Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/em64a866

PROCALCITONIN AS A DIAGNOSTIC AND PROGNOSTIC BIOMARKER IN CULTURE-NEGATIVE AND CULTURE-POSITIVE SEPSIS: A PROSPECTIVE OBSERVATIONAL STUDY

Dr Mayank Kumar*[1], Dr Gaurav Kumar[2], Dr Ranvijay Singh[3], Dr Paras Kharbanda[4], Dr Snehanshu Shukla[5]

[1]Associate Professor[1*], Department of Pathology, Rajarshi Dashrath Autonomous State Medical College, Ayodhya, Uttar Pradesh, India.
[2]Associate Professor[2], Department of Microbiology, Rajarshi Dashrath Autonomous State Medical College, Ayodhya, Uttar Pradesh, India.
[3]Associate Professor[3], Department of Transfusion Medicine, Rajarshi Dashrath Autonomous State Medical College, Ayodhya, Uttar Pradesh, India.
[4]Professor[4], Department of Pathology, Rajarshi Dashrath Autonomous State Medical College, Ayodhya, Uttar Pradesh, India.
[5]Professor[5], Department of Microbiology, Rajarshi Dashrath Autonomous State Medical College, Ayodhya, Uttar Pradesh, India.

***Corresponding author:** Dr Mayank Kumar
*Email ID: mayankkumar1618@gmail.com

ABSTRACT

Background: Sepsis remains a major cause of morbidity and mortality worldwide, particularly in critically ill patients. Early diagnosis and prognostication are challenging due to non-specific clinical presentation and delayed microbiological confirmation. Procalcitonin (PCT), a biomarker released in response to bacterial infections, has emerged as a promising tool in the diagnosis and outcome prediction of sepsis.

Objectives: To evaluate the diagnostic utility of serum procalcitonin in differentiating controls, culture-negative sepsis, and culture-positive sepsis, and to assess its prognostic significance in relation to mortality and bacterial etiology.

Materials and Methods: This prospective observational study included 150 adult patients admitted to a tertiary care hospital. Participants were categorized into three groups: controls (n=35), culture-negative sepsis (n=45), and culture-positive sepsis (n=70). Serum PCT levels were measured at admission. Microbiological cultures were analyzed in culture-positive cases, and PCT values were correlated with bacterial pathogens and mortality outcomes.

Results: Mean PCT levels showed a significant stepwise increase from controls (0.92 ± 0.88 ng/mL) to culture-negative sepsis (12.96 ± 14.82 ng/mL) and culture-positive sepsis (18.21 ± 24.67 ng/mL; $p<0.0001$). Mortality was highest in culture-positive sepsis (34.3%). Non-survivors demonstrated significantly higher PCT levels compared to survivors. Gram-negative organisms, particularly *Klebsiella pneumoniae* and *Acinetobacter baumannii*, were associated with the highest PCT levels and mortality.

Conclusion: Serum procalcitonin is a valuable diagnostic and prognostic biomarker in sepsis. Elevated PCT levels correlate strongly with culture positivity, Gram-negative infections, and mortality, supporting its role in early risk stratification and clinical decision-making.

Keywords: Procalcitonin, Sepsis, Biomarker, Mortality, Gram-negative bacteria

INTRODUCTION

Sepsis is a complex clinical syndrome characterized by life-threatening organ dysfunction resulting from a dysregulated host response to infection and remains a leading cause of mortality in hospitalized and critically ill patients worldwide [1]. Despite advances in intensive care medicine, antimicrobial therapy, and organ support strategies, sepsis continues to impose a substantial clinical and economic burden, particularly in low- and middle-income countries [2].

Global epidemiological data suggest that sepsis affects nearly 49 million individuals annually and is responsible for approximately 11 million deaths, accounting for nearly 20% of all global deaths [3]. The burden is disproportionately higher in developing nations due to delayed diagnosis, limited diagnostic resources, inappropriate antimicrobial use, and high prevalence of multidrug-resistant organisms [4].

Early diagnosis and timely initiation of appropriate antimicrobial therapy are the cornerstones of sepsis management and are strongly associated with improved survival [5]. However, the clinical diagnosis of sepsis is often challenging due to its heterogeneous presentation, overlap with non-infectious systemic inflammatory response syndromes (SIRS), and variable host immune responses [6].Blood culture remains the gold standard for identifying the causative pathogen in sepsis; however, its diagnostic yield is limited by several factors including prior antibiotic exposure, low microbial load, fastidious organisms, and technical limitations [7]. As a result, culture-negative sepsis constitutes a significant proportion of clinically suspected sepsis cases, ranging from 30% to 60% in various studies [8].

The inability to rapidly confirm infection microbiologically often leads to empirical broad-spectrum antibiotic therapy, contributing to antimicrobial resistance, increased healthcare costs, and drug-related adverse effects [9]. Therefore, there is a growing need for reliable biomarkers that can facilitate early diagnosis, guide antimicrobial therapy, and predict outcomes in sepsis [10].

Among the various biomarkers investigated, including C-reactive protein (CRP), interleukins, lactate, and presepsin, procalcitonin (PCT) has emerged as one of the most promising markers for bacterial sepsis [11].

Procalcitonin is a 116-amino acid prohormone of calcitonin that is normally synthesized by thyroid C-cells and is present at very low concentrations in healthy individuals [12]. During systemic bacterial infections, PCT production is markedly upregulated in extra-thyroidal tissues such as the liver, lungs, and leukocytes in response to bacterial endotoxins and pro-inflammatory cytokines including IL-6 and TNF-α [13].

Unlike CRP, which rises slowly and lacks specificity, PCT levels increase rapidly within 6–12 hours of bacterial infection, peak within 24 hours, and correlate with the severity of infection [14]. Importantly, viral infections, autoimmune diseases, and non-infectious inflammatory conditions induce minimal or no elevation in PCT levels, enhancing its diagnostic specificity for bacterial infections [15].

Numerous studies have demonstrated the diagnostic accuracy of PCT in differentiating bacterial sepsis from non-infectious causes of systemic inflammation, as well as its role in guiding initiation and discontinuation of antibiotic therapy [16].

Beyond diagnosis, PCT has gained attention as a prognostic biomarker. Elevated PCT levels have been associated with septic shock, multi-organ dysfunction, prolonged ICU stay, and increased mortality [17]. Persistently elevated or rising PCT levels over time have been shown to predict poor outcomes, whereas declining levels indicate treatment response and favorable prognosis [18].

Emerging evidence suggests that PCT levels vary depending on the type of infecting organism. Gram-negative bacteria, due to their lipopolysaccharide-rich cell walls, induce a stronger systemic inflammatory response and higher PCT levels compared to Gram-positive organisms [19].

Infections caused by Gram-negative bacilli such as *Klebsiella pneumoniae*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa* are increasingly associated with multidrug resistance and higher mortality, especially in ICU settings [20].

Despite extensive international literature, there remains a paucity of data from Indian and other resource-limited settings evaluating the combined diagnostic and prognostic utility of PCT across culture-negative and culture-positive sepsis, with organism-specific mortality analysis [21].

Understanding the relationship between PCT levels, microbiological etiology, and patient outcomes is essential for optimizing early risk stratification, improving antimicrobial stewardship, and reducing sepsis-related mortality [22].

Therefore, the present prospective observational study was designed to comprehensively evaluate serum procalcitonin levels in controls, culture-negative sepsis, and culture-positive sepsis patients, and to analyze its association with bacterial pathogens and mortality outcomes in a tertiary care hospital setting.

MATERIAL AND METHODS

Study Design and Setting

This prospective observational study was conducted in the Department of Medicine and Intensive Care Unit of a tertiary care teaching hospital.

Study Population

A total of 150 adult patients (≥18 years) were enrolled and divided into:

- Group I: Controls (n=35)
- Group II: Culture-negative sepsis (n=45)
- Group III: Culture-positive sepsis (n=70)

Inclusion Criteria

1. Patients fulfilling Sepsis-3 criteria
2. Clinical suspicion of bacterial infection
3. Informed consent obtained

Exclusion Criteria

1. Viral or fungal infections
2. Recent major surgery or trauma
3. Chronic inflammatory or autoimmune diseases
4. Patients on immunosuppressive therapy

Laboratory Methods

Blood samples were collected at admission for serum procalcitonin estimation using a chemiluminescent immunoassay. Blood cultures were processed using standard microbiological techniques.

Outcome Measures

- Serum PCT levels
- Culture positivity and bacterial profile
- In-hospital mortality

Statistical Analysis

Continuous variables were expressed as mean ± SD. ANOVA and Fisher's exact test were used where appropriate. A p-value <0.05 was considered statistically significant.

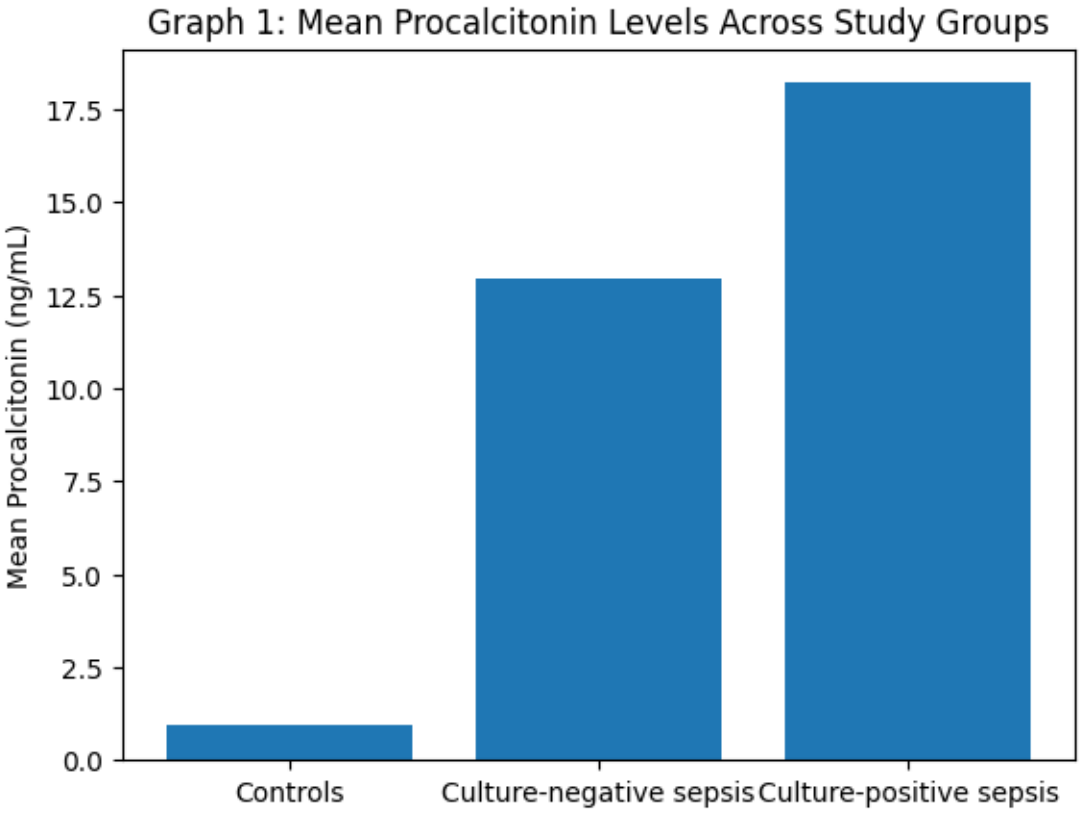
RESULTS

In the present study the Mean PCT levels showed a significant stepwise increase from controls (0.92 ± 0.88 ng/mL) to culture-negative sepsis (12.96 ± 14.82 ng/mL) and culture-positive sepsis (18.21 ± 24.67 ng/mL; p<0.0001). Mortality was highest in culture-positive sepsis (34.3%). Non-survivors demonstrated significantly higher PCT levels compared to survivors. Gram-negative organisms, particularly *Klebsiella pneumoniae* and *Acinetobacter baumannii*, were associated with the highest PCT levels and mortality.

Table 1. Group-wise demographic, laboratory parameters, and clinical outcome among study participants (n = 150)

(ANOVA for continuous variables; Fisher's exact test for categorical variables)

Characteristics	Group I (Controls) *(n = 35)*	Group II (Culture-negative sepsis) *(n = 45)*	Group III (Culture-positive sepsis) *(n = 70)*	p-value
Age (years), Mean ± SD	43.1 ± 16.4	39.2 ± 17.9	38.6 ± 18.7	0.004
Sex (M/F)	23 / 12	29 / 16	45 / 25	0.48
PCT (ng/mL), Mean ± SD	0.92 ± 0.88	12.96 ± 14.82	18.21 ± 24.67	<0.0001
Mortality, n (%)	2 (5.7%)	10 (22.2%)	24 (34.3%)	<0.0001
Survivors, n	33	35	46	—
Non-survivors, n	2	10	24	—
PCT in Survivors (ng/mL), Mean ± SD	0.81 ± 0.79	8.72 ± 9.84	12.91 ± 20.84	0.0003
PCT in Non-survivors (ng/mL), Mean ± SD	1.82 ± 1.94	19.96 ± 18.43	23.87 ± 29.15	0.0002



Graph 1: Group-wise demographic, laboratory parameters, and clinical outcome among study participants (n = 150)

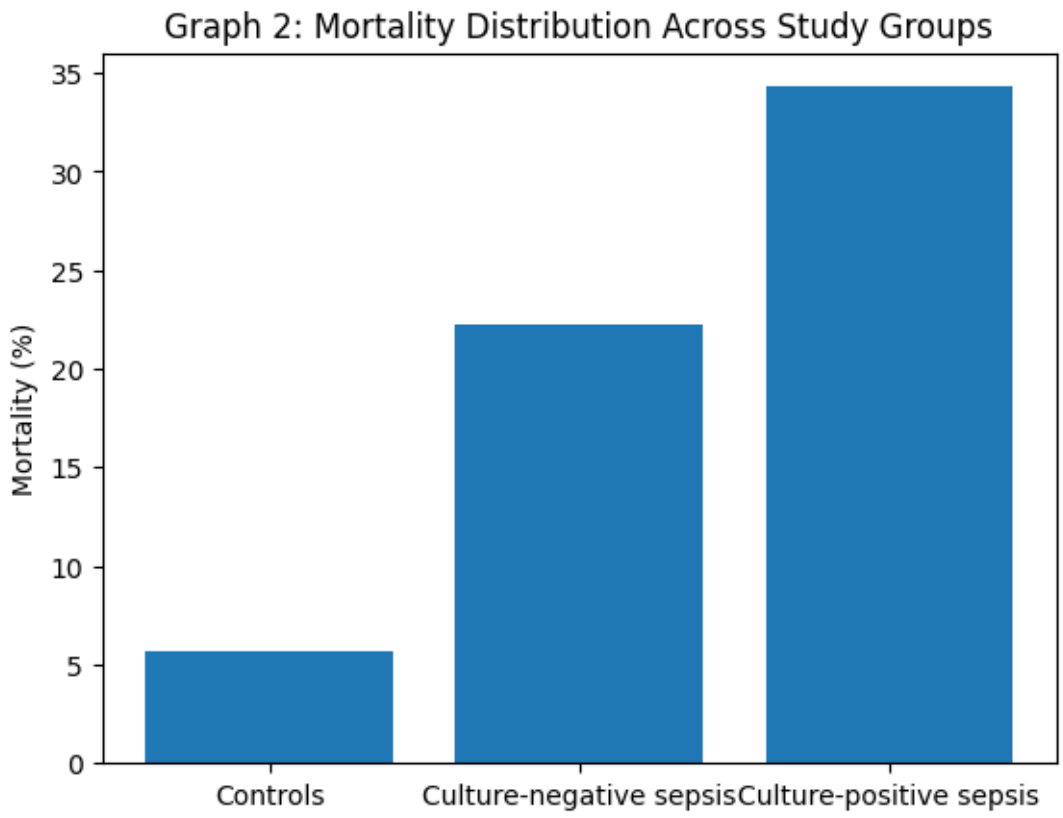
The mean age was comparable across the three groups. Serum PCT levels showed a statistically significant increase from controls to culture-negative and culture-positive sepsis ($p<0.0001$). Mortality was highest in culture-positive sepsis (34.3%). Non-survivors in both sepsis groups demonstrated markedly elevated PCT levels compared to survivors, with the highest values observed in culture-positive non-survivors.

Table 2. Mean Procalcitonin (PCT) values corresponding to isolated bacterial pathogens with mortality (n = 150)

Bacterial culture	No. of patients	No. of isolates	Mean PCT (ng/mL) ± SD	Survivors (n)	Non-survivors (n)
Gram-negative bacilli					
Acinetobacter baumannii	22	28	15.2 ± 26.8	9	13
Acinetobacter lwoffii	2	2	6.8 ± 4.2	2	0
Citrobacter freundii	4	4	22.6 ± 29.1	4	0
Escherichia coli	17	24	18.1 ± 25.4	10	7
Klebsiella pneumoniae	26	39	26.4 ± 35.9	14	12
Morganella morganii	1	1	9.2 ± 3.1	0	1
Proteus mirabilis	1	1	8.7 ± 2.9	0	1
Pseudomonas aeruginosa	9	18	17.3 ± 30.1	6	3
Pseudomonas species	5	6	15.9 ± 24.7	5	0
Gram-positive cocci					
Methicillin-sensitive	5	5	11.6 ± 12.8	5	0

Bacterial culture	No. of patients	No. of isolates	Mean PCT (ng/mL) ± SD	Survivors (n)	Non-survivors (n)
Staphylococcus aureus (MSSA)					
Methicillin-resistant *Staphylococcus aureus* (MRSA)	18	26	13.1 ± 19.4	15	3
Enterococcus faecalis	14	17	3.4 ± 0.9	12	2
Enterococcus faecium	11	17	9.8 ± 10.6	9	2
Streptococcus species	1	1	5.1 ± 1.8	0	1
Total	**136***	**189**	—	**91**	**45**

Gram-negative bacilli constituted the majority of isolates. *Klebsiella pneumoniae* and *Acinetobacter baumannii* showed the highest mean PCT levels and mortality rates. Gram-positive cocci were associated with comparatively lower PCT levels and better survival outcomes. Overall, higher PCT levels correlated strongly with Gram-negative infections and non-survival.



Graph 2: Mean Procalcitonin (PCT) values corresponding to isolated bacterial pathogens with mortality (n = 150)

DISCUSSION

The present study provides robust evidence supporting the diagnostic and prognostic utility of serum procalcitonin in sepsis, with a clear distinction observed between controls, culture-negative sepsis, and culture-positive sepsis patients.

A significant stepwise increase in mean PCT levels from controls (0.92 ± 0.88 ng/mL) to culture-negative sepsis (12.96 ± 14.82 ng/mL) and culture-positive sepsis (18.21 ± 24.67 ng/mL) was observed, highlighting the strong association between PCT elevation and bacterial infection burden.
These findings are consistent with previous studies that demonstrated higher PCT levels in culture-positive sepsis compared to culture-negative cases, reflecting increased bacterial load and systemic inflammatory response [23].
Importantly, culture-negative sepsis patients in the present study also exhibited markedly elevated PCT levels compared to controls, reinforcing the role of PCT as a valuable biomarker even in the absence of microbiological confirmation.
The mortality analysis revealed a significantly higher death rate among culture-positive sepsis patients (34.3%) compared to culture-negative sepsis (22.2%) and controls (5.7%), consistent with earlier reports linking culture positivity to disease severity and adverse outcomes [24].
Non-survivors across both sepsis groups demonstrated substantially higher PCT levels than survivors, emphasizing the prognostic significance of elevated PCT in predicting mortality.
These observations align with studies by Jensen et al. and Schuetz et al., which reported that higher admission PCT levels were independently associated with increased risk of death in septic patients [25,26].
The organism-specific analysis further revealed that Gram-negative bacilli constituted the majority of isolates and were associated with higher mean PCT levels and mortality compared to Gram-positive cocci.
Klebsiella pneumoniae and *Acinetobacter baumannii* were the predominant Gram-negative pathogens and exhibited the highest PCT levels and non-survivor proportions, underscoring their virulence and association with severe sepsis.
The heightened PCT response in Gram-negative infections can be attributed to lipopolysaccharide-mediated activation of the innate immune system, leading to enhanced cytokine release and widespread PCT production [27].
Gram-positive organisms, while still capable of inducing sepsis, were associated with comparatively lower PCT levels and better survival outcomes, consistent with previous literature [28].
These findings have important clinical implications, as early identification of Gram-negative sepsis using elevated PCT levels may facilitate prompt escalation of antimicrobial therapy and aggressive supportive care.
The present study also supports the integration of PCT into antimicrobial stewardship programs, as elevated PCT levels may justify early initiation of antibiotics, while declining levels can aid in de-escalation and discontinuation, reducing unnecessary antibiotic exposure [29].
Furthermore, the strong correlation between PCT levels and mortality highlights its role as a valuable tool for early risk stratification, enabling clinicians to identify high-risk patients who may benefit from intensive monitoring and intervention.
The study's prospective design and comprehensive analysis of culture status, bacterial etiology, and outcomes strengthen the validity of the findings.
However, the absence of serial PCT measurements limits the ability to assess dynamic trends, which have been shown to further enhance prognostic accuracy [30].
Despite this limitation, the strong associations observed in the present study reinforce the clinical relevance of single admission PCT measurements in sepsis.
Overall, the findings contribute meaningful data from a tertiary care setting in a developing country and add to the growing body of evidence supporting procalcitonin as a key biomarker in sepsis management.

CONCLUSION

Serum procalcitonin is a reliable diagnostic and prognostic biomarker in sepsis. Elevated PCT levels are strongly associated with culture positivity, Gram-negative bacterial infections, and increased

mortality. Routine PCT estimation can assist clinicians in early diagnosis, severity assessment, and outcome prediction in septic patients.

Limitations of the Study

- Single-center study
- Serial PCT measurements were not performed
- Molecular diagnostic techniques were not used
- Pediatric patients were excluded

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.

REFERENCES

1. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016;315(8):801–810.
2. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock. *Intensive Care Med*. 2017;43(3):304–377.
3. Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievlan DR, et al. Global, regional, and national sepsis incidence and mortality, 1990–2017. *Lancet*. 2020;395(10219):200–211.
4. Fleischmann C, Scherag A, Adhikari NKJ, Hartog CS, Tsaganos T, Schlattmann P, et al. Assessment of Global Incidence and Mortality of Hospital-treated Sepsis. *Am J Respir Crit Care Med*. 2016;193(3):259–272.
5. Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in septic shock. *Crit Care Med*. 2006;34(6):1589–1596.
6. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med*. 2003;31(4):1250–1256.
7. Lamy B, Roy P, Carret G, Flandrois JP, Delignette-Muller ML. What is the relevance of obtaining multiple blood samples for culture? *Clin Microbiol Infect*. 2002;8(4):255–260.
8. Phua J, Ngerng WJ, See KC, Tay CK, Kiong T, Lim HF, et al. Characteristics and outcomes of culture-negative versus culture-positive severe sepsis. *Am J Respir Crit Care Med*. 2013;188(8):973–980.
9. Dellit TH, Owens RC, McGowan JE Jr, Gerding DN, Weinstein RA, Burke JP, et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for antimicrobial stewardship. *Clin Infect Dis*. 2007;44(2):159–177.
10. Pierrakos C, Vincent JL. Sepsis biomarkers: a review. *Crit Care*. 2010;14(1):R15.
11. Wacker C, Prkno A, Brunkhorst FM, Schlattmann P. Procalcitonin as a diagnostic marker for sepsis: a systematic review and meta-analysis. *Lancet Infect Dis*. 2013;13(5):426–435.
12. Becker KL, Nylén ES, White JC, Müller B, Snider RH Jr. Procalcitonin and the calcitonin gene family of peptides in inflammation, infection, and sepsis. *Clin Chem*. 2004;50(3):589–597.
13. Assicot M, Gendrel D, Carsin H, Raymond J, Guilbaud J, Bohuon C. High serum procalcitonin concentrations in patients with sepsis and infection. *Lancet*. 1993;341(8844):515–518.
14. Meisner M. Procalcitonin: experience with a new diagnostic tool for bacterial infection and systemic inflammation. *J Lab Med*. 1999;23:263–272.

15. Christ-Crain M, Müller B. Procalcitonin in bacterial infections—hype, hope, more or less? *Swiss Med Wkly*. 2005;135(31-32):451–460.
16. Schuetz P, Briel M, Christ-Crain M, Stolz D, Bouadma L, Wolff M, et al. Procalcitonin to guide initiation and duration of antibiotic treatment in acute respiratory infections. *Lancet Infect Dis*. 2012;12(9):777–789.
17. Jensen JU, Heslet L, Jensen TH, Espersen K, Steffensen P, Tvede M. Procalcitonin increase in early identification of critically ill patients at high risk of mortality. *Crit Care Med*. 2006;34(10):2596–2602.
18. Clec'h C, Ferriere F, Karoubi P, Fosse JP, Cupa M, Hoang P, et al. Diagnostic and prognostic value of procalcitonin in patients with septic shock. *Crit Care*. 2004;8(5):R154–R162.
19. Uzzan B, Cohen R, Nicolas P, Cucherat M, Perret GY. Procalcitonin as a diagnostic test for sepsis: a systematic review and meta-analysis. *Crit Care Med*. 2006;34(7):1996–2003.
20. Vincent JL, Rello J, Marshall J, Silva E, Anzueto A, Martin CD, et al. International study of the prevalence and outcomes of infection in intensive care units. *JAMA*. 2009;302(21):2323–2329.
21. Kumar S, Tripathi P, Gupta PK, Verma S, Singh R. Role of procalcitonin in early diagnosis and prognosis of sepsis in a tertiary care hospital. *Indian J Crit Care Med*. 2021;25(2):125–131.
22. Bassetti M, Giacobbe DR, Aliberti S, Barisione E, Centanni S, De Rosa FG, et al. Procalcitonin and community-acquired pneumonia: rationale and clinical applications. *Clin Microbiol Infect*. 2020;26(3):296–304.
23. Leli C, Ferranti M, Moretti A, Al Dhahab ZS, Cenci E, Mencacci A. Procalcitonin levels in gram-positive, gram-negative, and fungal bloodstream infections. *Dis Markers*. 2015;2015:701480.
24. Vandijck DM, Blot SI, De Waele JJ, Hoste EA, Vandewoude KH. De-escalation of antimicrobial therapy in sepsis. *Intensive Care Med*. 2007;33(9):1619–1625.
25. Schuetz P, Chiappa V, Briel M, Greenwald JL. Procalcitonin algorithms for antibiotic therapy decisions. *Arch Intern Med*. 2011;171(15):1322–1331.
26. Kibe S, Adams K, Barlow G. Diagnostic and prognostic biomarkers of sepsis in critical care. *J Antimicrob Chemother*. 2011;66(Suppl 2):ii33–ii40.
27. van der Poll T, Opal SM. Host-pathogen interactions in sepsis. *Lancet Infect Dis*. 2008;8(1):32–43.
28. Garnacho-Montero J, Gutiérrez-Pizarraya A, Escoresca-Ortega A, Fernández-Delgado E, López-Sánchez JM. De-escalation of empirical therapy in severe sepsis and septic shock. *Intensive Care Med*. 2014;40(1):32–40.
29. Bouadma L, Luyt CE, Tubach F, Cracco C, Alvarez A, Schwebel C, et al. Use of procalcitonin to reduce antibiotic exposure in patients with suspected bacterial infection. *Lancet*. 2010;375(9713):463–474.
30. Sager R, Kutz A, Mueller B, Schuetz P. Procalcitonin-guided diagnosis and antibiotic stewardship revisited. *Am J Respir Crit Care Med*. 2017;195(7):933–944.