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Original Article

Assessing Neutrophil CD64 Expression: A Key Biomarker for Diagnosing Infections and Evaluating Antibiotic Therapy in Acute Leukemia Patients

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Abstract

Introduction: Patients with acute leukemia (AL) are at an increased risk of infection, particularly in acute or critical situations, where timely identification of the cause of infection is crucial. While traditional methods such as microbial cultures remain the gold standard, they require 24–48 hours for results. In recent years, novel biomarkers like neutrophil CD64 expression have been widely investigated as indicators of infection. However, the diagnostic utility of CD64 within the clinical context of AL patients, especially those who are neutropenic and undergoing treatment, has not been extensively studied. Therefore, this study aimed to assess the diagnostic potential of neutrophil CD64 expression in monitoring the progression of infection and evaluating antibiotic therapy in AL patients complicated by infection.

Methods: Forty AL patients (20 in the infection group and 20 in the non-infection group), along with 40 healthy controls, were recruited. Data on the percentage of neutrophil CD64+ (%CD64+), CD64 index, C-reactive protein (CRP), white blood cell (WBC) count, and absolute neutrophil count (ANC) were collected.

Results: Patients with infection exhibited higher %CD64+, CD64 index, and CRP levels compared to those without infection ($p<0.001$). The sensitivity of both %CD64+ and the CD64 index in diagnosing infection was 90%, while their specificities were 83.3% and 86.7%, respectively. Furthermore, in the infection group, both %CD64+ and the CD64 index were significantly down-regulated after effective antibiotic therapy ($p<0.001$).

Conclusion: CD64 shows significant promise in enhancing diagnostic precision and in assessing the effectiveness of antibiotic therapy in AL patients.

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1. INTRODUCTION

Leukemia is a widespread malignant disorder with varying impacts across global populations. Developed nations experience higher incidence and mortality rates while developing countries have increased mortality rates [1]. Acute leukemia (AL) is marked by the abnormal clonal proliferation of immature blood cells within the bone marrow [2]. Classification is based on cell origin, distinguishing between lymphoid and myeloid types. Acute lymphoblastic leukemia (ALL), which predominantly affects children and adolescents, accounts for approximately 75% of leukemia cases in individuals under the age of 20. Its highest occurrence is observed between the ages of 2 and 5 [3]. In contrast, acute myeloblastic leukemia (AML) primarily affects adults, with an overall incidence rate of 3–5 cases per 100,000 individuals. AML is typically diagnosed around the age of 66, with a substantial portion of patients receiving their diagnosis after age 65, and a notable proportion being diagnosed after the age of 75 [3].

Patients with AL face an elevated risk of infections due to the disease and its treatments [4]. The primary risk factor is neutropenia, with infection severity and frequency rising as the absolute neutrophil count (ANC) decreases [5]. Febrile neutropenia occurs in more than 80% of patients undergoing chemotherapy for AL, however, less than 50% of episodes can be attributed to an infectious etiology [6]. Other risk factors include compromised immunity, the breakdown of protective barriers, and the presence of medical devices. Frequently, multiple risk factors coexist within the same patient [5]. Additionally, repeated administration of antimicrobial agents has altered infection patterns, raising concerns about multidrug-resistant (MDR) organisms [7-9]. Fever may present with or without other specific symptoms [10]. In neutropenic AL patients, over 90% of fever episodes are likely due to infections [5].

In acute or critical situations, timely identification of infection causes is a major concern. Recent advances in diagnostics, including molecular tools like real-time polymerase chain reaction (PCR) and rapid immunological tests, have revolutionized the field. Traditional methods such as blood and fluid cultures remain the gold standard but require 24–48 hours for results. However, negative cultures do not definitively rule out suspected bacterial infection [11-13]. Researchers are exploring biomarkers for quicker diagnosis and treatment assessment. Biomarkers such as C-reactive protein (CRP) and procalcitonin (PCT) have strong supporting evidence, but emerging biomarkers hold great potential, providing more precise insights into inflammation, bacteremia, and response to therapy. [13-15]. Dysregulation of immunity plays a key role in sepsis, where CD64, a Fc gamma receptor with high affinity, emerges as an early immune response indicator. Resting neutrophils have low CD64 expression, but it surges upon bacterial activation [16, 17]. Previous investigations have established that CD64 expression on neutrophils (nCD64) is increased in patients with sepsis, making it a powerful biomarker for diagnosing the disease [14-18]. However, its diagnostic utility in the clinical context of patients with AL, particularly those who are neutropenic and undergoing antibiotic therapy, has not been extensively studied. Therefore, the objective of our study was to assess the diagnostic potential of nCD64 compared to well-established biomarkers, including CRP level, ANC, and white blood cell (WBC) count within the clinical setting of AL patients with concurrent infections.

2. MATERIALS AND METHODS

2.1. Study design

A prospective observational study was conducted at Shahid Baghaei Hospital, Ahvaz Jundishapour University of Medical Sciences, Ahvaz, Iran, between September 2022 and March 2023.

Consecutive adult patients (>18 years old) with AL (with or without infection) were recruited. All patients received diagnosis and treatment in accordance with the clinical practice guidelines outlined by the National Comprehensive Cancer Network (NCCN). Based on their infection status, we further divided them into two groups: the suspected infection group and the non-infection group. Infection was suspected if a patient exhibited one or more symptoms such as fever, chills, coughing, sneezing, tachypnea, or developed acute respiratory distress syndrome (ARDS). Additionally, the presence of positive microbiological cultures and/or elevated inflammatory markers was considered in defining suspected infections. Neutropenia was defined as an ANC <1.5×10^9/L. Forty healthy individuals were also recruited as a control group. We excluded patients who (1) were <18 years old, (2) had taken antibiotics before enrollment, (3) were pregnant at any stage, (4) had any form of organ dysfunction, or (5) were diagnosed with an inflammatory disease or immune dysfunction syndrome.

2.2. Ethical considerations

The study protocol was approved by the Research Ethics Committee of Tehran University of Medical Sciences (IR.TUMS.SPH.REC.1401.104). Both written and oral informed consent were provided by all patients.

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2.3. Patient evaluation

Data collected at the time of enrollment included age, gender, WBC counts, absolute ANC, CRP levels, the presence of clinical symptoms, and the results of microbiological cultures. Blood samples were obtained from patients within 24 hours of study enrollment to evaluate nCD64 expression. In the infection group, blood samples were initially collected from patients who exhibited clinical symptoms, had elevated inflammatory biomarkers, or tested positive in microbiological cultures. Subsequently, additional blood samples were taken once the infection had been brought under control.

2.4. Flow cytometry

Whole blood samples (using EDTA as an anticoagulant) were processed for evaluation within 24 hours. Fifty microliters of whole blood were mixed with twenty microliters each of CD64-Apc and CD45-PerCP antibodies (Exbio, Czech Republic) and incubated in the dark for 15 minutes. Then, 450 microliters of lysing solution (FACS Lysing Solution, BD Biosciences, USA) were added, and the mixture was incubated for another 15 to 30 minutes. Finally, the samples were analyzed using a BD FACSLyric flow cytometer (BD Biosciences, USA). Data analysis was conducted using FlowJo 7.6 software (LLC, USA).

Initial gating was performed by creating a forward scatter (FSC) versus side scatter (SSC) plot to distinguish cell types based on their size and granularity. Neutrophils typically appear in a distinct region, characterized by medium to high SSC (due to their granularity) and medium FSC (due to their size). This plot was used to exclude debris (low FSC and SSC) and to select the granulocyte population. Next, the gating was refined using a CD45 versus SSC plot. In this plot, neutrophils cluster in a specific region, characterized by high SSC and moderate to high CD45 expression. This allowed us to exclude other leukocytes, such as lymphocytes and monocytes, which exhibit different CD45 levels and lower SSC. Finally, a CD64 versus CD45 (or SSC) plot was generated to specifically gate the neutrophil population that is positive for these markers. CD64 expression data were reported as both the percentage of neutrophils expressing CD64 (%CD64+) and the CD64 index, calculated using the formula provided by Gao and colleagues. [18].

2.5. Statistical analysis

Statistical analysis was conducted using SPSS version 26.0, while graphs were created with Prism version 9. Fisher's exact test was employed to analyze the categorical variables, such as gender. Normality of continuous variables was assessed with the Shapiro–Wilk test. Subsequently, one-way ANOVA was employed for normally distributed data and Kruskal-Wallis test for non-normally distributed data, to assess between-group comparisons. Statistical significance set at $p < 0.05$ (two-tailed). Pearson correlation coefficients were used to evaluate relationships between biomarkers. To assess the effectiveness of CD64 index, %CD64$^+$, CRP level, WBC count, and ANC in detecting infections in AL patients, we conduct a receiver operating characteristic (ROC) analysis, with thresholds determined by Youden's index.

3. RESULTS

3.1. Clinical characteristics of patients

Out of 45 consecutive adult patients diagnosed with ALL or AML who were screened according to the study criteria, 40 were recruited for the investigation and 5 were excluded. Exclusions were due to prior antibiotic use (4 patients) and organ dysfunction (1 patient). The median age of these patients was 57 years, with a range of 20 to 86 years. The cohort comprised 23 men and 17 women. The control group consisted of 40 healthy age- and gender-matched individuals (20 men and 20 women), with a median age of 54.5 years and a range of 19 to 83 years. Among the AL patients, 12 had ALL and 28 had AML. The clinical characteristics of the included patients are detailed in **Table 1**.

3.2. Biomarkers for diagnosis of infection in patients with AL during induction treatment

Compared to the control group, patients with AL had higher %CD64$^+$ ($p < 0.001$) (**Fig. 1, A**), CD64 index ($p < 0.001$) (**Fig. 1, B**), CRP levels ($p < 0.001$) (**Fig. 1, C**), and WBC count ($p < 0.008$), while ANC did not differ between the two groups ($p = 0.275$). Moreover, %CD64$^+$ and CD64 index were higher in the infection group compared to the non-infection group ($p < 0.001$) (**Fig. 1, A** and **B**). CRP levels were also higher in AL patients with infection compared to those without it ($p < 0.003$) (**Fig. 1, C**). However, the differences in ANC and WBC count were not statistically significant between the two groups ($p = 0.963$ and $p = 0.943$, respectively). A summary of laboratory measures of the investigated biomarkers among different groups is presented in **Table 2**. Furthermore, %CD64$^+$ showed a positive correlation with CD64 index and CRP ($p = 0.001$) (**Table 3**).

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Table 1. Patient demographics and baseline characteristics.

Variable	Control (n= 40)	Acute Leukemia Patients		P *
		W/ Infection (n=20)	W/o Infection (n=20)	
Age, years	54.50 (19-83)	54 (20-80)	59 (24-86)	0.662
Sex				
Male	20 (50)	14 (70)	9 (45)	0.227
Type of Leukemia				
AML	0 (0)	12 (60)	16 (80)	
ALL	0 (0)	5 (40)	7 (20)	

Data presented as Median (min-max), number (%)
* For comparison between three group
w/, with; w/o, without; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia

Table 2. Key laboratory measures among different groups.

Biomarkers	Control (n= 40)	AL Patients w/o Infection (n= 20)	AL Patients w/ Infection (n= 20)	P *
% CD64+	24.23% ± 1.61	44.5% ± 4.74	75.15% ± 4.17	<0.001
CD64 Index	0.745 (0.2-1.8)	1.585 (0.18-3.5)	3.79 (1.41-4.5)	<0.001
CRP	6.05 (1.8-16.34)	10.31 (3.10-31.5)	24.18 (6.5-80.60)	0.003
ANC	3.37 ± 0.24	3.44 ± 0.29	3.43 ± 0.26	0.96
WBC Count	6.7 (3.20-14.9)	8.6 (3.2-31-2)	8.7 (3.7-32.5)	0.94

Data presented as Median (min-max), Mean ± standard deviation
* For comparison between AL patient's w/ infection and those w/o infection
AL, acute leukemia; w/, with; w/o, without; % CD64+, percentage of CD64+ neutrophils; CRP, C-reactive protein; ANC, absolute neutrophil count; WNC; white blood cell

Table 3. Pearson correlation coefficient between classical biomarkers and CD64 expression.

Biomarkers	% $CD64^+$	CD64 Index	CRP	ANC	WBC
% CD64+	-	0.984 **	0.656 **	- 0.041	0.098
CD64 Index	0.984 **	-	0.665 **	- 0.049	0.073
CRP	0.656 **	0.665 **	-	0.065	0.198
ANC	-0.041	- 0.049	0.065	-	0.500 **
WBC Count	0.098	0.073	0.198	0.500 **	-

** Correlation is significant at 0.01 level (two-tailed)
% CD64+, percentage of CD64+ neutrophils; CRP, C-reactive protein; ANC, absolute neutrophil count; WNC; white blood cell

Table 4. Diagnostic performance of biomarkers in diagnosing infection.

Biomarkers	AUC	95% CI	Cut-off Value	Sensitivity	Specificity	P-value
% CD64+	0.945	0.896 – 0.994	53%	90%	83.3%	<0.001
CD64 Index	0.948	0.901 - 0.994	1.95	90%	86.7%	<0.001
CRP	0.866	0.778 – 0.954	12.3 mg/L	85%	73.3%	<0.001
ANC	0.520	0.377 – 0.663	3.4 × 103/µL	55%	58.3%	0.79
WBC Count	0.560	0.411 – 0.710	9.2 × 103/µL	50%	66.7%	0.42

AUC, area under the curve; % $CD64^+$, percentage of CD64+ neutrophils; CRP, C-reactive protein; ANC, absolute neutrophil count; WBC; white blood cell.

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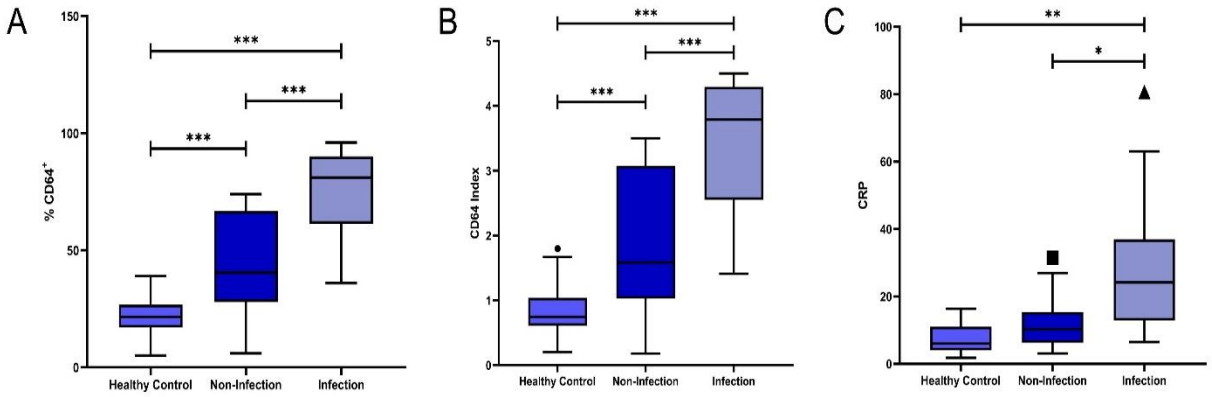


Figure 1. Comparison of % CD64+ (A), CD64 index (B), and CRP (C) among different groups. % CD64+, percentage of CD64+ neutrophils; CRP, C-reactive protein.

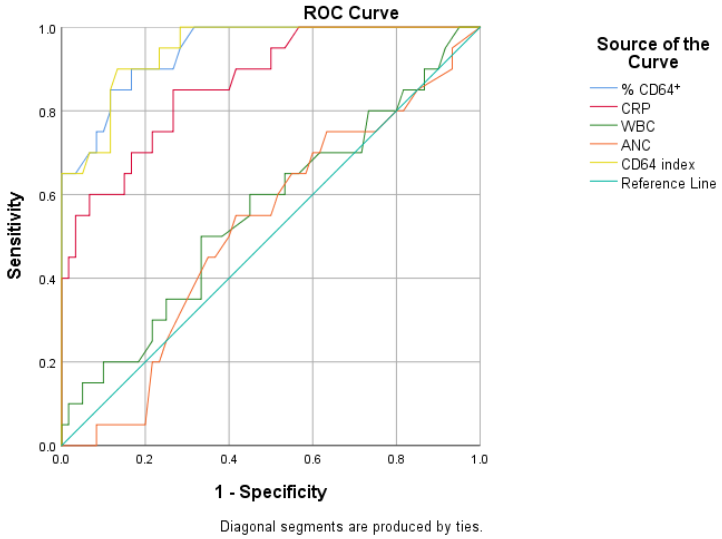


Figure 2. ROC curve for neutrophil CD64 index, % CD64+, CRP level, ANC, and WBC count, ROC, receiver operating characteristic; % CD64+, percentage of CD64+ neutrophils; CRP, C-reactive protein; ANC, absolute neutrophil count; WNC; white blood cell.

3.3. ROC curve and area under the curve (AUC) of CD64, CRP, ANC, and WBC count

Figure 2 shows ROC curves for the investigated biomarkers. The AUC for %CD64$^+$ was 0.945 (95% confidence interval (CI), 0.896–0.994), 0.948 (95% CI, 0.901–0.994) for the CD64 index, 0.866 (95% CI, 0.778–0.954) for CRP levels, 0.560 (95% CI, 0.411–0.710) for WBC count, and 0.520 (95% CI, 0.377–0.683) for ANC ($p < 0.05$) (**Fig. 2** and **Table 4**). At a cut-off value of 46.5%, %CD64$^+$ exhibited a sensitivity of 90% and specificity of 83.3% for detecting infection in patients with AL (**Table 4**). The CD64 index also had a sensitivity of 90%, with a higher specificity of 86.7% at a cut-off value of 1.95 (**Table 4**). The CRP test showed a sensitivity of 85% and specificity of 73.3% at a cut-off value of 12.3 mg/L. For WBC count and ANC, at cut-off values of 9.2 × 10^3/µL and 3.4 × 10^3/µL, respectively, the sensitivities were 50% and 55%, while the specificities were 66.7% and 58.3%, respectively (**Table 4**).

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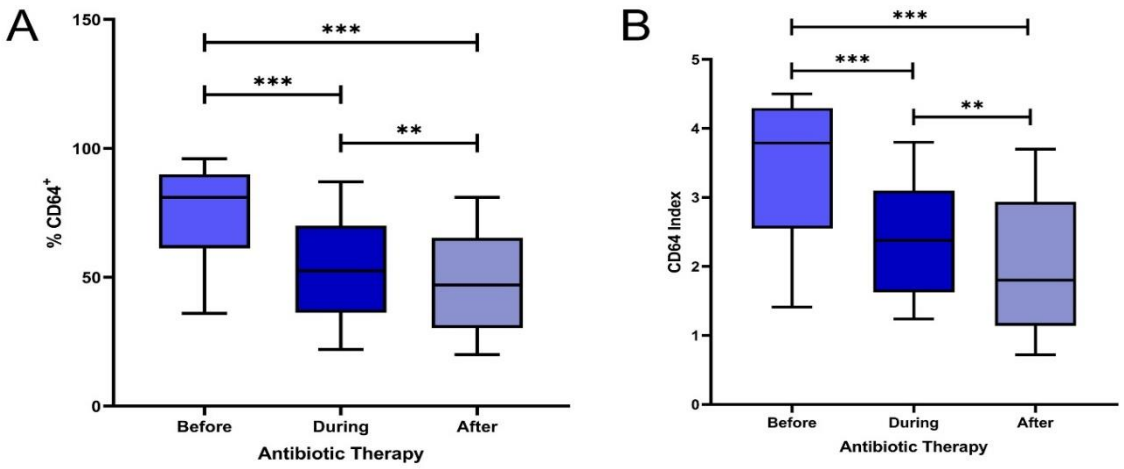


Figure 3. Comparison of % CD64+ (A) and CD64 index (B) among patients with infection before the initiation of antibiotic therapy, on 3rd day of antibiotic therapy and when clinical symptoms of infection resolved. % CD64+, percentage of CD64+ neutrophils.

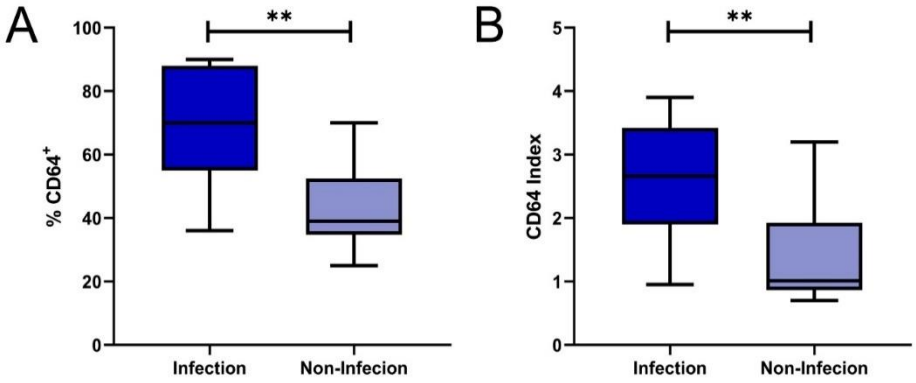


Figure 4. Comparison of % CD64+ (A) and CD64 index (B) among neutropenic patients with and without. % CD64+, percentage of CD64+ neutrophils.

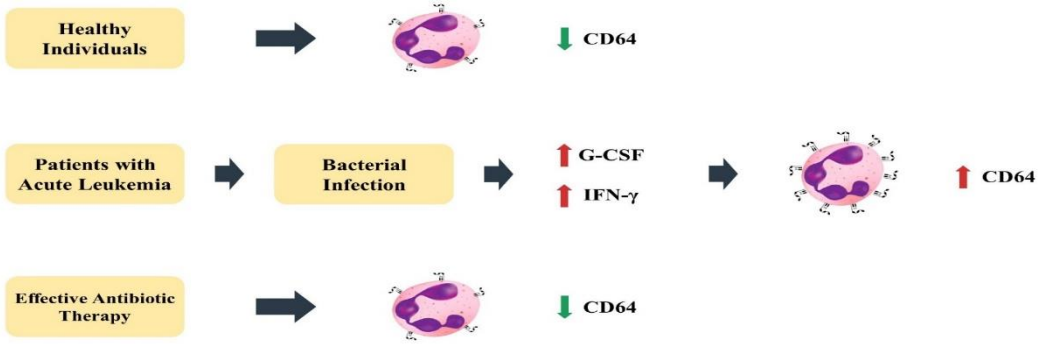


Figure 5. CD64 expression on neutrophils (nCD64) is low in healthy individuals but can be upregulated during bacterial infection by cytokine stimulation. nCD64 levels drop significantly within 72 hours of starting antibiotic therapy.

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3.4. Antibiotic treatment in infection group

The potential utility of the CD64 index and the percentage of $CD64^+$ neutrophils in monitoring antibiotic treatment in AL patients with underlying infections was assessed. Samples were obtained from 20 infected patients before the initiation of antibiotic treatment, on the third day of treatment, and when clinical symptoms of infection resolved. Our results revealed a significant decrease in both the CD64 index and the percentage of $CD64^+$ neutrophils three days after the initiation of antibiotic treatment and upon resolution of clinical symptoms, compared to the pre-treatment values (**Fig. 3**).

3.5. Subgroup analysis

Twenty-five patients with AL (15 with infection and 10 without infection) developed neutropenia during induction therapy. The evaluation of the CD64 index and $\%CD64^+$ in the infection and non-infection groups revealed significant increases in neutropenic patients with underlying infections compared to those without infection ($p < 0.001$) (**Fig. 4**). ROC curve analysis determined the cut-off values for the CD64 index and $\%CD64^+$ in identifying infection in neutropenic patients to be 1.7 and 52%, respectively. Both tests showed a sensitivity of 80% and a specificity of 87%. The AUC values for the CD64 index and $\%CD64^+$ were 0.823 (95% CI: 0.637–1) and 0.877 (95% CI: 0.739–1), respectively.

4. DISCUSSION

CRP, a liver-produced acute-phase protein, is one of the oldest biomarkers, with its discovery dating back to 1930 [19]. It has been shown that CRP can have a sensitivity of 75% and specificity of 67% in distinguishing sepsis from systemic inflammation [20]. Although meta-analyses indicate that CRP has moderately high sensitivity, its specificity is only marginally satisfactory. Elevated CRP levels are associated with various conditions, including cardiovascular diseases, inflammatory malignancies, and burn injuries, which limits its use as a specific biomarker for sepsis [19]. Procalcitonin (PCT), first identified in 1993 as a biomarker for bacterial infection, is the peptide precursor of calcitonin [21]. A study found that CRP and PCT have similar sensitivity profiles for diagnosing sepsis (CRP: 80%; PCT: 80%). However, CRP exhibited notably lower specificity at 61% compared to PCT's 77% [22] . Furthermore, Vassallo et al., in an investigation of PCT and the CRP/PCT ratio in patients with solid tumors, showed that PCT has high sensitivity for indicating sepsis in these patients but lacks specificity. The CRP/PCT ratio improves specificity, offering a more reliable method for detecting infections in patients with solid tumors [23].

Several recent investigations have focused on diagnosing infections in leukemia patients, particularly within the Chinese population [24-28]. Guo et al. studied 100 patients with AL and found that CD64, neutrophil percentage (Neu%), PCT, and CRP had sensitivities of 88%, 82%, 74%, and 70%, respectively, with specificities of 80%, 78%, 82%, and 84% [24]. Another study reported sensitivities for CD64, CRP, PCT, and Neu% of 71%, 85%, 67%, and 60%, respectively, and specificities of 92%, 76%, 89%, and 85% [28]. Our findings align with these studies, showing sensitivities of 90% for both $\%CD64^+$ and CD64 index, and 85% for CRP, with specificities of 83.3%, 86.7%, and 73.3%, respectively (**Fig. 2**). Dai and colleagues also observed elevated levels of CD64 index, CRP, PCT, and neutrophil count in patients with hematological malignancies complicated by infections, which decreased following effective antibiotic treatment [25].

Recently, CD64 has been recognized as a key biomarker for bacterial infections [11, 13, 16, 18, 25, 29]. Neutrophil CD64 overexpression occurs within just 12 hours after the onset of infection and remains elevated for at least 36 hours [30] (**Fig. 5**). Consequently, nCD64 has the potential to be a robust biomarker for the early diagnosis [16].

A recent study involving 160 participants, patients suffering from bacterial infections, particularly those with respiratory tract and bloodstream infections, exhibited significantly elevated CD64 index levels [18]. Similarly, our observations indicate that AL patients with infections have increased levels of the $\%CD64^+$ and the CD64 index compared to those without infection and healthy controls. This pattern correlates with well-established infection biomarkers such as CRP and PCT [13, 18]. Notably, in follow-up investigations with 24 infected patients, the CD64 index decreased shortly after effective antibiotic therapy but remained elevated with ineffective treatment.[18]. We further confirm this observation and provide evidence that, upon successful antibiotic therapy, the initially elevated $\%CD64^+$ and CD64 index were significantly downregulated within 72 hours (**Fig. 5**)

This suggests that CD64 is a superior marker for tracking infections and assessing the efficacy of antibiotic treatment [18]. Additionally, nCD64 increases rapidly in response to cytokine stimulation during infections and its levels drop significantly within 48 hours after the infection is resolved

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[18]. These findings align with our observations, where the CD64 index and %CD64$^+$ decreased in infected patients following antibiotic therapy **(Fig. 2** and **Fig. 3)**.

Notably, both %CD64$^+$ and the CD64 index exhibit distinct cut-off values in the present study, offering high sensitivity and specificity for diagnosing infections in AL patients. A meta-analysis conducted in 2015, which included 8 studies with 1986 patients, investigated the effectiveness of nCD64 for diagnosing sepsis [31]. The pooled sensitivity was 0.76, and specificity was 0.85, concluding that nCD64 is a valuable tool for early diagnosis of sepsis [31]. Subsequent studies have further supported this finding. An updated meta-analysis reported that the CD64 index had a sensitivity of 0.87 and specificity of 0.89 [32]. Additionally, another study found that CD64 index displayed comparable sensitivity (0.87) and notably superior specificity (0.99, 95% CI: 0.92–1.00) compared to seven other biomarkers in detecting systemic infections and sepsis as defined by Sepsis-3 criteria [33]. Our investigation corroborates these findings, showing a sensitivity and specificity for the CD64 index of 90% and 86.7%, respectively **(Fig. 2)**.

We acknowledge several limitations within this investigation. First, the number of enrolled infected patients was limited, which constrained the breadth of our analysis. Future prospective studies with larger cohorts are encouraged. Another limitation is related to our evaluation of the CD64 index and % CD64$^+$ in assessing antibiotic efficacy. Our methodology allowed for measurements only before and after antibiotic therapy, making continuous monitoring throughout the treatment period unfeasible. As a result, these findings should be interpreted with caution. Additionally, this study did not evaluate the source and site of infection in the patients. Focusing on patients with a single pathogen infection could provide more relevant insights. Investigating the performance of the CD64 index and %CD64$^+$ specifically in AL patients with bacterial infections may present a more promising area for further research.

5. CONCLUSION

In summary, CD64 has proven to be an exceptional marker for tracking infections and assessing the effectiveness of antibiotic treatment. Compared to markers like CRP, WBC count, and ANC, CD64 expression demonstrates greater sensitivity and specificity in diagnosing infections in leukemia patients, making it invaluable for timely detection of infections. It shows considerable promise in improving diagnosis of infection and providing a new way to monitor disease progression and evaluate the efficacy of treatment.

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None.

Conflict of interest

The authors declare that they have no competing interests.

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Ethical statement

The study protocol was approved by the Research Ethics Committee of Tehran University of Medical Sciences and was performed in accordance with the Helsinki Declaration. Informed consent was obtained from participants or their legal guardians.

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