but as it stands, it may place the study at risk for selection bias.

Additionally, the decision to remove patients currently on antibiotics in the last week could have led to an overestimation of diagnostic performance when assuming that patients were in a more controlled environment.

The assessment of PCT was performed at presentation only, when a serial assessment of PCT levels may allow for a better assessment of the dynamics of the disease state and response.

Finally, while blood culture is regarded as the gold standard, it has its own limitations (false negatives, delayed results) that could impact the assessment of PCT accuracy.

It is necessary to test the validity of the findings further in future research and make them more clinically useful through larger samples and serial assessment in multicenter research.

Conclusion

Serum procalcitonin is a useful and valuable biomarker that has a good overall diagnostic accuracy, high sensitivity, and moderate specificity in the early diagnosis of severe sepsis. The ability of procalcitonin to distinguish between septic and non-septic patients justifies the application of this biomarker in the clinical routine, especially in cases where time and resources are restricted and the biomarker is used alongside clinical examination and blood cultures. Sepsis screening conducted with the help of a procalcitonin-based sepsis screening tool may lead to better outcomes in the case of sepsis early diagnosis and treatment.

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