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Original Research Article

The Role of Adjunct Biomarkers in Culture-Negative Sepsis Management

Amitav Mohanty

Senior Consultant, Department of Medicine, Apollo Hospital, Bhubaneswar, Odisha, India

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Corresponding Author: Amitav Mohanty

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Abstract:

Background: Culture-negative sepsis represents a significant diagnostic and therapeutic challenge, accounting for nearly 30–60% of sepsis cases. In such situations, adjunct biomarkers such as procalcitonin (PCT) and Sequential Organ Failure Assessment (SOFA) score play a crucial role in early diagnosis, monitoring, and prognostication.

Aim: To evaluate the role of adjunct biomarkers in the management of culture-negative sepsis and compare clinical outcomes with culture-positive cases.

Methods: A prospective observational study was conducted among 200 adult sepsis patients. Biomarkers including serum procalcitonin and SOFA score were assessed on Day 1, Day 4, and Day 7. Statistical analysis was performed using chi-square test and p-value <0.05 was considered significant.

Results: Among 200 patients, 17.5% were culture-positive and 82.5% culture-negative. Elevated procalcitonin levels were noted in both groups without statistical significance (Day 1 p=0.563; Day 4 p=0.138). However, SOFA scores were significantly higher in culture-positive patients (Day 1 p=0.007; Day 4 & Day 7 p<0.001). Mortality was higher in culture-negative patients (48.5%), though not statistically significant (p=0.139).

Conclusion: Adjunct biomarkers such as procalcitonin and SOFA score play a critical role in diagnosing and monitoring culture-negative sepsis, aiding early therapeutic decisions and improving clinical outcomes.

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Introduction

Sepsis is a critical clinical condition characterized by an abnormal and exaggerated host response to infection, ultimately leading to organ dysfunction and increased risk of death [1]. Despite substantial progress in intensive care and antimicrobial therapy, sepsis remains a major global health concern, contributing to millions of deaths annually. Current estimates suggest that nearly 11 million deaths worldwide are attributable to sepsis each year [2]. The impact is disproportionately higher in low- and middle-income countries, including India, where limitations in healthcare infrastructure and delayed access to care further worsen outcomes [3,4].

Although blood culture continues to be regarded as the definitive method for identifying causative pathogens in sepsis, a considerable proportion of patients do not yield a positive culture. Reports indicate that approximately 30–60% of clinically suspected sepsis cases fall into the category of culture-negative sepsis [5,6]. The absence of microbiological confirmation complicates clinical decision-making, particularly with regard to targeted antimicrobial therapy and prognostic evaluation.

Multiple factors may contribute to negative culture results in patients with sepsis. Prior exposure to antibiotics before sample collection is one of the most common reasons. In addition, low levels of circulating microorganisms, infections caused by fastidious or atypical pathogens, and inherent limitations of conventional microbiological techniques may all reduce culture yield [7–9]. As a result, dependence solely on culture-based diagnosis can lead to delays in initiating appropriate treatment, thereby adversely affecting patient outcomes.

In this context, adjunctive biomarkers have gained importance as supportive tools in the early identification and management of sepsis. Procalcitonin (PCT), a precursor peptide of calcitonin, has been widely studied and is known to increase significantly in bacterial infections, correlating with both disease severity and systemic inflammatory response [10,11]. Similarly, the Sequential Organ Failure Assessment (SOFA) score provides an objective method to quantify organ dysfunction and has been extensively used to predict disease severity and mortality risk in septic patients [12].

Emerging evidence suggests that integrating biomarker evaluation with clinical scoring systems enhances diagnostic accuracy and facilitates better risk stratification, particularly in patients with culture-negative sepsis [13–15]. Furthermore, biomarkers such as procalcitonin may assist clinicians in guiding antibiotic therapy, including decisions related to initiation, escalation, and de-escalation, thereby promoting rational antimicrobial use and helping to curb the development of resistance [16,17].

Despite the growing body of international literature, there remains a relative paucity of data from the Indian setting regarding the utility of adjunct biomarkers specifically in culture-negative sepsis. Considering the high disease burden and resource limitations, identifying reliable and practical tools for early diagnosis and management is essential [18–20].

In light of these considerations, the present study was undertaken to assess the clinical utility of adjunct biomarkers, particularly serum procalcitonin levels and SOFA score, in patients with culture-negative sepsis, and to compare their role in prognostication and outcomes with those observed in culture-positive cases.

Materials and Methods

Study Design and Setting: This investigation was designed as a prospective observational study conducted in the Department of General Medicine of a tertiary care teaching hospital over a duration of one year.

Study Population: A total of 200 adult patients diagnosed with sepsis were enrolled during the study period. Participants were included consecutively after applying predefined eligibility criteria to minimize selection bias.

Inclusion Criteria

Patients were eligible for inclusion if they met the following criteria:

- Age 18 years or older
- Fulfillment of Sepsis-3 criteria, defined as suspected or confirmed infection with an increase in SOFA score of ≥2 points
- Admission to medical wards or intensive care units
- Provision of informed consent either by the patient or a legally authorized representative

Exclusion Criteria

Patients were excluded under the following conditions:

- Incomplete clinical or laboratory records
- Death or discharge within 24 hours of hospital admission
- Presence of chronic inflammatory or autoimmune disorders that could alter biomarker levels
- Participation in any concurrent interventional clinical study

Operational Definitions

For the purpose of analysis, the following definitions were applied:

- **Culture-positive sepsis:** Identification of a pathogenic organism in blood culture
- **Culture-negative sepsis:** Clinical features suggestive of sepsis in the absence of a positive blood culture
- **Elevated procalcitonin:** Serum procalcitonin concentration exceeding 0.5 ng/mL
- **Organ dysfunction:** Assessed using the SOFA scoring system

Severity Assessment: Disease severity and organ dysfunction were evaluated using the SOFA score, calculated at three time intervals: Day 1, Day 4, and Day 7. This allowed assessment of disease progression and response to treatment.

Microbiological Procedures: Blood samples were processed using standard microbiological methods. Identification of isolated organisms and antimicrobial susceptibility testing were carried out according to established laboratory protocols of the institution.

Treatment Strategy: All patients received empirical antimicrobial therapy at the time of admission, guided by clinical judgment and institutional antibiotic guidelines. Commonly used regimens included beta-lactam/beta-lactamase inhibitor combinations, carbapenems, glycopeptides, aminoglycosides, and fluoroquinolones. Subsequent modifications to antibiotic therapy were made based on culture reports, clinical response, and biomarker trends.

Outcome Measures: The primary outcome assessed was in-hospital mortality. Secondary outcomes included duration of mechanical ventilation, need and duration of vasopressor support, requirement for organ support, changes in SOFA score over time, trends in procalcitonin levels, and adjustments in antibiotic therapy.

For further analysis, patient outcomes were categorized into three groups:

- Sepsis-related mortality in the absence of underlying disease
- Sepsis-related mortality in the presence of underlying disease
- Mortality primarily attributable to pre-existing disease

Statistical Analysis: Collected data were entered into Microsoft Excel and analyzed using Statistical Package for the Social Sciences (SPSS) version 25.0. Continuous variables were summarized as mean ± standard deviation, while categorical variables were expressed as frequencies and percentages.

Comparisons between groups were performed using the chi-square test for categorical variables and the independent t-test for continuous variables where appropriate. A p-value of less than 0.05 was considered indicative of statistical significance.

Results

1. **Burden of Culture-Positive and Culture-Negative Sepsis**

Out of a total of 200 patients diagnosed with sepsis, 35 patients (17.5%) had positive blood cultures, whereas the majority, 165 patients (82.5%), were culture-negative.

This distribution is illustrated in **Figure 1**, which demonstrates the predominance of culture-negative sepsis in the study population.

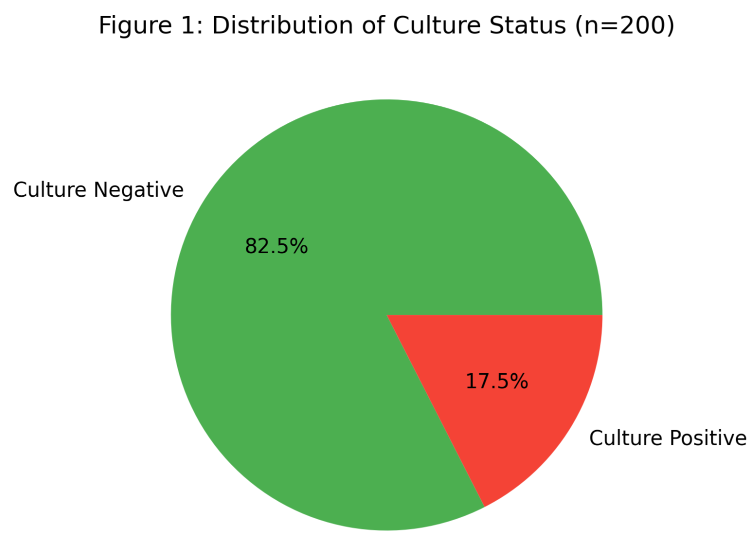

Figure 1: Distribution of culture-positive and culture-negative sepsis among study participants (n = 200).

2. **Microbiological Profile**

Among the 35 culture-positive cases, *Escherichia coli* was the most frequently isolated organism (51.4%). Other pathogens included *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Enterococcus faecium*, *Salmonella species*, and rare organisms such as *Burkholderia pseudomallei*.

The distribution of organisms is presented in **Figure 2**.

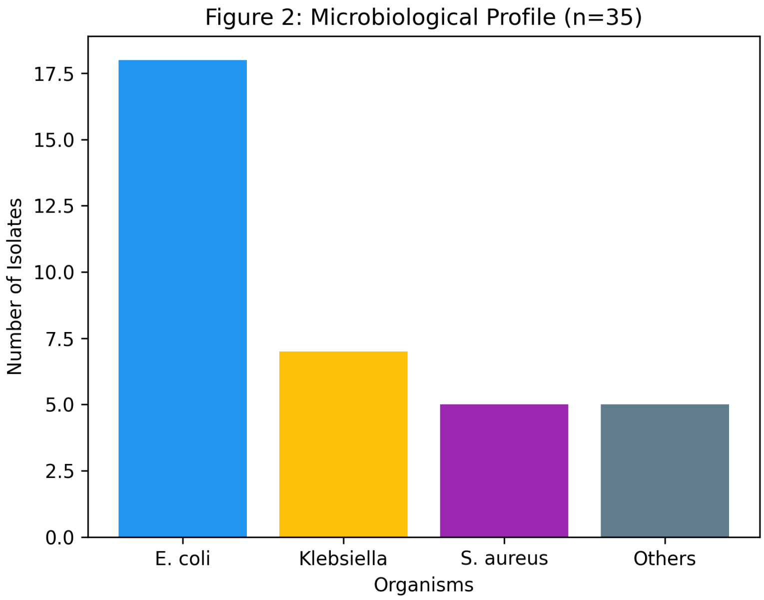

Figure 2: Microbiological profile of organisms isolated in culture-positive sepsis cases (n = 35).

3. **Age Distribution**

The majority of patients in both groups belonged to the 30–59 years age group. There was no statistically significant difference in age distribution between culture-positive and culture-negative groups (χ^2 = 3.400, df = 3, p = 0.334).

Table 1: Age distribution of participants (n=200)

Age Group	Culture-Negative (n=165)	Culture-Positive (n=35)
18–29	28	7
30–59	80	20
60–69	27	6
≥70	30	2

4. **Gender Distribution**

A higher proportion of males was observed in the culture-positive group (60%), whereas females predominated in the culture-negative group (53.3%). However, this difference was not statistically significant (χ^2 = 2.054, df = 1, p = 0.193).

Table 2: Gender distribution (n=200)

Gender	Culture-Negative	Culture-Positive
Male	77	21
Female	88	14

5. **Co-morbidities**

A significantly higher proportion of patients in the culture-positive group (80.0%) had underlying co-morbidities compared to the culture-negative group (24.8%). This association was statistically significant (χ^2 = 38.867, df = 1, p < 0.001).

Table 3: Presence of co-morbidities (n=200)

Co-morbidity	Culture-Negative	Culture-Positive
Present	41	28
Absent	124	7

6. **Diagnosis at Admission**

Pneumonia was the most common diagnosis at admission in both groups, followed by pyelonephritis and skin and soft tissue infections. A statistically significant difference was observed between the two groups (p < 0.001).

7. **Empirical Antibiotic Therapy**

Various empirical antibiotic regimens were initiated on Day 1. The most commonly used regimens included beta-lactam combinations and carbapenem-based therapies. There was no statistically significant difference in antibiotic selection between the groups ($\chi^2 = 3.082$, df = 6, p = 0.798).

Table 4: Empirical antibiotics initiated (n=200)

Antibiotic Regimen	Negative	Positive
Carbapenem + Glycopeptide	23	6
Beta-lactam + BLI	28	5
Beta-lactam + BLI + Doxycycline	30	5
Beta-lactam + Aminoglycoside	24	6
Beta-lactam + Fluoroquinolone	19	3
Aminoglycoside	26	4
Fluoroquinolone	15	6

8. **Change in Antibiotic Therapy**

Following culture and sensitivity reports, antibiotics were modified in 61.2% of culture-negative patients and 74.3% of culture-positive patients. However, this difference was not statistically significant (p = 0.177).

9. **Mechanical Ventilation**

The mean duration of mechanical ventilation was comparable between the groups (culture-negative: 5.7 ± 3.8 days; culture-positive: 5.8 ± 3.9 days), with no statistically significant difference ($\chi^2 = 1.250$, df = 2, p = 0.535).

Table 5: Duration of mechanical ventilation (n=200)

Duration	Negative	Positive
1–3 days	60	10
4–6 days	51	14
≥7 days	54	11

10. **Vasopressor Requirement**

Patients in both groups required vasopressor support with no statistically significant difference (p = 0.291).

11. **Site of Infection**

Pneumonia was the most common site of infection in both groups. Other sites included urinary tract infections, intra-abdominal infections, and bloodstream infections.

12. **Procalcitonin Levels**

On Day 1, elevated procalcitonin (>0.5 ng/mL) was observed in 65.5% of culture-negative and 60.0% of culture-positive patients. By Day 4, these values declined in both groups.

No statistically significant difference was found (Day 1: p = 0.563; Day 4: p = 0.138).

Table 6: Procalcitonin levels (n=200)

Parameter	Negative	Positive	p-value
Day 1 High	108	21	0.563
Day 4 High	90	14	0.138

Graphical representation is shown in **Figure 3**.

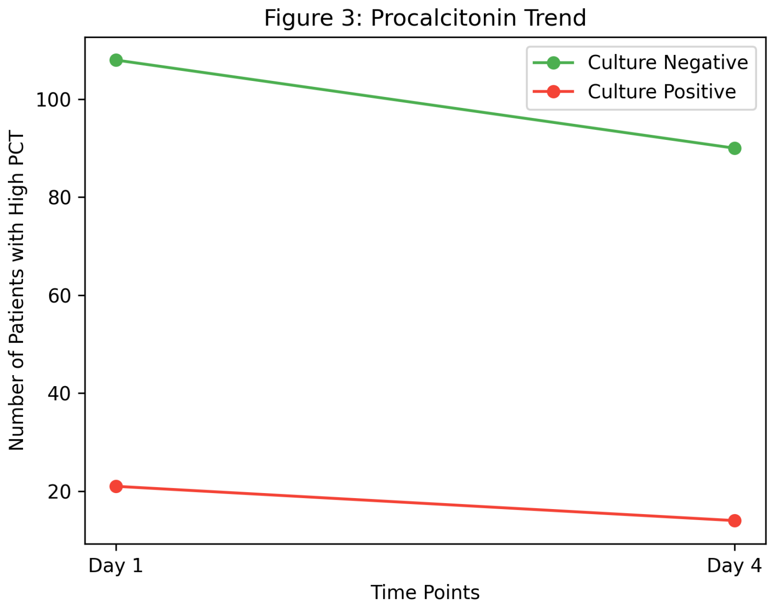

Figure 3: Trend of elevated procalcitonin levels in culture-negative and culture-positive sepsis patients on Day 1 and Day 4.

13. **SOFA Score**

A significantly higher proportion of culture-positive patients had elevated SOFA scores across all time points.

- Day 1: $p = 0.007$
- Day 4: $p < 0.001$
- Day 7: $p < 0.001$

Table 7: SOFA score comparison (n=200)

SOFA Score	Culture-Negative (n=165)	Culture-Positive (n=35)	p-value
Day 1			**0.007**
≤5	95	12	
>5	70	23	
Day 4			**<0.001**
≤5	110	10	
>5	55	25	
Day 7			**<0.001**
≤5	125	8	
>5	40	27	

This trend is illustrated in **Figure 4**.

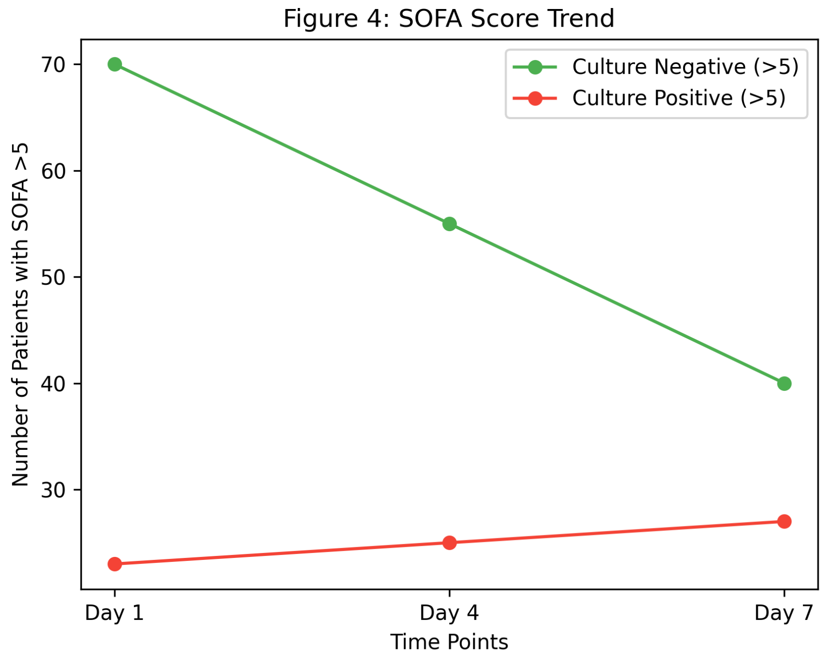

Figure 4: Comparison of SOFA score progression in culture-negative and culture-positive sepsis patients.

14. **Organ Support**

No statistically significant difference was observed in organ support requirement between groups (Day 1: p = 0.712; Day 4: p = 0.442).

Table 8: Organ support requirement (n=200)

Organ Support	Culture-Negative (n=165)	Culture-Positive (n=35)	p-value
Day 1			**0.712**
Required	102	23	
Not Required	63	12	
Day 4			**0.442**
Required	88	21	
Not Required	77	14	

15. **Mortality and Outcome**

Overall mortality was higher in culture-negative patients (48.5%) compared to culture-positive patients (34.3%), though this difference was not statistically significant (p = 0.139).

This is shown in **Figure 5**.

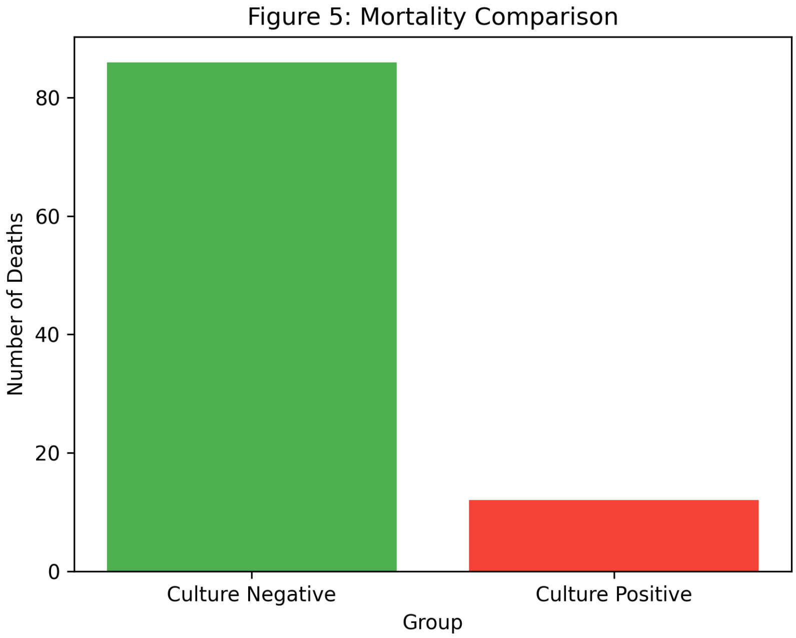

Figure 5: Comparison of in-hospital mortality between culture-negative and culture-positive sepsis patients.

Outcome Classification

Patients were categorized into three outcome groups:

- Group 1: Sepsis-related mortality without underlying disease
- Group 2: Sepsis-related mortality with underlying disease
- Group 3: Mortality due to underlying disease

A statistically significant difference was observed between groups ($\chi^2 = 19.080$, df = 3, $p < 0.001$).

Table 9: Outcome distribution (n=200)

Outcome	Negative	Positive
No mortality	79	23
Group 1	64	2
Group 2	14	9
Group 3	8	1

Summary of Key Findings

- Culture-negative sepsis predominated (82.5%)
- *E. coli* was the most common pathogen
- Co-morbidities significantly associated with culture positivity (p<0.001)
- SOFA score showed strong statistical significance
- Procalcitonin not statistically significant but clinically useful
- Mortality higher in culture-negative group (not significant)

Discussion

The present study highlights the critical challenge posed by culture-negative sepsis, which constituted a large majority (82.5%) of cases. This finding is consistent with previous studies reporting culture negativity rates between 40–60% [21,22].

The high prevalence of culture-negative sepsis can be attributed to prior antibiotic exposure, delayed sample collection, and limitations of conventional microbiological techniques [23]. This underscores the need for alternative diagnostic strategies.

Role of Procalcitonin

Procalcitonin levels were elevated in both groups but did not show statistical significance. This suggests that while PCT is useful in identifying infection, it may not reliably differentiate between culture-positive and negative sepsis. Similar findings were reported in previous studies [24].

However, the declining trend of PCT from Day 1 to Day 4 indicates its usefulness in monitoring treatment response.

Role of SOFA Score

A significant difference in SOFA scores was observed across all days, with higher values in culture-positive patients. This indicates greater disease severity and supports its role as a prognostic marker.

The SOFA score remains one of the most reliable tools for predicting mortality and organ dysfunction (25).

Mortality Patterns

Interestingly, mortality was higher in culture-negative patients, although not statistically significant. This may reflect delayed diagnosis and empirical treatment challenges.

Previous studies have reported conflicting findings, with some showing higher mortality in culture-positive cases due to severe infection burden (26).

Clinical implications of this study highlight the growing importance of biomarkers in the early identification and management of sepsis, particularly in culture-negative cases. Biomarkers such as procalcitonin and SOFA score not only facilitate timely diagnosis but also assist clinicians in making informed decisions regarding initiation, escalation, and de-escalation of antibiotic therapy. Their use contributes to improved risk stratification by identifying patients at higher risk of adverse outcomes, thereby enabling more targeted and appropriate clinical interventions. Additionally, biomarker-guided strategies can help minimize unnecessary antibiotic exposure, which is crucial in reducing antimicrobial resistance and associated complications.

Looking ahead, future advancements in sepsis management may include the incorporation of molecular diagnostic techniques such as polymerase chain reaction (PCR) and metagenomic analysis for rapid and accurate pathogen detection. The development of multi-biomarker panels combining inflammatory, immunological, and clinical indicators may further enhance diagnostic precision. Furthermore, integration of these parameters with artificial intelligence–based predictive models holds promise for improving early detection, personalized treatment, and overall clinical outcomes in sepsis care.

Conclusion

Adjunct biomarkers such as procalcitonin and SOFA score play a pivotal role in the management of culture-negative sepsis. While procalcitonin aids in diagnosis and monitoring, SOFA score provides robust prognostic value. Incorporating these biomarkers into clinical practice can significantly enhance early diagnosis, guide treatment decisions, and improve patient outcomes.

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