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Estimation and Correlation of IL-6 And TNF Alpha with Procalcitonin as Biomarkers in Cases of Sepsis in a Tertiary Care Hospital in Western Uttar Pradesh

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ABSTRACT

Introduction: Sepsis is one of the grave concerns in public health. Despite the recent advances in medical practice, the mortality rate and diagnostic uncertainty remains high. Hence, reliable biomarkers are essential for timely diagnosis and prediction of outcomes.

Aim and Objective: This study aimed to estimate and correlate Interleukin 6 (IL-6) and Tumour Necrosis Factor alpha (TNF α) with Procalcitonin (PCT) in cases of sepsis.

Methods and Material: This cross-sectional study (the ethical clearance number 67/2022-23 and REF NO: 516/UPUMS/DSW/Ethical/2022-23) was conducted from 1st December 2022 to 30th June, 2024. In this study, 100 clinically suspected sepsis patients were enrolled from Emergency department and Intensive Care Unit.
Each patient was investigated for serum PCT, IL-6 and TNFα and blood cultures using the BACTEC automated blood culture system.
Statistical analysis used: The collected data was analysed by using IBM SPSS Statistics Version 29.0.

Results: The cut-off value for PCT was 2.3 ng/ml (sensitivity, 89.3%; specificity, 79.4%), 203 pg/ml for IL-6 (sensitivity, 75.0%; specificity, 64.7%), 83.5pg/ml for TNF-α (sensitivity, 78.1%; specificity, 77.9%,). PCT showed significant positive correlation($r = 0.529$) with IL-6 (p-value < 0.001) and TNF α ($r = 0.639$) (p-value < 0.001).

Conclusions: PCT proved an excellent marker and a promising diagnostic tool for diagnosing sepsis. Additionally, the current study also confirmed its positive correlation with IL-6 and TNF α.

Keywords: Procalcitonin, Interleukin-6, Tumour Necrosis Factor, Sepsis, Blood culture, Biomarker.

INTRODUCTION

Sepsis is life-threatening organ dysfunction caused by dysregulated host response to infection.[1] Worldwide, sepsis prevalence is estimated to be 30 million cases and more than 8 million deaths per year.[2] In India, the total sepsis burden is approximately 89.6 lakhs with a mortality of about 25–30%.[3]. In 2016, a definition of sepsis was revised as Sepsis-3

by Society of critical care medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) which eliminated the terms Systemic Inflammatory Response Syndrome (SIRS) and severe Sepsis.[4]

Revised definition of sepsis includes a ≥2 point increase in Sequential Organ Failure Assessment**(SOFA)** score is associated with a hospital mortality rate greater than 10%.[5] The **SOFA** score has 6 systems – each system has score a 0-4 (max. score is 24). Components of the **SOFA** score include:

1) **Central Nervous System:** Glasgow Coma Scale
2) **Respiratory System:** PaO_2/FiO_2 (partial pressure of arterial oxygen/fraction of inspired oxygen)
3) **Cardiovascular system:** Mean Arterial Pressure (MAP)
4) **Hematology:** platelet count
5) **Renal function:** Serum creatinine levels, urine output
6) **Hepatobiliary system:** Serum bilirubin.[6]

In order to avoid delays in the treatment of patients who are placed outside the ICU, a simplified version called **Quick Sequential Organ Failure Assessment (qSOFA)** is used to identify patients with suspected infection, who are at greater risk of poor outcome.[7] The qSOFA comprises the following criteria :

- Low blood pressure (systolic BP ≤100 mmHg)
- High respiratory rate (≥22 breaths/min)
- Altered mentation (Glasgow Coma Scale score<15).

Presence of 2 or more signs near the onset of infection indicates a positive qSofa score.[7]

For sepsis diagnosis blood culture is considered gold standard, which enables isolation and identification of the causative agents and the antimicrobial sensitivity testing. However, due to its delayed turnaround time, rapid diagnostic methods are crucial for timely intervention. [8] [9] To achieve this, biomarkers like procalcitonin, interleukin 6, and tumour necrosis factor alpha with diagnostic significance are being explored.[10] [11]

Procalcitonin (PCT), a prohormone precursor to calcitonin, serves as a sensitive acute-phase reactant protein. [12] The PCT level rises rapidly 6-12 hours after exposure to bacterial infection and remains high for 24 hours [13]

Interleukin-6 (IL-6),) is a cytokine that has both pro-inflammatory as well as anti-inflammatory properties. Due to its pivotal role in various disease processes, including sepsis, cancer, cardiovascular disease, and autoimmune disorders, IL-6 has emerged as a significant biomarker. [14]

TNF-α is a pro-inflammatory cytokine that stimulates the acute phase reaction and involved in systemic inflammation. Some studies, have shown that the plasma levels of TNF-α increased significantly in patients with sepsis. [15]

A laboratory test with more specificity is essential because despite the recent advances in medical practice, the diagnostic uncertainty and mortality rate in sepsis remains high.[16] The present study aimed to estimate and correlate the biomarkers Il-6 and TNF alpha with PCT in cases of sepsis. We conducted this study to evaluate the role of biomarkers in the diagnosis of sepsis.

MATERIALS AND METHODS

This cross-sectional study was conducted in the Departments of Microbiology and Biochemistry at Uttar Pradesh University of Medical Sciences (UPUMS), Saifai, Etawah. The study included clinically suspected sepsis patients admitted in the Emergency department and Intensive Care Unit of our hospital. Written informed consent was obtained from patient attendants, and the study was performed after approval by the Institutional Ethics Committee (the ethical clearance number 67/2022-23 and REF NO: 516/UPUMS/DSW/Ethical/2022-23).

Patients of Age ≥ 18 years and both the sexes with clinical suspicion of sepsis fulfilling the qSOFA criteria [7] and having temperature ≥38 º C or<36 ºC were enrolled in the study.

Patients with cardiogenic shock, burns, trauma, post-surgeries and malignancy were excluded from the study because in these cases PCT might be falsely elevated. [17]

Various patient data such as age, gender and other relevant clinical parameters were recorded from their medical records and bedside charts.

Blood culture and serum samples were collected and processed for aerobic culture and sensitivity and biomarkers on the day of admission. Serum was separated by centrifugation at 2500 rotation per minute for 20 minutes. PCT levels in serum were measured by the ARCHITECT B.R.A.H.M.S PCT assay (ARCHITECT B.R.A.H.M.S PCT 6P22), a chemiluminescent microparticle immunoassay (CMIA) for the quantitative determination of Procalcitonin in human serum. Serum IL-6 and TNF-α levels were measured using commercially available enzyme-linked immunosorbent assays (ELISA: ELK1156 and ELK1190, Denver, USA for IL-6 & TNF-α respectively).

Blood culture bottles were incubated in BACTEC automated blood culture system. Further phenotypic identification of micro-organism was based on the colony morphology and biochemical reactions.

Statistical analysis: The collected data was analysed using IBM SPSS Statistics for Windows, Version 29.0.(Armonk, NY: IBM Corp). To find the significance in qualitative categorical data Chi-Square test was used.

Figure 1: Culture showing colony morphology of *Staphylococcus aureus* on 5 % sheep Blood agar

Figure 2: Culture showing colony morphology of *Klebsiella pneumoniae* on MacConkey agar

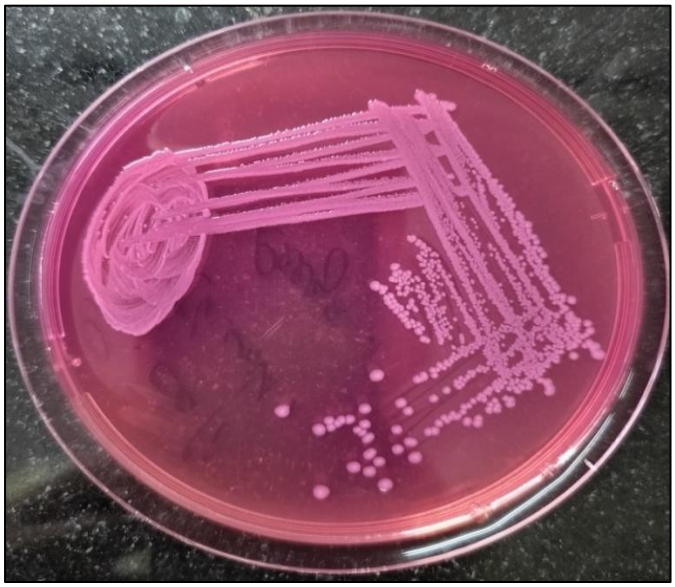

Figure 3: Culture showing colony morphology of *Escherichia coli* on MacConkey agar

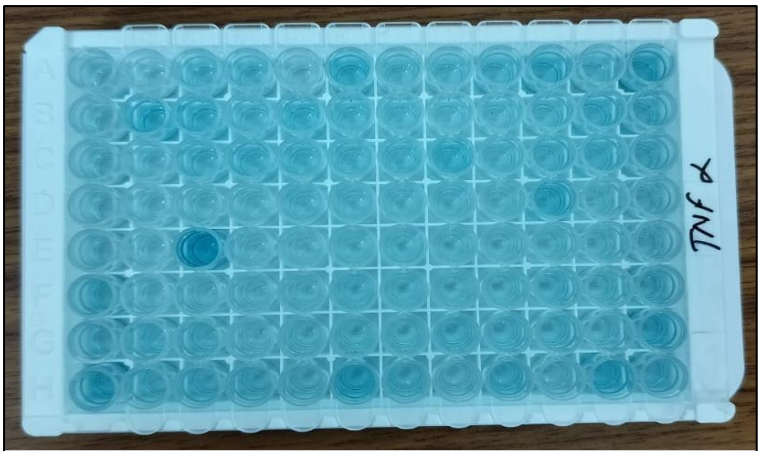

Figure 5: Quantitative detection of serum biomarker by ELISA

RESULTS

In the present study, blood samples were taken from 100 adults clinically suspected of having sepsis. Of the total 100 patients that met the inclusion criteria, 32 were identified as blood culture-positive and 68 were identified as blood culture-negative sepsis patients [Figure 6]. Most of the patients (25%) belonged to the 61-70 years age group followed by the 41-50 years (24%) age group [Table 1]. Males (63%) were more commonly seen than females (37%). [Table 2]

Out of 32 blood culture-positive patients, 15 cases (46.9%) isolated Gram-positive bacteria and 7 cases (21.8%) isolated Gram-negative bacteria, 3 cases of Fungal infection and rest were contaminants [Table. 3]. *Staphylococcus aureus* were predominantly isolated from sepsis patients while out of Gram-negative bacteria most predominant was *Escherichia coli* (3, 9.4%) followed by *Acinetobacter baumannii* (2, 6.2%), *Klebsiella pneumonia*e (1, 3.1%) and *Citrobacter koseri* (1, 3.1%) [Table 3].

Different laboratory parameters were also measured as listed on [Table 4]. PCT levels ranged from 0.01 to 100 (ng/ml) with a mean value of 8.8 ng/ml, and a standard deviation of 19.9 ng/ml. IL-6 levels ranged from 0.0 to 492.5 (pg/ml) with a mean value of 200.2 pg/ml and a standard deviation of 154.7 pg/ml. TNF α levels ranged from 0.0 to 718.0 (pg/ml) with a mean value of 148.2 pg/ml and a standard deviation of 213.5 pg/ml.

Patients with culture-positive sepsis (bacterial infection confirmed by blood culture) had significantly higher levels of all three inflammatory markers (PCT, IL-6, TNF-α) compared to patients with culture-negative sepsis ($p<0.001$) [Table 5]

Our study also found that higher levels of PCT were associated with higher levels of IL-6 and TNF-α in all cases of sepsis. There was a significant correlation (r = 0.529) of PCT with IL-6 (pg/ml) (p-value < 0.001) and (r = 0.639) TNF alpha (pg/ml) (p-value < 0.001) [Table 6].

Association of the discrimination capabilities of these biomarkers were measured as (AUC) area under the receiver operating characteristic (ROC) curve [Figure 7].

Procalcitonin (PCT) with a cut off value of 2.3 ng/ml, the AUC was 0.879. Its sensitivity and specificity were 81.3% and 79.4% respectively with a confidence interval ranging from 0.663 to 0.857, and a p-value less than 0.001, indicating significant results. For IL-6, with a cut off value of 203 pg/ml, the AUC was 0.760 with a sensitivity and specificity of 75.0% and 64.7% respectively. The confidence interval for this AUC ranged from 0.793 to 0.965. TNF α at a cut off value of 83.5pg/ml showed an AUC of 0.857. This biomarker had a sensitivity of 78.1% and a specificity of 77.9%, with its confidence interval ranging from 0.771 to 0.944 [Table 7].

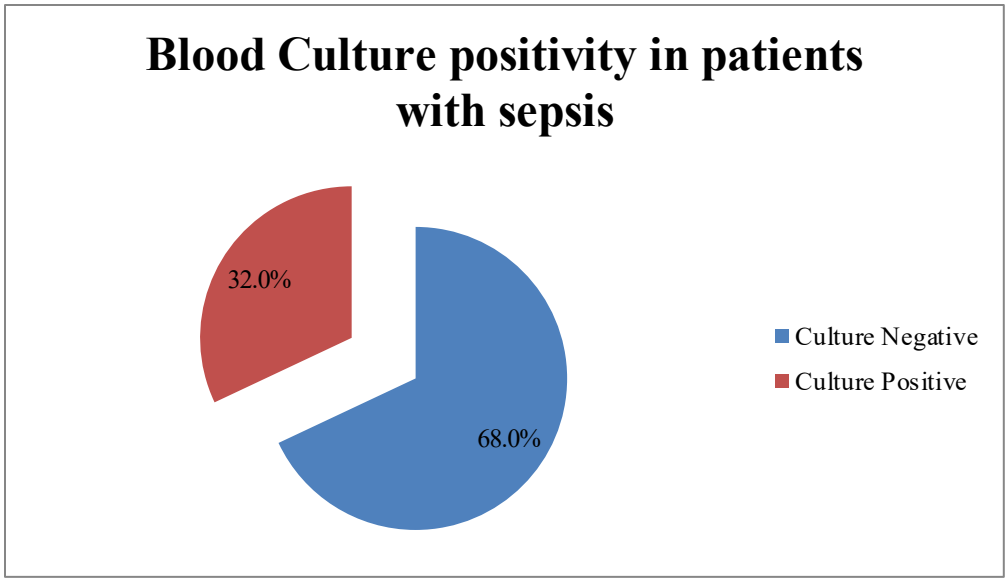

Figure 6: Pie chart showing distribution of patients with respect to blood culture

Table 1: Showing distribution of patients with respect to age (N=100)

Age (in years)	Frequency	Percentage
<= 20	5	5.0
21 - 30	13	13.0
31 - 40	4	4.0
41 - 50	24	24.0
51 - 60	21	21.0
61 - 70	25	25.0
>70	8	8.0
Mean±SD	51.5±16.4 years (Range: 18-85 years)	

Table 2: Showing distribution of patients with respect to Gender (N=100)

Gender	Frequency	Percentage
Male	63	63.0
Female	37	37.0

Table 3: Showing distribution of Organism involved in sepsis culture positive (N=32)

Organism	Frequency (N=32)	Percentage (%)
Staphylococcus aureus	15	46.9
Contaminant	6	18.8

Escherichia coli	3	9.4
Candida species	3	9.4
Acinetobacter baumanii	2	6.2
Citrobacter koseri	1	3.1
Klebsiella pneumoniae	1	3.1
Cryptococcus neoformans	1	3.1

Table 4: Showing mean value of inflammatory biomarkers in studied patients (N=100)

Parameters	Mean± Std. Deviation	Range (Min.- Max.)
PCT(ng/ml)	8.8±19.9	0.01-100
IL-6(pg/ml)	200.2±154.7	0.0-492.5
TNF α(pg/ml)	148.2±213.5	0.0-718.0

Table 5: Showing association of inflammatory biomarkers with bacterial isolation

Particulars	Culture positive sepsis (N=32)	Culture negative sepsis (N=68)	P value
PCT(ng/ml)	24.3±29.7	1.5±2.5	**<0.001**
IL-6 (pg/ml)	291.8±137.3	157.2±144.1	**<0.001**
TNF α (pg/ml)	360.6±259.1	48.3±68.1	**<0.001**

Table 6: Showing correlation of IL-6, TNF alpha with Procalcitonin biomarkers in studied patients (N=100)

		PCT(ng/ml)	IL-6(pg/ml)	TNF α(pg/ml)
PCT(ng/ml)	**Pearson Correlation**	1	0.529**	0.639**
	P value	0.000	0.000	0.000
	N	100	100	100
**. Correlation is significant at the 0.01 level (2-tailed).				

Table 7: Showing comparisons of Discrimination Capabilities of the Biomarkers Presented as Area Under Curve

Area Under the ROC Curve							
Test Result Variable(s)	Cut off value	Area	Sensitivity	Specificity	P value	Asymptotic 95% Confidence Interval	
						Lower Bound	Upper Bound
PCT(ng/ml)	2.3	0.879	81.3	79.4	**<0.001**	.793	.965
IL-6(pg/ml)	203	0.760	75.0	64.7	**<0.001**	.663	.857
TNF α(pg/ml)	83.5	0.857	78.1	77.9	**<0.001**	.771	.944
SOFA	6.5	0.821	84.4	50.0	**<0.001**	.724	.917
The test result variable(s): PCT (ng/ml), IL-6(pg/ml), TNF α(pg/ml), SOFA has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.							
a. Under the nonparametric assumption							
b. Null hypothesis: true area = 0.5							

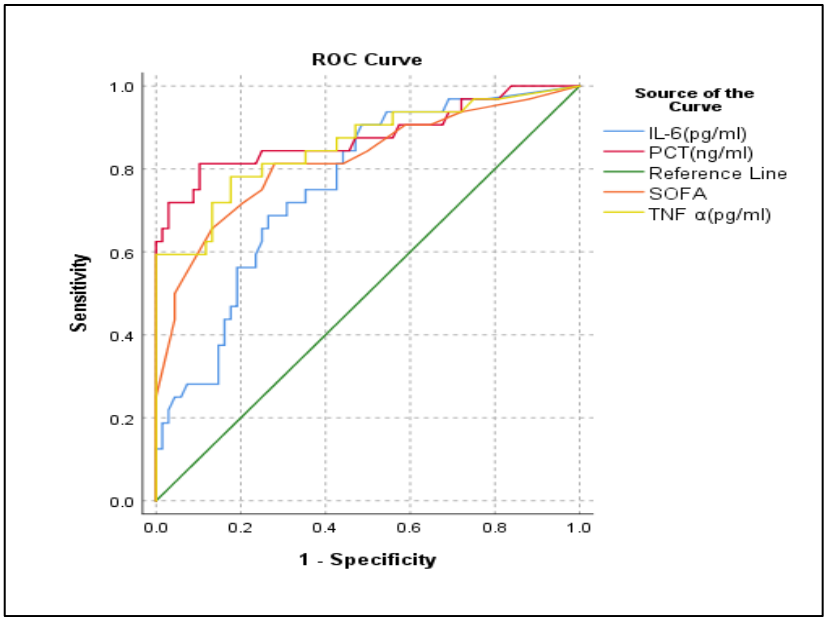

Figure 7: Showing discrimination capabilities of biomarkers, as the area under the receiver operating characteristic curve (AUC)

DISCUSSION

Sepsis, being a multifaceted systemic inflammatory response, continues to pose a major challenge in clinical practice due to its high morbidity, mortality, and diagnostic ambiguity. The present study aimed to evaluate and correlate the diagnostic potential of procalcitonin (PCT), interleukin-6 (IL-6), and tumour necrosis factor-alpha (TNF-α) in sepsis patients. The findings demonstrated that PCT is a robust biomarker with superior diagnostic performance, exhibiting higher sensitivity and specificity compared to IL-6 and TNF-α. The positive correlation observed between PCT and both IL-6 and TNF-α reinforces the hypothesis that simultaneous elevation of these inflammatory mediators reflects the intensity of systemic inflammation in sepsis.

Early initiation of antibiotics remains the mainstay in the management of septic patients.[2]An increased certainty in the diagnosis of sepsis will help initiate anti-microbial in critically ill patients.[18-20] Inflammatory markers may be helpful in early diagnosis, prompt treatment as well as prognosis in septic patients. [21]

In the present study, blood samples were taken from 100 adults clinically suspected of having sepsis, from the ICU and Emergency ward of our hospital. Of the 100 patients that met the inclusion criteria, 32 were identified as culture-positive and 68 were identified as culture-negative sepsis patients. Similar results were seen in several studies.[22],[23] Whereas other studies showed conflicting results.[24],[25] Out of 32 culture-positive patients, 15(46.9%) of total isolates were of Gram-positive bacteria and 7(21.8%) were of Gram-negative bacteria. *Staphylococcus aureus* was the most commonly found Gram-positive bacteria. Among Gram-negative bacteria, *Escherichia coli* (3, 9.4%) was the most common followed by *Acinetobacter baumannii* (2, 6.2%), *Klebsiella pneumonia*e (1, 3.1%) and *Citrobacter koseri* (1, 3.1%). A similar pattern of culture isolates has been observed in a study done by Sakshi Shah *et al.* [26] while in contrast to our findings a study conducted by Ruchi Agrawal *et al.* [27] found Gram-negative bacteria to be 68.35% of total isolates whereas Gram-positive bacteria were 31.65%.

In the current study, we evaluated PCT and its cut-off value was estimated to be 2.3ng/ml with sensitivity of 81.3% and specificity of 79.4% which is similar to the study done by Shefali Gupta *et al.* [28] Similar to our study, S Ahmed *et al.* [29] observed cut-off value of PCT to be 2.14ng/ml with sensitivity of 93.75% and specificity of 43.59%. PPV and NPV in this study was 80.95% and 73% respectively. Contrary to the current study, Hongmin Zhang *et al.* [30] observed a lower PCT value of 0.75 ng/ml and also lower sensitivity (70.8%) and specificity (61.5%).

Dimple Anand *et al.* [31] observed PCT cut off value, sensitivity, and specificity of 1.43ng/ml, 92 %, 83% respectively. They also measured IL-6 and cut-off value was found to be 423.5pg/ml with sensitivity of 63.9% and NPV 63.7% which was similar to our study.

In our study IL-6 was evaluated and the cut off value, sensitivity, and specificity were 203pg/ml, 75.0%, 64.7% respectively. This result is consistent with the study done by Baozhong Yu *et al.* [32] While J Song *et al.* [1] in their study, estimated IL-6 value in case of sepsis and septic shock patients. In their study, cut off value, sensitivity and specificity in sepsis patients were 52.60pg/ml, 80.4%, 88.9S% respectively while in case of septic shock the values were 348.92pg/ml, 91.8%, 63.2% respectively.

In this study we also evaluated TNF-α and observed cut-off value of 83.5 pg/ml with sensitivity of 78 % and specificity of 77.9%. Similar to this study, **A.** Gharamati *et al.* [15] observed TNF-α cut-off value, sensitivity and specificity to be 66.2pg/ml, 82.6%, 91.7% respectively. While Xuguang Li *et al.* [33] in their study observed TNF-α value of 20.71pg/ml. The results of this study suggest that PCT is more sensitive followed by IL-6 and TNF-α. PCT showed the best diagnostic performance with sensitivity 81.3% and specificity 79.4%. Dong Wook Jekarl *et al.* [34] concluded that PCT can support diagnosis of bacterial infection while IL-6 proved better biomarker for monitoring the effectiveness of antibiotic treatment.

Furthermore, this study was conducted also to evaluate the levels of biomarkers with bacterial isolation. All culture-positive sepsis cases (32%) had PCT cut off value of 2.3ng/ml, IL-6 203pg/ml, TNF α 83.5pg/ml. Even in culture-negative sepsis patients high PCT, IL-6 and TNF α levels were evident. However, PCT was a better predictor of sepsis in both culture-positive and culture-negative sepsis followed by IL-6 and TNF α. Similar results were observed in various studies. [35]

In the present study, PCT was found to be more sensitive and specific than IL-6 and TNF α in the detection of sepsis. Some studies reveal that serum PCT levels are elevated in patients with bacterial infections but are below the detection limit in healthy individuals and in patients with viral infections. This indicates that PCT level is useful and reliable for diagnosis of systemic bacterial infections. [36]

In the study, PCT at a cut-off value of 2.3 ng/ml showed an AUC of 0.879 with a sensitivity of 81.3% and specificity of 79.4%, aligning with prior findings that highlight PCT's reliability in early identification and prognosis of bacterial sepsis. IL-6 and TNF-α, though less specific than PCT, exhibited moderate sensitivity and specificity values and correlated positively with disease severity, underscoring their adjunctive role in sepsis diagnosis and monitoring. These observations are congruent with contemporary literature which has established PCT as a dynamic and reliable biomarker for systemic infections, particularly in distinguishing bacterial from non-bacterial causes of inflammation [36].

The study also revealed a substantial proportion of culture-negative sepsis cases with elevated biomarkers, suggesting that clinical reliance solely on blood cultures may lead to under-diagnosis or delayed intervention. The incorporation of PCT, IL-6, and TNF-α in diagnostic algorithms can mitigate this gap by allowing early and accurate identification, thereby facilitating timely antimicrobial therapy. Recent literature supports this integration of biomarkers into early warning scores or sepsis bundles to enhance clinical judgment and patient outcomes [37].

From a clinical perspective, PCT serves not only as a diagnostic biomarker but also as a valuable tool for antibiotic stewardship. Its rapid kinetics and ability to reflect bacterial burden make it an ideal candidate for guiding the initiation and discontinuation of antibiotic therapy, particularly in intensive care settings [38]. On the other hand, IL-6 and TNF-α, being upstream cytokines in the inflammatory cascade, can offer prognostic insights, especially in stratifying patients at risk of progression to septic shock. Together, this panel of biomarkers enhances the predictive accuracy and clinical utility of sepsis diagnostics.

Despite these promising findings, certain limitations warrant consideration. The study was cross-sectional in design and limited to a single tertiary care center. Serial monitoring of biomarker kinetics over the course of illness and correlation with clinical outcomes such as mortality, ICU stay, and antibiotic duration were not explored. Further, the exclusion of pediatric and immunocompromised populations limits the generalizability of these findings. Larger multicentric studies, ideally with prospective designs and follow-up analysis, are necessary to validate these biomarkers across diverse clinical settings [39,40].

To conclude, this study confirms that PCT is a highly sensitive and specific marker for sepsis, significantly correlating with IL-6 and TNF-α levels. While PCT alone shows strong diagnostic utility, combining it with IL-6 and TNF-α enhances diagnostic confidence and supports earlier therapeutic interventions. The integration of these biomarkers into standard sepsis protocols could potentially transform the early diagnosis and management of sepsis, especially in resource-constrained settings where time is a critical determinant of survival. Future research should focus on creating unified biomarker-based diagnostic and prognostic models tailored for use in Indian healthcare systems [41-43].

CONCLUSION

The principal findings of this study include the utility of biomarkers for the diagnosis of sepsis. In our study PCT, IL-6, TNF α were high in both culture-positive and culture-negative sepsis patients. However, PCT proved a better predictor of sepsis and its correlation to IL-6 and TNF α in all included subjects was well established.

From this study, we conclude that PCT is a reliable marker for diagnosis of sepsis. However, it cannot be recommended as the single definitive test for diagnosis rather it must be clinically correlated and combined with other biomarkers like IL-6 and TNF α which would prove to be a promising diagnostic tool for sepsis.

DECLARATIONS:

Conflicts of interest: There is no any conflict of interest associated with this study

Consent to participate: There is consent to participate.

Consent for publication: There is consent for the publication of this paper.

Authors' contributions: Author equally contributed the work.

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