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Original Research Article

NEUTROPHIL–LYMPHOCYTE COUNT RATIO AS A MARKER OF CULTURE POSITIVITY IN SEPSIS: A CROSS-SECTIONAL STUDY

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ABSTRACT

Background: Sepsis is a life-threatening condition characterized by a dysregulated host response to infection, and microbiological cultures remain the gold standard for etiological confirmation. However, a substantial proportion of sepsis cases are culture-negative, limiting early pathogen-directed management. The neutrophil–lymphocyte count ratio (NLCR), derived from routine complete blood counts, has emerged as a potential marker of systemic inflammation. This study aimed to evaluate the role of NLCR in differentiating culture-positive from culture-negative sepsis.

Materials and Methods: This single-centre cross-sectional observational study included 147 adult patients diagnosed with sepsis based on Sepsis-3 criteria. Demographic, clinical, laboratory, and microbiological data were collected at admission. NLCR was calculated using absolute neutrophil and lymphocyte counts. Patients were classified as culture-positive or culture-negative sepsis based on microbiological results. Comparisons between groups were performed using appropriate statistical tests, and receiver operating characteristic (ROC) curve analysis was used to assess the diagnostic performance of NLCR.

Results: Of the 147 patients, 62 (42.2%) had culture-positive sepsis and 85 (57.8%) had culture-negative sepsis. Culture-positive patients had significantly higher total leukocyte count, absolute neutrophil count, C-reactive protein levels, and significantly lower absolute lymphocyte count. Mean NLCR was significantly higher in culture-positive sepsis compared to culture-negative sepsis (16.4 ± 6.9 vs 8.9 ± 4.8; $p < 0.001$). An NLCR cut-off of ≥10 showed a sensitivity of 79.0% and specificity of 67.1% for predicting culture positivity, while a cut-off of ≥15 demonstrated high specificity (89.4%). ROC analysis yielded an area under the curve of 0.82 (95% CI: 0.75–0.89), indicating good discriminatory ability.

Conclusion: NLCR is a simple, inexpensive, and readily available biomarker that is significantly associated with culture-positive sepsis and demonstrates good diagnostic accuracy. It may serve as a useful adjunct in the early identification and risk stratification of sepsis, particularly in settings with limited resources.

Keywords: Sepsis; Neutrophil-lymphocyte count ratio; Culture-positive sepsis; Inflammatory biomarkers; Blood culture.

INTRODUCTION

Sepsis remains a major global health challenge, contributing significantly to morbidity and mortality among hospitalized patients, particularly in intensive care units.[1] It is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection and represents the severe end of the spectrum of infectious diseases.[2] Despite advances in antimicrobial therapy and critical care, sepsis continues to account for a substantial proportion of in-hospital deaths, with reported mortality ranging

from 20–40% depending on severity and comorbidities.[3]

Microbiological culture remains the gold standard for identifying the causative pathogen in sepsis and guiding targeted antimicrobial therapy. However, blood and other relevant cultures often yield negative results, even in patients with strong clinical evidence of sepsis.[4] Culture negativity may occur due to prior antibiotic exposure, low bacterial load, fastidious organisms, or limitations of conventional culture techniques.[5] Studies have reported that nearly 30–50% of clinically diagnosed sepsis cases are culture-negative, posing diagnostic and therapeutic challenges.[5,6] Differentiating culture-positive from culture-negative sepsis is clinically relevant, as culture-positive sepsis is often associated with higher inflammatory burden, disease severity, and worse outcomes.[6]

Early identification of sepsis and assessment of its severity rely on clinical parameters supported by laboratory biomarkers.[7] Commonly used inflammatory markers such as total leukocyte count, C-reactive protein, and procalcitonin have variable sensitivity, specificity, cost, and availability, particularly in resource-limited settings.[8] In recent years, there has been growing interest in simple hematological indices derived from routine complete blood counts as potential markers of systemic inflammation and infection.[9,10]

The neutrophil-lymphocyte count ratio (NLCR) has emerged as a promising, inexpensive, and readily available biomarker reflecting the balance between innate immune activation (neutrophilia) and adaptive immune suppression (lymphopenia), both of which are hallmark features of sepsis.[11] Neutrophilia results from bone marrow stimulation and demargination in response to infection, while lymphopenia reflects stress-induced apoptosis and immune dysregulation. An elevated NLCR therefore mirrors the intensity of the host inflammatory response.[12]

Several studies have demonstrated the utility of NLCR in diagnosing sepsis, predicting disease severity, and assessing prognosis, with higher values being associated with increased mortality and organ dysfunction.[12,13] Emerging evidence also suggests that NLCR may differ between culture-positive and culture-negative sepsis, potentially reflecting differences in pathogen burden and immune response. However, data on the role of NLCR in distinguishing culture-positive from culture-negative sepsis remain limited and inconsistent, particularly in the Indian subcontinent and tertiary care settings. Given the high burden of sepsis, frequent culture negativity, and the need for rapid, cost-effective biomarkers to aid clinical decision-making, evaluating the role of NLCR as an indicator of culture positivity in sepsis is of considerable clinical importance. This study aimed to assess and compare NLCR values in patients with culture-positive and culture-negative sepsis in a single-centre tertiary care hospital, thereby exploring its potential utility as a supportive diagnostic and prognostic marker.

MATERIALS AND METHODS

Study Design and Setting

This was a hospital-based, single-centre cross-sectional observational study conducted under the department of Microbiology at a tertiary care teaching hospital for a period of 1 year between June 2023 to May 2024. The study was carried out in the emergency department, medical wards, and intensive care units, where patients with suspected or confirmed sepsis are routinely managed. The objective was to evaluate the role of the neutrophil-lymphocyte count ratio (NLCR) in differentiating culture-positive from culture-negative sepsis at the time of clinical presentation.

Study Population

The study population consisted of adult patients admitted with a clinical diagnosis of sepsis during the study period. Sepsis was defined in accordance with the Sepsis-3 criteria as suspected or documented infection accompanied by acute organ dysfunction. All eligible patients underwent routine laboratory investigations and microbiological cultures as part of standard clinical care.

Inclusion and Exclusion Criteria

Adult patients aged 18 years and above who fulfilled the diagnostic criteria for sepsis and had blood cultures and/or relevant site-specific cultures sent within 24 hours of admission were included in the study. Patients were excluded if they had received systemic corticosteroids, immunosuppressive therapy, or chemotherapy prior to admission, or if they had underlying hematological malignancies, chronic inflammatory or autoimmune diseases, human immunodeficiency virus infection, or other conditions known to significantly alter leukocyte counts. Patients with incomplete laboratory or microbiological data were also excluded.

Data Collection

Demographic details, including age and sex, along with clinical information such as presenting symptoms, suspected source of infection, comorbidities, and vital parameters at admission were recorded from patient case records. Laboratory parameters were obtained from samples collected at the time of initial evaluation, prior to or within a short interval of initiation of antibiotic therapy wherever feasible.

Laboratory Investigations

Venous blood samples were collected under aseptic precautions for complete blood count analysis, which was performed using an automated hematology analyzer. Absolute neutrophil count and absolute lymphocyte count were recorded, and the neutrophil-lymphocyte count ratio was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. Other routine laboratory

investigations were performed as per institutional sepsis protocol.

Microbiological Assessment

Blood cultures were obtained from all patients before the initiation of antimicrobial therapy whenever possible, following standard aseptic techniques. In addition to blood cultures, site-specific cultures such as urine, sputum, endotracheal aspirate, pus, or body fluids were collected based on clinical suspicion. Samples were processed in the microbiology laboratory using standard culture methods. Patients were classified into culture-positive sepsis if any blood or relevant site culture yielded a pathogenic organism and culture-negative sepsis if all cultures remained sterile after the standard incubation period.

Grouping of Study Participants

Based on microbiological results, patients were categorized into two groups: culture-positive sepsis and culture-negative sepsis. NLCR values at admission were compared between the two groups to assess differences in inflammatory response.

Outcome Measures

The primary outcome measure was the difference in neutrophil-lymphocyte count ratio between culture-positive and culture-negative sepsis patients. Secondary analyses included the evaluation of the association between NLCR and selected clinical and laboratory parameters at presentation.

Statistical Analysis

Data were entered into a spreadsheet and analyzed using standard statistical software. Continuous variables were assessed for normality and expressed as mean ± standard deviation or median with interquartile range as appropriate. Categorical variables were expressed as frequencies and percentages. Comparison of continuous variables between culture-positive and culture-negative groups was performed using the independent sample t-test or Mann–Whitney U test, depending on data distribution. Categorical variables were compared using the chi-square test or Fisher's exact test. A p-value of less than 0.05 was considered statistically significant.

Ethical Considerations

The study was conducted after obtaining approval from the Institutional Ethics Committee. As the study was observational and utilized data collected as part of routine clinical care, informed consent was obtained from patients or their legally authorized representatives in accordance with institutional guidelines. Patient confidentiality was maintained throughout the study, and all data were anonymized prior to analysis.

RESULTS

A total of 147 patients with sepsis were included in the study, of whom 62 (42.2%) had culture-positive sepsis and 85 (57.8%) were classified as culture-negative sepsis based on microbiological evaluation. The mean age of the study population was 54.6 ± 16.2 years, with a male predominance (63.9%). There was no statistically significant difference in age or sex distribution between culture-positive and culture-negative groups. A significantly higher proportion of patients with culture-positive sepsis required intensive care unit admission compared to those with culture-negative sepsis (71.0% vs 52.9%, p = 0.02). The prevalence of common comorbidities such as diabetes mellitus and hypertension was higher in the culture-positive group, although these differences did not reach statistical significance. Respiratory tract infections constituted the most common suspected source of sepsis in both groups, followed by urinary and abdominal sources. No significant differences were observed in the distribution of suspected infection sources between culture-positive and culture-negative patients (Table 1).

Table 1: Baseline Demographic and Clinical Characteristics of Study Population (n = 147)

Variable	Overall (n = 147)	Culture-Positive Sepsis (n = 62)	Culture-Negative Sepsis (n = 85)	p-value
	Frequency (%)/mean ± SD			
Age (years)	54.6 ± 16.2	56.8 ± 15.4	53.0 ± 16.7	0.18
Gender				
Male	94 (63.9)	41 (66.1)	53 (62.4)	0.64
Female				
ICU admission	89 (60.5)	44 (71.0)	45 (52.9)	0.02
Diabetes mellitus	58 (39.5)	28 (45.2)	30 (35.3)	0.21
Hypertension	61 (41.5)	29 (46.8)	32 (37.6)	0.26
Suspected source				
Respiratory	46 (31.3)	21 (33.9)	25 (29.4)	0.56
Urinary	38 (25.9)	19 (30.6)	19 (22.4)	0.27
Abdominal	29 (19.7)	15 (24.2)	14 (16.5)	0.24
Skin/soft tissue	21 (14.3)	6 (9.7)	15 (17.6)	0.18

Patients with culture-positive sepsis demonstrated significantly higher inflammatory burden at admission. The mean total leukocyte count was significantly elevated in the culture-positive group compared to the culture-negative group (15.9 ± 6.4 vs 12.8 ± 5.9 $\times 10^9$/L, p = 0.003). Absolute neutrophil count was markedly higher among culture-positive patients (13.2 ± 5.7 vs 9.6 ± 4.8 $\times 10^9$/L, p < 0.001), while absolute lymphocyte count was significantly lower (0.86 ± 0.42 vs 1.21 ± 0.56 $\times 10^9$/L, p < 0.001). C-reactive protein levels were also significantly higher in the culture-positive group (p < 0.001).

Hemoglobin and platelet counts were comparable between the two groups (Table 2).

Table 2: Hematological and Inflammatory Parameters at Admission

Parameter	Culture-Positive (n = 62)	Culture-Negative (n = 85)	p-value
	mean ± SD/median (IQR)		
Total leukocyte count (×10⁹/L)	15.9 ± 6.4	12.8 ± 5.9	0.003
Absolute neutrophil count (×10⁹/L)	13.2 ± 5.7	9.6 ± 4.8	<0.001
Absolute lymphocyte count (×10⁹/L)	0.86 ± 0.42	1.21 ± 0.56	<0.001
Hemoglobin (g/dL)	10.9 ± 1.8	11.2 ± 1.9	0.29
Platelet count (×10⁹/L)	178 ± 74	201 ± 82	0.09
C-reactive protein (mg/L)	112 (74–168)	78 (46–121)	<0.001

Among the culture-positive cases, gram-negative organisms predominated (61.3%), with Escherichia coli and Klebsiella pneumoniae being the most frequently isolated pathogens. Gram-positive organisms accounted for 27.4% of isolates, predominantly Staphylococcus aureus. Fungal isolates, mainly Candida species, were identified in 11.3% of cases (Table 3).

Table 3: Microbiological Profile of Culture-Positive Sepsis (n = 62)

Isolated Organism	Frequency (%)
Gram-negative bacteria	38 (61.3)
Escherichia coli	14 (22.6)
Klebsiella pneumoniae	11 (17.7)
Acinetobacter baumannii	7 (11.3)
Pseudomonas aeruginosa	6 (9.7)
Gram-positive bacteria	17 (27.4)
Staphylococcus aureus	9 (14.5)
Enterococcus species	6 (9.7)
Streptococcus species	2 (3.2)
Fungal isolates (Candida spp.)	7 (11.3)

The mean NLCR at admission was significantly higher in patients with culture-positive sepsis compared to those with culture-negative sepsis (16.4 ± 6.9 vs 8.9 ± 4.8, $p < 0.001$). Median NLCR values showed a similar trend (15.2 vs 7.6, $p < 0.001$). A substantially higher proportion of culture-positive patients had NLCR values ≥10 (79.0% vs 32.9%, $p < 0.001$) and ≥15 (51.6% vs 10.6%, $p < 0.001$). When NLCR was categorized, more than half of culture-positive patients had NLCR values greater than 15, whereas the majority of culture-negative patients had NLCR values below 10, demonstrating a strong association between increasing NLCR and culture positivity ($p < 0.001$) (Table 4).

Table 4: Comparison of Neutrophil-Lymphocyte Count Ratio (NLCR) Between Groups

NLCR Parameter	Culture-Positive (n = 62)	Culture-Negative (n = 85)	p-value
	Frequency (%)/mean ± SD/median (IQR)		
NLCR	16.4 ± 6.9	8.9 ± 4.8	<0.001
NLCR	15.2 (11.1–20.6)	7.6 (5.2–11.4)	<0.001
NLCR < 5	4 (6.5%)	29 (34.1%)	<0.001
NLCR 5–10	9 (14.5%)	28 (32.9%)	
NLCR 10–15	17 (27.4%)	19 (22.4%)	
NLCR > 15	32 (51.6%)	9 (10.6%)	

Receiver operating characteristic (ROC) curve demonstrating the diagnostic performance of neutrophil–lymphocyte count ratio (NLCR) in differentiating culture-positive from culture-negative sepsis. The area under the curve (AUC) was 0.82 (95% CI: 0.75–0.89), indicating good discriminatory ability. An NLCR cut-off value of ≥10 provided optimal sensitivity (79.0%) and specificity (67.1%), while a higher cut-off of ≥15 improved specificity (89.4%) at the expense of sensitivity (51.6%) (Figure 1).

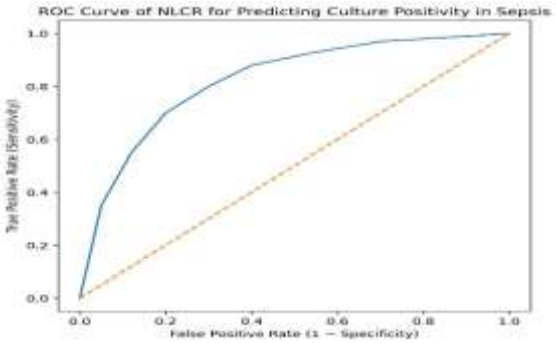

Figure 1: Receiver Operating Characteristic (ROC) Curve of Neutrophil–Lymphocyte Count Ratio for Predicting Culture Positivity in Sepsis

DISCUSSION

In this single-centre cross-sectional study, neutrophil–lymphocyte count ratio (NLCR) at admission was found to be significantly higher in patients with culture-positive sepsis compared to culture-negative sepsis and demonstrated good diagnostic accuracy for predicting microbiological positivity. These findings reinforce the growing body of evidence supporting NLCR as a reliable inflammatory marker in sepsis and extend its utility to differentiating culture-positive from culture-negative cases.

The culture positivity rate of 42.2% observed in our cohort is comparable to rates reported in earlier Indian and international studies by Shetty et al., and Sigakis et al., which have documented culture yields ranging from 35% to 50% in clinically diagnosed sepsis.[14,15] Kumar et al. from a North Indian ICU reported a culture positivity rate of 39%, while Mehta et al., in a multinational Asian sepsis cohort, reported positivity in approximately 45% of cases.[16,17] Similar to our findings, culture-positive sepsis in these studies was associated with greater illness severity and higher ICU utilization, supporting the observation that microbiological confirmation often reflects a higher inflammatory and pathogen burden.[16,17]

The significantly higher total leukocyte count and absolute neutrophil count, coupled with lower absolute lymphocyte count in culture-positive sepsis, observed in this study are pathophysiologically plausible and consistent with prior literature by Sumardi et al., and Marik et al.[18,19] Neutrophilia represents activation of innate immunity mediated by pro-inflammatory cytokines such as interleukin-6 and tumor necrosis factor-α, while lymphopenia reflects sepsis-induced immune dysregulation through apoptosis and impaired lymphocyte proliferation.[20] Manohar et al., also highlighted that the neutrophil-to-lymphocyte ratio reflects the balance between inflammatory activation and immune suppression in critically ill patients, making it a biologically meaningful marker in sepsis.[21]

Our finding of a markedly higher NLCR in culture-positive sepsis (mean 16.4 ± 6.9) compared to culture-negative sepsis (8.9 ± 4.8) aligns closely with previous studies by Li et al., and Afzal et al.[22,23] Li et al., demonstrated that NLCR was significantly higher in patients with bacteremia compared to those without (median 18.3 vs 8.7, $p < 0.001$) and outperformed total leukocyte count in predicting bloodstream infection.[22] Similarly, Afzal et al., reported a median NLCR of 17.2 in bacteremic patients compared to 7.9 in non-bacteremic infections, concluding that NLCR had diagnostic accuracy comparable to C-reactive protein.[23] The median NLCR values in our study (15.2 vs 7.6) are remarkably consistent with these findings, despite differences in population and healthcare settings.

The ROC analysis in the present study further substantiates the diagnostic utility of NLCR, with an AUC of 0.82, indicating good discriminatory power. This performance is comparable to previously published studies by Ljungström et al., Lowsby et al., and Jiang et al., where reported AUC values for NLCR in predicting bacteremia or severe infection range from 0.75 to 0.85.[24,25,26] In our study, an NLCR cut-off of ≥10 provided optimal sensitivity (79.0%) and specificity (67.1%), similar to the cut-offs proposed by Afzal et al. (NLCR >10) and Ljungström et al., who reported improved diagnostic yield for bacteremia at NLCR thresholds between 8 and 12.[23,24] A higher cut-off of ≥15 in our cohort increased specificity to 89.4%, suggesting that very high NLCR values strongly indicate true culture-positive sepsis, albeit at the cost of reduced sensitivity.

The predominance of gram-negative organisms among culture-positive cases in our study is consistent with the microbiological profile reported in Indian sepsis literature by Dutta et al., Garg et al., and Bajaj et al., where gram-negative pathogens account for 55–70% of isolates.[27,28,29] Gram-negative bacteria, through lipopolysaccharide-mediated endotoxemia, provoke a more intense neutrophil-driven inflammatory response, which may partly explain the significantly higher NLCR values observed in culture-positive patients.[28] This biological plausibility strengthens the association between NLCR elevation and microbiological confirmation.

From a practical standpoint, NLCR offers distinct advantages over other biomarkers. Unlike procalcitonin or interleukin assays, NLCR is inexpensive, rapidly available, and universally accessible as part of routine complete blood count testing.[30] Several studies by Sarı et al., and Zhou et al., have emphasized its usefulness as an adjunct rather than a replacement for cultures, particularly in resource-constrained settings where delays in microbiological confirmation are common.[30,31]

In such contexts, NLCR may aid early risk stratification, guide empirical antibiotic decisions, and identify patients requiring closer monitoring or ICU care.[31]

Limitations

Nevertheless, the findings of this study must be interpreted with caution. As a single-centre study, the results may reflect local microbiological and patient characteristics. The cross-sectional design limits assessment of serial NLCR trends and their relationship with outcomes such as mortality or treatment response. Prior antibiotic exposure, which is common in sepsis referrals, may also influence both culture yield and inflammatory markers. Despite these limitations, the consistency of our findings with multiple peer-reviewed studies strengthens the validity of NLCR as a clinically relevant marker.

CONCLUSION

This single-centre cross-sectional study demonstrates that the neutrophil–lymphocyte count ratio is significantly higher in patients with culture-positive sepsis compared to those with culture-negative sepsis and exhibits good diagnostic accuracy for predicting microbiological positivity. An NLCR cut-off value of ≥10 provides an optimal balance between sensitivity and specificity, while higher values (≥15) are highly specific for culture-positive sepsis. Given its simplicity, cost-effectiveness, and universal availability, NLCR may serve as a valuable adjunctive biomarker in the early evaluation and risk stratification of patients with sepsis, particularly in resource-limited settings where culture results are delayed or frequently negative. Incorporation of NLCR into routine sepsis assessment may help guide early clinical decision-making and prioritization of care. Further multicentric and prospective studies are warranted to validate these findings and to explore the prognostic implications of serial NLCR measurements.

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