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# Early and Effective Diagnosis of Sepsis Using Flow Cytometry

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## Abstract

**Objective** Sepsis is a major global health issue due to its high death and morbidity rates. To avoid the negative effects of sepsis and decrease mortality, it is vital to diagnose and treat it as soon as possible. Blood cultures can take up to 2 days to give result, and they are not always reliable. According to recent studies, neutrophil CD64 expression might be a sensitive and specific option for assessing sepsis. This study aimed to evaluate the diagnostic performance of a flow cytometry analysis for the expression of neutrophil CD64 in sepsis and its comparison with other standard tests in a tertiary care center.

**Materials and Methods** Prospective analysis on 40 blood samples from suspected sepsis patients admitted to intensive care units with criteria for the systemic inflammatory response syndrome on presentation was performed for expression of neutrophil CD64, C-reactive protein, procalcitonin, and complete blood count. Ten healthy volunteers were also enrolled in this prospective study. The laboratory results were compared in different groups.

**Results** The neutrophil CD64 had the highest diagnostic value to differentiate between patients of sepsis and nonsepsis groups with a sensitivity of 100% (95% confidence interval [CI]: 77.19–100%) and 100% (95% CI: 55.32–86.83%); specificity of 90.00% (95% CI: 59.58–99.49%) and 87.24% (95% CI: 66.69–99.61%); and likelihood ratio of 10.00 and 7.84, respectively.

**Conclusion** The neutrophil CD64 expression provides a more sensitive, specific, and novel marker for the early detection of sepsis in critically ill patients.

**Keywords**
- CD64
- sepsis
- biomarker
- flow cytometry
- intensive care unit

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## Introduction

In critical care units, sepsis is one of the most prevalent causes of morbidity and death in intensive care units (ICUs). It is extremely difficult to diagnose sepsis in people with a variety of comorbidities and underlying illnesses.[1,2] According to the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD 2017), sepsis caused 48.9 million cases and 11.0 million deaths worldwide in 2017, accounting for more than 20% of all global fatalities.[3] Sepsis remains a serious global health problem with potentially deadly consequences that require immediate attention, particularly in terms of early detection and innovative and effective therapy. Early identification of sepsis and immediate medical intervention are crucial for better clinical results and decreased mortality.[4] Traditionally, sepsis is diagnosed through serum analysis and molecular methods. Sepsis diagnosis is compounded further by vague signs and symptoms and can be difficult due to the lack of a gold standard test for confirmation.[5]

A blood culture test is the most common method for identifying infectious bacteria in the circulation. Blood cultures can take up to 2 days to provide a result, and they are not always accurate. The detection of infection-causing microorganisms also relies on several molecular methods, such as polymerase chain reaction, isothermal amplification, hybridization, and microarray. The sensitivity and specificity of each strategy differ. Sepsis-specific biomarkers are still lacking, despite their importance in diagnostic techniques and the necessity of monitoring sepsis via biomarkers. Even though more than 170 biomarkers have been developed for the screening of sepsis, only a handful are significant in real practice and each has specific benefits and drawbacks.[6]

Flow cytometry, a relatively new approach in this field, may detect many cellular, functional, dissolved, and pathophysiological components of sepsis. The cell surface biomarker CD64, the high-affinity immunoglobin receptor, is widely expressed on monocytes and, to a lesser extent, resting neutrophils. CD64 expression in neutrophils is graded, which corresponds to the severity of the inflammatory response to infection or tissue injury. When the proinflammatory cytokines interferon gamma and granulocyte colony-stimulating factor activate neutrophils, CD64 expression rises.[7] Neutrophil CD64 (nCD64) is a remarkably accurate and selective marker for systemic infections and sepsis in all age groups.[8] Flow cytometry's clinical relevance remains limited despite recent breakthroughs in both technology and methodology. The merits and demerits of promising novel parameters for flow cytometry-based sepsis detection, particularly nCD64 and human leukocyte antigen–DR isotype (HLA-DR), are discussed in this article. In the present study, we aim to employ flow cytometry to identify cell surface indicators as an early and effective diagnostic tool for the management of sepsis.

## Materials and Methods

A prospective study was conducted from September 2020 to August 2021 at the Department of Pathology, in coordination with the Departments of Critical Care Medicine and Internal Medicine at King George's Medical University, Lucknow (Uttar Pradesh, India). After receiving institutional ethical permission (ECR/262/Inst/UP/2013/RR-19), a total of 40 patients with systemic inflammatory response syndrome (SIRS) criteria were admitted to the ICU, and 10 healthy volunteers as controls were recruited in the study. In the case of children or if the patient was unable to sign, informed written consent was obtained from each individual or their guardian. SIRS was defined as per the criteria of the American College of Chest Physicians.[9] The diagnosis of sepsis was based on the presence of a confirmed or suspected infection with SIRS. Patients in the ICU were split into two groups: sepsis and nonsepsis (SIRS). Patients with confirmed sepsis had positive blood cultures, whereas those with suspected sepsis had contaminated samples with SIRS criteria and were clinically suspected of infection because of a high-grade fever and X-ray evidence of pneumonia, or leukocyte- and nitrite-positive urine.[10] Patients who refused to enroll in the study, those with an immune disease, or who received potent immunosuppressive agents within 30 days were excluded from the study.

Detailed clinical evaluation with history and examination specifically to look for signs and symptoms of sepsis were recorded. For complete blood count (CBC) and flow cytometry analysis, 2 mL of blood was collected in EDTA vacutainer under an aseptic condition within 6 hours of admission to the ICU, and 2 mL of blood was also collected in plain vials for analysis of C-reactive protein (CRP) and procalcitonin (PCT). CBC was performed on an automated six-part cell counter (Sysmex XN-550) and flow cytometry was done on BD FACS Canto 8 color flow cytometer, Becton Dickson within 24 hours when kept at 2 to 8°C. Flow cytometric estimation of antibodies bound per cell to quantify CD64 expression on neutrophils, lymphocytes, and monocytes and HLA-DR expression on monocytes and neutrophils was done. In cases of low white blood cell (WBC) count or neutropenia, a double volume of samples was processed for flow cytometry to acquire an adequate number of neutrophils.

## Statistical Analysis

The statistical analysis was performed using SPSS software for Windows (SPSS Inc., Chicago, Illinois, United States) (21.0 version). When relevant, the continuous variables were assessed using the mean (standard deviation) or range value. The dichotomous variables were provided as number/frequency and evaluated with the chi-square or Fisher's exact test. A Student's *t*-test with a 95% confidence interval (CI) was performed to compare the means of the two groups. A *p*-value of less than 0.05 was considered significant.

## Results

From September 2020 to August 2021, 40 patients met the inclusion criteria for the present study. Twenty-seven had

 

symptoms of SIRS (nonsepsis group) and 13 had documented or suspected sepsis (sepsis group). The majority of the study population ($n = 10$) in the control group were between 25 and 34 years ($n = 5$ [50.00%]) followed by 15 and 24 years ($n = 3$ [30.00%]) and 35 and 44 years ($n = 1$ [10.00%]), whereas the majority of ICU patients (sepsis and nonsepsis groups) were between 25 and 34 years ($n = 11$ [27.50%]) followed by 35 and 44 years ($n = 9$ [22.50%]) and 5 and 24 years ($n = 7$ [17.5%]). The majority of the population in the control group were males ($n = 6$ [60.00%]) followed by females ($n = 4$ [40.00%]), while the majority of ICU patients (sepsis and nonsepsis groups) were females ($n = 24$ [60.00%]) followed by males ($n = 16$ [40.00%]). As shown in ►**Table 1**, there was no significant difference noted between cases and controls for age and sex distribution.

There was a significant increase noted for mean fluorescence intensity (MFI) for nCD64 expression in nonsepsis ($4,308.30 \pm 3,725.59$) and sepsis ($12,602.38 \pm 8,573.90$) groups as compared with controls ($880.60 \pm 419.36$), while MFI for monocyte HLA-DR (mHLA-DR) expression showed a significant decrease in nonsepsis ($25,661.81 \pm 14,814.42$) and sepsis ($1,962.46 \pm 1,964.06$) groups as compared with controls ($40,626.30 \pm 13,842.79$). The mean MFI for lymphocyte CD64 and MFI for neutrophil HLA-DR were not significantly different between control and ICU patient groups (nonsepsis and sepsis) as shown in ►**Table 2**.

The mean CRP (mg/L) and PCT (ng/mL) levels were significantly increased in the sepsis group ($71.20 \pm 22.63$ mg/L and $42.31 \pm 29.04$ ng/mL) as compared with the nonsepsis group ($23.23 \pm 18.69$ mg/L and $6.87 \pm 6.59$ ng/mL) as shown in ►**Table 3**.

The CBC parameters such as total leucocyte count, platelets, and hematocrit were not significantly different between control, nonsepsis, and sepsis group patients. However, the mean difference of hemoglobin was significantly lower in nonsepsis ($8.95 \pm 1.92$) and sepsis ($8.43 \pm 1.08$) as compared with the control group ($12.09 \pm 1.78$) as shown in ►**Table 4**.

The receiver operating characteristic curve was analyzed for CRP, PCT, nCD64, and HLA-DR levels as shown in ►**Table 5** and ►**Fig. 1**. These tests were demonstrated to differentiate between the nonsepsis and sepsis groups of patients in the ICU. The cutoff points for CRP were more than 9.9 and more than 1.84 mg/L, PCT were more than 10.65 and more than 10.69 ng/mL, nCD64 were more than 5,509 and more than 1,620, and HLA-DR were less than 6,737 and less than 23,427 in nonsepsis and sepsis groups, respectively. The nCD64 test

**Table 1** Distribution of study population according to age and gender in control and ICU patient groups

| | | Control ($n = 10$) | | ICU patients ($n = 40$) | | *p*-Value |
|---|---|---|---|---|---|---|
| | | *N* | % | *N* | % | |
| Age (y) | 15–24 | 3 | 30 | 7 | 17.5 | 0.574 |
| | 25–34 | 5 | 50 | 11 | 27.5 | |
| | 35–44 | 1 | 10 | 9 | 22.5 | |
| | 45–54 | 0 | 0 | 6 | 15.0 | |
| | 55–64 | 1 | 10 | 4 | 10.0 | |
| | 65–74 | 0 | 0 | 2 | 5.0 | |
| | 75–84 | 0 | 0 | 1 | 2.5 | |
| Gender | Female | 4 | 40 | 24 | 60.0 | 0.433 |
| | Male | 6 | 60 | 16 | 40.0 | |

Abbreviation: ICU, intensive care unit.

**Table 2** Comparisons of mean CD64 and HLA-DR in control and ICU patient (nonsepsis and sepsis) groups

| MFI CD64/HLA-DR | Control ($n = 10$) | | Nonsepsis ($n = 27$) | | Sepsis ($n = 13$) | | *p*-Value |
|---|---|---|---|---|---|---|---|
| | Mean | ± SD | Mean | ± SD | Mean | ± SD | |
| MFI nCD64 | 880.60 | 419.36 | 4,308.30 | 3,725.59 | 12,602.38 | 8,573.90 | $< 0.001$[a] |
| MFI mHLA-DR | 40,626.30 | 13,842.79 | 25,661.81 | 14,814.42 | 1,962.46 | 1,964.06 | $< 0.001$[a] |
| MFI LyCD64 | 251.20 | 52.53 | 243.19 | 42.20 | 230.15 | 32.50 | 0.476 |
| MFI nHLA-DR | 427.20 | 170.33 | 511.11 | 306.91 | 686.08 | 995.81 | 0.508 |

Abbreviation: ICU, intensive care unit; LyCD64, lymphocyte CD64; MFI, mean fluorescence intensity; mHLA-DR, monocyte human leukocyte antigen – DR isotype; nCD64, neutrophil CD64; nHLA-DR, neutrophil human leukocyte antigen – DR isotype; SD, standard deviation.
[a]Significant ($p < 0.05$).

 

**Table 3** Comparison of mean CRP and procalcitonin in nonsepsis and sepsis groups

| Biochemical parameter | Nonsepsis ($n = 27$) | | Sepsis ($n = 13$) | | *p*-Value |
|---|---|---|---|---|---|
| | Mean | ± SD | Mean | ± SD | |
| CRP (mg/L) | 23.23 | 18.69 | 71.20 | 22.63 | $< 0.001$[a] |
| Procalcitonin (ng/mL) | 6.87 | 6.59 | 42.31 | 29.04 | $< 0.001$[a] |

Abbreviations: CRP, C-reactive protein; SD, standard deviation.
[a]Significant ($p < 0.05$).

**Table 4** Comparisons of complete blood count parameters in control and ICU patient (nonsepsis and sepsis) groups

| CBC parameter | Control ($n = 10$) | | Nonsepsis ($n = 27$) | | Sepsis ($n = 13$) | | *p*-Value |
|---|---|---|---|---|---|---|---|
| | Mean | ± SD | Mean | ± SD | Mean | ± SD | |
| TLC (cells/mm$^3$) | 7,560.00 | 1,313.16 | 16,307.67 | 17,432.15 | 10,196.85 | 5,162.59 | 0.150 |
| Hb (g/dL) | 12.09 | 1.78 | 8.95 | 1.92 | 8.43 | 1.08 | $< 0.001$[a] |
| Hematocrit (%) | 35.17 | 8.13 | 32.73 | 41.57 | 23.30 | 3.09 | 0.5940 |

Abbreviations: CBC, complete blood count; Hb, hemoglobin; ICU, intensive care unit; SD, standard deviation; TLC, total leucocyte count.
[a]Significant ($p < 0.05$).

was more sensitive (100 and 100%) and specific (87.24 and 90.0%) and showed a maximum likelihood ratio of 7.84 and 10.0 in the nonsepsis and sepsis groups, respectively. The CRP, PCT, and HLA-DR tests showed 86.50, 76.92, and 75.00% sensitivity with 66.67, 62.50, and 60.00% specificity, respectively, in the nonsepsis group. The likelihood ratios in the nonsepsis group for CRP, PCT, and HLA-DR were 2.60, 2.05, and 1.88, respectively. The CRP, PCT, and HLA-DR tests were 100.0, 92.31, and 84.62% sensitive and showed 80.00, 80.00, and 70.00% specificity in the sepsis group. The likelihood ratios in the sepsis group for CRP, PCT, and HLA-DR were 5.0, 4.62, and 2.82, respectively.

## Discussion

Blood culture is a gold standard approach for diagnosing sepsis, with positive rates ranging from 30 to 87%.[11] Blood cultures can take up to 2 days to give a response, and they are not always reliable. Carvalho and Trotta stated that despite all efforts to exclude microorganisms from blood cultures, they will often be positive in an average of 34% (range of 9–64%) of patients.[12] As a result, additional diagnostic tests are required to speed up the diagnosis and management of sepsis. The increased interest in using nCD64 expression as a biomarker for sepsis may be due to its clinical importance and the need for early detection of sepsis and treatment.

Monocytes, macrophages, low numbers of polymorphonuclear neutrophils, and a subset of circulating dendritic cells express the CD64 antigen. Neutrophils with high levels of CD64 expression are more likely to have been infected or to have been responding to an acute inflammatory response. Macrophages, B lymphocytes, activated T lymphocytes, monocytes, natural killer lymphocytes, and human progenitor cells express the anti-HLA-DR antigen.[13]

In our study, the MFI of nCD64 was considerably higher in the nonsepsis and sepsis groups compared with controls. Moreover, the nCD64 had the highest diagnostic value for sepsis and nonsepsis groups with a sensitivity of 100% (95% CI: 77.19–100%) and 100% (95% CI: 55.32–86.83%); specificity of 90.00% (95% CI: 59.58–99.49%) and 87.24 (95% CI: 66.69–99.61%); and a likelihood ratio of 10.00 and 7.84, respectively. For the first time, Davis et al (2006) reported the diagnostic potential of nCD64 in sepsis patients for the first time.[14] They reported that nCD64 was an outscored sepsis diagnostic marker compared with WBC count, erythrocyte sedimentation, and CRP. Several studies published in the past 10 years have established the clinical use of CD64 in the detection of sepsis. In respiratory critical care unit patients, Hsu et al discovered that nCD64 was more accurate than PCT in separating SIRS from severe sepsis and septic shock.[15] In a few studies, nCD64 showed lower sensitivity in detecting sepsis in critically ill patients.[16] Due to its high specificity, it may help in the clinical diagnosis of sepsis when combined with other sensitive indicators. In recent study, nCD64 expression was reported to be able to differentiate sepsis from the SIRS with 82.1% accuracy early on admission to the emergency department.[17]

A study revealed that the nCD64 index of 1.19 could predict a diagnosis of sepsis with a sensitivity of 94.6%, a specificity of 88.7%, a positive predictive value of 89.8%, and a negative predictive value of 94%. The nCD64 levels may be a useful diagnostic tool to improve the early diagnosis and management of patients with sepsis.[18] With a sensitivity of 88.3% (95% CI: 78.1–94.1%) and a specificity of 87.6% (95%, 71.8–95.2%), the nCD64 could identify sepsis in adult

 

**Table 5** ROC analysis of CRP, PCT, nCD64, and HLA-DR in the study group

| Parameters | Cutoff | Sensitivity % (95% CI) | Specificity % (95% CI) | Likelihood ratio | |
|---|---|---|---|---|---|
| | | | | +LR | −LR |
| Nonsepsis group | | | | | |
| CRP | > 9.9 mg/L | 86.50 (77.19–100.0%) | 66.67 (51.52–84.15%) | 2.60 | 0.20 |
| PCT | > 10.65 ng/mL | 76.92 (57.77–97.27%) | 62.50 (57.77–97.27%) | 2.05 | 0.37 |
| nCD64 | > 5,509 | 100 (55.32–86.83%) | 87.24 (66.69–99.61%) | 7.84 | 0.00 |
| HLA-DR | < 6,737 | 75.00 (66.69–99.61%) | 60.00 (76.63–98.68%) | 1.88 | 0.42 |
| Sepsis group | | | | | |
| CRP | > 1.84 mg/L | 100.0 (77.19–100.0%) | 80.00 (59.58–99.49%) | 5.00 | 0.00 |
| PCT | > 10.69 ng/mL | 92.31 (55.32–86.83%) | 80.00 (59.58–99.49%) | 4.62 | 0.10 |
| nCD64 | > 1,620 | 100.0 (77.19–100.0%) | 90.00 (59.58–99.49%) | 10.00 | 0.00 |
| HLA-DR | < 23,427 | 84.62 (77.19–100.0%) | 70.00 (59.58–99.49%) | 2.82 | 0.22 |

Abbreviations: CRP, C-reactive protein; HLA-DR, human leukocyte antigen – DR isotype; nCD64, neutrophil CD64; PCT, procalcitonin; ROC, receiver operating characteristic; SD, standard deviation.

patients.[19] The study evaluated CD64 expression in sepsis patients and found that patients with sepsis had a higher percentage of CD64-bearing neutrophils (69%) than healthy controls (17%).[20] The study performed by Zhou et al invested a biomarker panel (CD25, CD64, and CD69 antigens) for the diagnosis of sepsis with the help of flow cytometry, and the results showed that this panel improved diagnosis ability. The CD64 is the best single biomarker for sepsis detection. Patients with septic shock and healthy volunteers could be distinguished with high accuracy by the expression of CD64 on neutrophils.[21] Another study analysis revealed that CD64 expression is a useful marker for detecting early sepsis in severely sick individuals. The test results should not be used to diagnose sepsis on their own, but rather in conjunction with the medical history, physical examination, and other test results.[22]

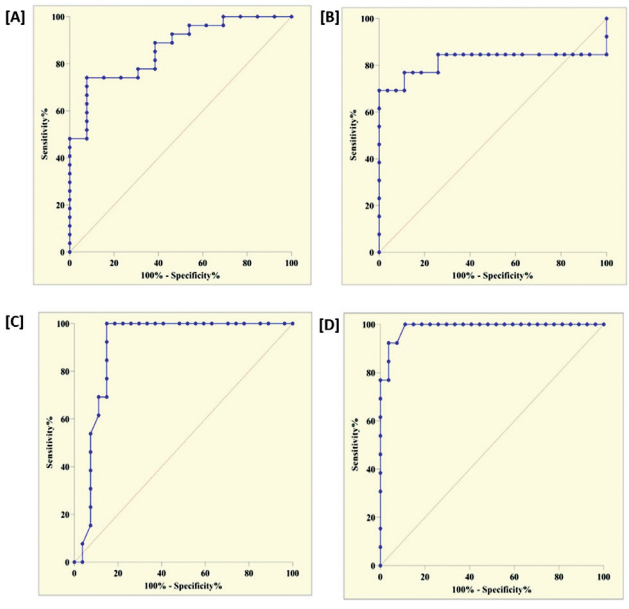


**Fig. 1** Receiver operating curve analysis of (**A**) human leukocyte antigen – DR isotype, (**B**) procalcitonin, (**C**) C-reactive protein, and (**D**) neutrophil CD64 in sepsis group patients.

In our study, the sensitivity of CRP, PCT, and HLA-DR tests were 86.50, 76.92, and 75.00% with a specificity of 66.67, 62.50, and 60.00%, respectively, in the nonsepsis group. The CRP, PCT, and HLA-DR tests showed 100.0, 92.31, and 84.62% sensitivity with 80.00, 80.0, and 70.00% specificity, respectively, in the sepsis group. The likelihood ratio in the nonsepsis and sepsis groups for CRP, PCT, and HLA-DR was 2.60 and 5.0, 2.05 and 4.62, and 1.88 and 2.82, respectively. Dimoula et al showed that routinely measuring CRP concentration in conjunction with the expression of nCD64 was a good way to diagnose sepsis. Flow cytometry was used to monitor treatment response via the expression of nCD64 daily from the time of admission until the patient was discharged or died.[23] Chauhan et al used a flow cytometer to analyze nCD64 and mHLA-DR for the diagnosis of sepsis in their study. They observed that nCD64 expression is useful in detecting sepsis, but its diagnostic sensitivity and specificity ranged from 26 to 100%. It was concluded that flow analysis is superior to all other currently available modalities for detecting sepsis in adults.[24]

 

In this study, the mean CRP (mg/L) and PCT (ng/mL) levels in the sepsis group ($71.20 \pm 22.63$ mg/L and $42.31 \pm 29.04$ ng/mL) were considerably higher than in the nonsepsis group ($23.23 \pm 18.69$ mg/L and $6.87 \pm 6.59$ ng/mL). A study by Nargis et al[25] found that people with moderate to severe sepsis had higher PCT levels than people with no or local infections. The mean levels of serum PCT and CRP increased significantly, indicating greater severity. When sepsis, severe sepsis, and septic shock patients were compared with SIRS and no SIRS at different levels of systemic inflammation and sepsis, their mean PCT and CRP values were significantly higher.[25–28] However, a previous study was unable to demonstrate a significant relationship between PCT or CRP and the severity of sepsis.[29]

This study had certain limitations, primarily as a small sample size and results being limited to a single tertiary care center that may not be generalized.

## Conclusion

In contrast to the CRP, PCT, and HLA-DR tests, nCD64 has the highest diagnostic value for distinguishing between early sepsis and nonsepsis (SIRS) with high sensitivity, specificity, and likelihood ratio in nonsepsis and sepsis groups. Furthermore, nCD64 assessments are equivalent to a CBC in terms of speed, and so may play an important role in the early management of sepsis.

### Ethical Approval

Approved by the Institutional Ethics Committee, reference no: 102ECM IIB/Thesis P-46, dated 05.09.2020.

### Authors' Contribution

R.K. did study designing, conceptual analysis, data acquisition, and literature search. P.V. did data analysis and designing. A.S. did a literature search and proof correction. G.Y. did data analysis and proofreading. A.A. contributed to clinical studies and literature searches. H.D.R. contributed to clinical studies and design. S.P.V. did clinical studies and data analysis. U.S.S. did study design and literature search.

### Conflict of Interest

None declared.

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