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Evaluation of Neutrophil cluster of differentiation 64 in adult sepsis as a novel diagnostic biomarker

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Abstract

Background: Sepsis stands as a leading cause of mortality among critically ill patients in intensive care units (ICUs). Bacterial infections, including sepsis, upregulate Neutrophilic cluster of differentiation 64 (nCD64) expression on activated polymorphonuclear leukocytes (PMNs). Prompt diagnosis of sepsis is crucial for initiating timely and targeted treatment. Consequently, a rapid laboratory test with high specificity for sepsis in adults would significantly aid therapeutic decision-making and help reduce the overuse of antibiotics.

Methods: This study enrolled 40 sepsis patients diagnosed according to the Sepsis-3 definition. For biomarker evaluation, 2 mL blood samples were collected from each patient in both ethylenediaminetetraacetic acid (EDTA) and plain vials. In addition, nCD64 was analyzed using flow cytometry, high-sensitivity C-reactive protein (hs-CRP) via nephelometry, and procalcitonin (PCT) using chemiluminescence.

Results: For sepsis prediction, nCD64 demonstrated a positive predictive value (PPV) of 92.68% and a negative predictive value (NPV) of 94.87%. A receiver operating characteristic (ROC) curve was generated to assess the diagnostic accuracy of nCD64 (≥ 1.8), hS-CRP (≥ 3 mg/L), and PCT (≥ 0.4 ng/mL). The area under the curve (AUC) for nCD64 was highest at 0.938 (95% confidence interval [CI] = 0.876-0.999), followed by hS-CRP at 0.888 (95% CI = 0.807-0.968) and PCT at 0.850 (95% CI = 0.759-0.941).

Conclusion: These findings strongly suggest that nCD64 determination is a valuable diagnostic tool for identifying infections in patients with septic syndrome. Its performance appears to be superior to that of hs-CRP and PCT.

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Introduction

Sepsis represents a leading cause of death among critically ill patients in intensive care units (ICUs). It is a medical emergency characterized by a dysregulated systemic immune response to infection, which can culminate in end-organ dysfunction and mortality (1).

The septic response represents an intricate series of physiological events, encompassing both inflammatory and anti-inflammatory processes, alongside humoral and cellular reactions, and notable circulatory abnormalities. Crucially, for the host to effectively combat pathogens, innate immune cells-including neutrophils, macrophages, monocytes, and natural killer cells-must undergo initial activation. This activation also triggers the release of key pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6). These cytokines lead to an up-regulation of endothelial adhesion molecules, the activation and proliferation of leukocytes, complement system activation, tissue factor production, and the induction of hepatic acute phase reactants. Consequently, an over-response of these immune processes can result in collateral damage to host tissues and organs (1). In sepsis, inflammatory and coagulative cascades are activated simultaneously, and their interaction can result in conditions ranging from mild thrombocytopenia to disseminated intravascular coagulation (DIC) (2). Hypoperfusion, characterized by reduced oxygen delivery and cellular utilization, is a primary driver of tissue damage and organ dysfunction. This hypoperfusion is often exacerbated by the cardiovascular dysfunction commonly observed in septic states (3). Consequently, sepsis is a critical condition leading to systemic inflammation and organ dysfunction.

Early diagnosis and accurate severity stratification of sepsis are crucial for initiating prompt and targeted treatment (4). While blood culture remains the gold standard for sepsis diagnosis, its utility is limited by the 24-to-48-hour turnaround time (5). Consequently, biomarkers play a vital role in identifying sepsis severity and in differentiating between bacterial, viral, and fungal infections. Beyond diagnosis, biomarkers hold diverse potential in prognostication, guiding antibiotic therapy, assessing treatment response, differentiating gram-positive from gram-negative sepsis, and predicting sepsis complications. While high-sensitivity C-reactive protein (hS-CRP) and procalcitonin (PCT) are highly effective in diagnosing infections, they are limited by their inability to distinguish between infectious and inflammatory conditions (6).

Neutrophil cluster of differentiation 64 (nCD64) is a fragment crystallizable gamma (Fcγ) receptor primarily found on monocytes and resting polymorphonuclear leukocytes (PMNs). The expression of nCD64 on activated PMNs increases significantly in the presence of bacterial infection or sepsis. Additionally, nCD64 has been suggested as a potential diagnostic and prognostic biomarker for sepsis in hospitalized adults, neonates, and children, and is considered a novel diagnostic marker for adult sepsis (7). This study operates on the hypothesis that the expression of nCD64, alongside serum PCT and hs-CRP, could serve as beneficial indicators for sepsis.

The current study aimed to evaluate nCD64 as a diagnostic marker for adult sepsis. The primary objective was to quantify the percentage expression of nCD64, alongside serum PCT and hs-CRP levels, in newly diagnosed adult sepsis cases. Furthermore, the study compared the diagnostic accuracy of nCD64 percentage expression with that of serum PCT and hs-CRP for predicting adult sepsis.

Methods

This cross-sectional study was conducted at the Department of Pathology and General Medicine, Vardhman Mahavir Medical College & Safdarjung Hospital, New Delhi, following Institutional Ethical Committee approval. The study spanned an 18-month period from July 2021 to December 2022. It included adult patients (27-70 years old) newly admitted to the ICU with a clinical diagnosis of sepsis based on Sepsis-3 criteria (European Society of Intensive Care Medicine - Society of Critical Care Medicine guidelines) and who had not yet initiated antibiotic therapy.

Patients with a history of malignancy, hematological disease, those who had started antibiotic therapy, and individuals with severe liver or kidney disease were excluded from the study. After applying the inclusion and exclusion criteria and considering operational feasibility, a total of 40 cases and 40 age- and gender-matched healthy controls were enrolled. The severity of organ dysfunction or failure was assessed using various scoring systems that quantify abnormalities based on clinical observations, laboratory results, or therapeutic interventions. The sequential organ failure assessment (SOFA) score is the primary tool currently used, with higher scores correlating with an increased risk of mortality (8). We extracted all six systemic variables-Glasgow Coma Scale (GCS), mean arterial pressure (MAP), partial pressure of oxygen in arterial blood (PaO2)/fraction of inspired oxygen (FiO2) ratio, platelet count (PLT), serum bilirubin levels, and serum creatinine levels-from medical records for SOFA score calculation.

For the analysis of nCD64 expression, a 2 mL blood sample was collected in an ethylenediaminetetraacetic acid (EDTA) vial. Flow cytometry was performed using a Beckman Coulter Navios flow cytometer. nCD64 expression was determined by gating neutrophils based on CD45 versus side scatter (SS) graph, as illustrated in Figure 1.

For quantitative evaluation, 2 mL of blood was collected in a plain vial. Serum PCT was measured using chemiluminescence (ADVIA Centaur CP Immunoassay), while hS-CRP levels were assessed by nephelometry (Biocell Medicare BNII).

This study collected primary data using paper-based case report forms (CRFs). The information from these forms was subsequently entered into Microsoft Excel 2016 spreadsheets. For statistical analysis, IBM SPSS Statistics version 2020 was employed. Continuous variables are presented as their means ± standard deviation. Mean comparisons were performed using the Kruskal-Wallis test, as non-parametric tests were necessary due to the non-normal distribution of the data. Finally, median values are visually represented in column or bar graphs.

Categorical variables were analyzed using frequencies and proportions, with cross-tabulations performed for the selected parameters. A P-value < 0.05 was considered statistically significant, while a P-value < 0.01 indicated high significance. Based on identified cut-off values for true and false positives and negatives, sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio were calculated. A receiver operating characteristic (ROC) curve was then plotted using sensitivity and specificity, and the area under the curve (AUC) values for nCD64, PCT, and hS-CRP were subsequently compared.

Ethics code number for this study was IEC/VMMC/SJH/Thesis/2020-11/CC-240.

Results

We studied 40 newly diagnosed clinical sepsis cases, identified according to Sepsis-3 criteria (8), and 40 age- and gender-matched control subjects.

The study population exhibited a male predominance (Males = 68.75%, females = 31.25%), yielding a male-to-female ratio (M:F) of 2.2:1. The patients' mean age was 50 years (Age range = 27-70 years; median age = 51 years).

In sepsis patients, the SOFA score ranged from a minimum of 2 to a maximum of 5. The median and mean SOFA scores were 3 and 2.72 ± 0.7, respectively. In contrast, control subjects had a median SOFA score of 1. The difference in mean ranks between the septic patients and controls was highly statistically significant (P < 0.001).

Table 1 presents the descriptive statistics and mean rank comparisons for various sepsis parameters, including PaO2/FiO2, PLT, MAP, GCS score, serum bilirubin, and serum creatinine. Similarly, Table 2 displays the descriptive statistics and the mean rank comparisons for sepsis biomarkers like nCD64, PCT, and hs-CRP.

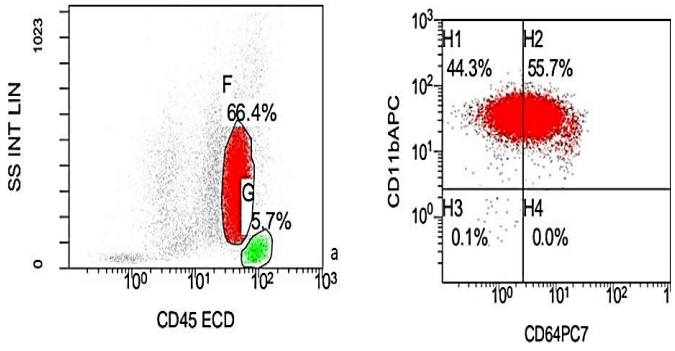


Figure 1. a) Events were gated based on cluster of differentiation 64 (CD45) versus side scatter (SS). This analysis revealed that granulocytes (F population) constituted 66.4% of total events, while lymphocytes (G population) comprised 5.7%. b) Within the granulocyte (F population), 55.7% of cells were positive for both CD11b and CD64.

Table 1. Descriptive statistics and mean rank comparison of different sepsis parameters

Variables	Groups	Mean	Standard Deviation	Median	Minimum	Maximum	Range	P-Value
PaO2/FiO2	Control	426.28	11.79	425.00	410.00	450.00	40.00	< 0.001
	Sepsis case	377.55	65.46	409.50	200.00	430.00	230.00	
PLT (10^3/dL)	Control	277.63	64.99	273.00	165.00	416.00	251.00	0.07
	Sepsis case	232.43	106.77	221.00	69.00	417.00	348.00	
MAP (mm Hg)	Control	80.18	5.43	81.00	70.00	88.00	18.00	< 0.001
	Sepsis case	76.60	3.14	77.00	71.00	81.00	10.00	
GCS score	Control	15.00	0.00	15.00	15.00	15.00	0.00	1.00
	Sepsis case	15.00	0.00	15.00	15.00	15.00	0.00	
Serum bilirubin (mg/dL)	Control	0.84	0.24	0.85	0.40	1.20	0.80	< 0.0001
	Sepsis case	1.63	0.53	1.60	0.90	3.40	2.50	
Serum creatinine (mg/dL)	Control	1.12	0.22	1.15	0.80	1.40	0.60	0.23
	Sepsis case	1.42	0.77	1.10	0.40	4.20	3.80	

Abbreviations: PaO2/FiO2: Partial pressure of Oxygen in arterial blood (PaO2)/Fraction of Inspired Oxygen (FiO2) ratio, PLT: Platelets count, MAP: Mean Arterial Pressure, GCS: Glasgow Coma Scale, dL: Deciliter, mg/dL: Milligram per deciliter, mm Hg: Millimeter of mercury.

The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy for nCD64, PCT, and hS-CRP, respectively, are presented in Table 3. ROC curves were plotted to illustrate the diagnostic accuracy of nCD64 (≥ 1.8), hS-CRP (≥ 3 mg/L), and PCT (≥ 0.4 ng/mL). The respective AUCs were 0.938 (95% confidence interval [CI] = 0.876-0.999), 0.888 (95% CI = 0.807-0.968), and 0.850 (95% CI = 0.759-0.941), as depicted in Figure 2.

Table 2. Descriptive statistics and mean rank comparison of different sepsis biomarkers

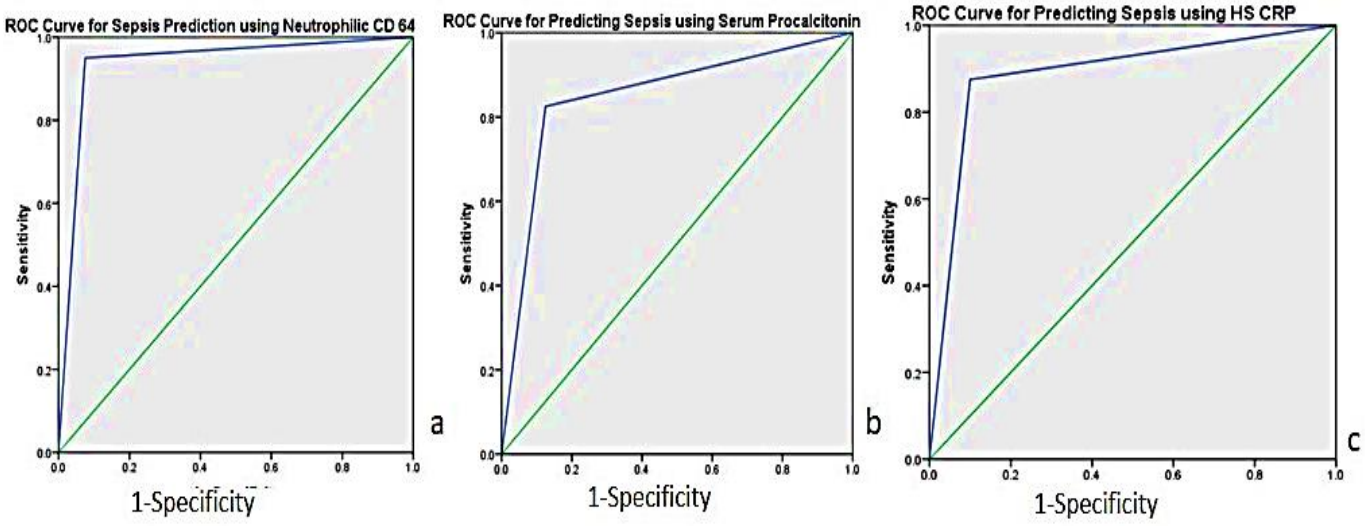
Variables	Groups	Mean	Standard Deviation	Median	Minimum	Maximum	Range	P-Value
nCD64 (Molecules/Cel)	Control	1.15	0.78	1.20	0.03	4.80	4.77	< 0.0001
	Sepsis case	16.17	15.67	9.45	1.32	55.70	54.38	
PCT (ng/mL)	Control	0.14	0.13	0.095	0.01	0.53	0.52	< 0.0001
	Sepsis case	1.38	1.89	0.790	0.05	9.90	9.85	
hS-CRP (mg/L)	Control	1.21	1.45	0.80	0.40	7.50	7.10	< 0.0001
	Sepsis case	26.99	35.71	15.50	1.20	154.00	152.80	

Abbreviations: nCD64: Neutrophil Cluster of Differentiation 64, PCT: Procalcitonin, hs-CRP: High-sensitivity C-Reactive Protein, ng/mL:Nanogram per milliliter, mg/L: Milligram per liter

Table 3. Descriptive statistics and mean rank comparison of different sepsis biomarkers

Indices	nCD64	PCT	hS-CRP
Sensitivity	95.00%	82.50%	87.50%
Specificity	92.50%	87.50%	90.00%
PPV	92.68%	86.84%	89.74%
NPV	94.87%	83.33%	87.80%
Accuracy	93.75%	85.00%	88.75%

Abbreviations: nCD64: Neutrophil Cluster of Differentiation 64, PCT: Procalcitonin, hs-CRP: High-sensitivity C-Reactive Protein, PPV: Positive Predictive Value, NPV: Negative Predictive Value



Test Result Variable(s)	Area under curve	Std. Error [a]	P value.[b]	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
nCD 64 (≥1.8)	0.938	0.031	0.000	0.876	0.999
HS CRP (≥3 mg/L)	0.888	0.041	0.000	0.807	0.968
PCT (≥0.4 ng/mL)	0.850	0.046	0.000	0.759	0.941
The test result variable(s): CD 64 (≥1.8), HS CRP (≥3 mg/l), PROCALCITONIN (≥0.4 ng/ml) 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					

a) NeutrophilicCD64(Ncd64) b) Proalcitonin (PCT) c) High Sensitivity CRP (hS-CRP)

Figure 2. Receiver operator curve (ROC) illustrating an area under curve (AUC) for neutrophil cluster of differentiation 64 (nCD64), procalcitonin (PCT) and high-sensitivity C-reactive protein (hs-CRP)

Discussion

Diagnosing sepsis continues to be a significant challenge for clinicians. A rapid laboratory test with high specificity for adult sepsis could greatly assist in therapeutic decision-making and help reduce the inappropriate use of antibiotics.

Our study's observation of a higher prevalence of sepsis in males aligns with common findings and may be attributable to the immunosuppressive effects of male sex hormones, specifically androgens, on cell-mediated immune responses (7,9).

In our investigation, the SOFA score demonstrated a minimum of 2 and a maximum of 5 in sepsis cases, yielding a statistically significant AUC of 0.96 ($P < 0.001$). This finding aligns with other studies, such as those by Kilinc Toker et al. and Liu C et al., who also reported high significance for SOFA score in sepsis prediction with AUCs of 0.89 and 0.80, respectively (10,11). However, upon individual analysis of the SOFA score's systemic variables, GCS, serum creatinine, and platelet counts did not show significant differences between the control and patient groups ($P > 0.05$). We observed significantly lower levels of serum bilirubin, PaO2/FiO2, and MAP in cases compared to controls ($P < 0.001$). These findings diverge from Liu et al.'s study, which reported a negative correlation with total bilirubin and serum creatinine, alongside a significant positive correlation with MAP, PaO2/FiO2, PLT, and GCS (11). This discrepancy may stem from differences in the stage of sepsis at which patients were assessed; our study included all newly diagnosed sepsis cases, regardless of their initial presentation stage.

This study analyzed the effectiveness of the biomarkers hS-CRP, PCT, and nCD64 for the early diagnosis of sepsis in adult patients, yielding variable results.

In the current research, hs-CRP demonstrated an 87.5% sensitivity and 90% specificity for sepsis prediction, utilizing a cutoff value of 3 mg/L and yielding an AUC of 0.88. These findings align with those of Wang et al.'s research, which reported a correlation between elevated baseline hs-CRP and an increased risk of subsequent septic events (12). While Lin CT et al. also identified hs-CRP as a predictor of sepsis, their study showed a lower AUC, potentially attributable to their higher hs-CRP cutoff value of 8 mg/L (13).

In the current study, PCT demonstrated a sensitivity of 82.50% and a specificity of 87.50% for predicting sepsis, with an AUC of 0.85. These findings align with previous studies, such as Zhang et al.'s research, which similarly reported high accuracy for PCT in diagnosing sepsis in patients with bacterial bloodstream infections when evaluating its diagnostic and prognostic value in combination with hs-CRP (14). Prior research on PCT as a diagnostic biomarker for sepsis has yielded conflicting results. L. Simon et al. and Hiromi Toh et al. identified PCT as a valuable tool, demonstrating high sensitivity and specificity in sepsis diagnosis (15,16). Conversely, Benjamin M.P. Tang et al. reported that PCT could not reliably distinguish sepsis from other non-infectious causes of systemic inflammatory response syndrome (SIRS) (17). They observed a comparatively low sensitivity and specificity for PCT (Approximately 70%), a finding they attributed to their study population consisting solely of critically ill patients.

In this study, the sensitivity and specificity of nCD64 were determined to be 95% and 92.50%, respectively. These figures are comparable to those reported by Cardelli P et al., who found a sensitivity of 96% and a specificity of 95% (18). In contrast, Li et al. and Cid et al. observed lower nCD64 sensitivities of 79% and 76%, respectively. They attributed these lower sensitivities to the use of methodologies of lower quality, although the specificities in their studies were consistent with our findings (19,20). The application of flow cytometry and the inclusion of adult sepsis cases in our study may have contributed to enhanced sensitivity and specificity. In contrast, previous research by A. Gros et al. and O. Livaditi et al. observed low nCD64 sensitivity for gram-positive infections and high sensitivity for gram-negative infections in medical ICU patients (21,22). Our study, however, did not categorize patients by pathogen type.

The ROC curve for nCD64 (≥ 1.8) yielded an AUC of 0.938, indicating strong diagnostic accuracy. This finding aligns with previous research, as Cid et al. reported a similar AUC of 0.94, Li et al. found 0.92, and Cardelli P et al. observed 0.97 (20,19,18). Furthermore, Patnaik et al.'s study highlighted nCD64's utility as both a diagnostic and prognostic marker in critically ill septic patients (23).

While most studies indicate that PCT is a superior predictor of sepsis compared to hs-CRP, H. Zhang et al. reported similar diagnostic utility for both biomarkers in sepsis and septic shock. This discrepancy might stem from Zhang's study exclusively featuring an older patient demographic (24,25). Our own research, however, aligns with the majority, identifying hs-CRP as a more effective biomarker for predicting adult sepsis, though our study did not stratify patients by age or sepsis stage.

Our literature review reveals a scarcity of studies that concurrently evaluate these three parameters for sepsis prediction. Notably, no such comprehensive research has been conducted in adult populations. While a study by Yin et al. identified nCD64 as superior to PCT and CRP for infection diagnosis, our investigation incorporated hS-CRP instead of CRP (26). KH Hsu et al.'s prospective study in 2011 revealed that nCD64 was superior to PCT for distinguishing SIRS from severe sepsis and septic shock, and also linked to the severity of SIRS and sepsis (27). Similarly, CF Yeh et al. identified nCD64 as a more effective biomarker than PCT for sepsis diagnosis (28). Consistently, the present study also found nCD64 to be a better marker than both hS-CRP and PCT.

In developing nations like India, the cost-effectiveness of diagnostic tests is a significant consideration, as high costs can impose an additional financial burden on patients and their caregivers. Within typical Indian laboratory settings, the approximate cost per test for hS-CRP is 800 rupees, PCT is 3100 rupees, and nCD64 is 2000 rupees. Consequently, nCD64 shows promise as an independent and cost-effective diagnostic tool for predicting sepsis in adult populations.

This study has a few limitations. A primary concern is the lack of standardized methods for determining nCD64, as various techniques are used for its expression. Furthermore, the optimal cut-off value for nCD64 remains undefined and contentious, leading to different diagnostic thresholds being employed across studies to differentiate between sepsis and non-sepsis.

Conclusion

nCD64 levels, in conjunction with clinical parameters, such as the SOFA score, show promise as an early diagnostic marker for sepsis in adult patients. This study demonstrated that nCD64 is a relatively simple, cost-effective, and superior biomarker for adult sepsis diagnosis compared to hs-CRP and PCT, exhibiting high sensitivity and specificity. Nevertheless, standardization of the nCD64 assay with appropriate cut-off levels is essential for distinguishing sepsis from non-sepsis conditions accurately.

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Ethical statement

This study was approved by the Ethical Committee of Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi (No. IEC/VMMC/SJH/Thesis/2020-11/CC-240).

Conflicts of interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Author contributions

Written by Anuradha Saini, and reviewed by Anjali Sharma, Mukul Singh, Shaily Goyal, Maninder Narang and Sunil Ranga.

Data availability statement

All the data supporting the results are included in the article, and no further source data is needed.

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