Original Article

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Website: https://journals.lww.com/ijhm

DOI: 10.4103/ijh.ijh_103_25

Interleukin-35-driven immune evasion in acute myeloid leukemia: Correlation with circulating (CD3+ CD56+) lymphocyte

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Abstract:

BACKGROUND: Acute myeloid leukemia (AML) is a heterogeneous hematologic malignancy. The altered immunological response in AML is profound, encompassing impaired T-cell proliferation and a perturbed cytokine profile. Immune markers, such as CD3+ CD56+ lymphocytes and interleukin-35 (IL-35), may reflect the immunosuppressive landscape in AML, which helps explain disease burden and treatment response.

OBJECTIVES: This study aimed to evaluate the immunological profiles of AML patients by quantifying CD3+ CD56+ circulating lymphocytes and the serum level of IL-35 in newly diagnosed and treated patients using treatment status and blast cell burden as indicators.

MATERIALS AND METHODS: This is a case–control study conducted on 50 AML patients (25 newly diagnosed and 25 on treatment) and 20 healthy controls. To assess the percentages of CD3+ CD56+ lymphocytes, the flow cytometry technique was used. The enzyme-linked immunosorbent assay technique was used to quantify IL-35 serum levels.

RESULTS: The newly diagnosed patients exhibited a significant reduction in the percentage of CD3+ CD56+ lymphocytes (28.0% ±18.1%) and elevated IL-35 levels (320.0 ± 102.7 pg/mL) compared to controls (15.0% ±7.7% and 208.2 ± 47.6 pg/mL, respectively; $P = 0.001$). The AML patients treated showed a significant increase in the percentage of CD3+ CD56+ lymphocytes (52.3 ± 21.4%) and a reduction in IL-35 levels (263.4 ± 58.7 pg/mL). Additionally, treated patients in remission had a higher percentage of CD3+ CD56+ lymphocytes (58.0% ±18.4%) and lower IL-35 levels (241.1 ± 37.7 pg/mL) compared to nonremission AML patients. A significant negative correlation was observed between the percentage of CD3+ CD56+ lymphocytes and blast cell count ($r = –0.267$, $P = 0.028$), while the IL-35 level showed a significant positive correlation ($r = 0.349$, $P = 0.004$).

CONCLUSION: This study demonstrates that CD3+ CD56+ lymphocytes and IL-35 serve as critical immunological biomarkers in AML, reflecting the balance between anti-tumor immunity and immune suppression. The inverse relationship between these markers and disease burden highlights their prognostic value, with CD3+ CD56+ depletion indicating impaired tumor surveillance and elevated IL-35 signifying a suppressive microenvironment.

Keywords:

Acute myeloid leukemia, CD3+ CD56+ lymphocytes, flow cytometry, immunophenotyping, interleukin-35

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Submission: 19-08-2025
Revised: 22-09-2025
Accepted: 22-09-2025
Published: 31-10-2025

Introduction

Acute myeloid leukemia (AML) is a form of cancer characterized by infiltration of the proliferative clonal poorly or abnormally differentiated hematopoietic to the bone

How to cite this article: Ashoor ZF, Mtashar BA, Al-Shawk RS. Interleukin-35-driven immune evasion in acute myeloid leukemia: Correlation with circulating (CD3+ CD56+) lymphocyte. Iraqi J Hematol 2025;14:278-83.

marrow, blood, and other tissues.[1] Classification of French–American–British for AML subtypes indicates M4 (acute myelomonocytic leukemia) and M5 (acute monocytic leukemia), which exhibit prominent monocytic differentiation and are associated with distinct molecular and immunophenotypic features, as well as different responses to chemotherapy.[2,3] Due to disease progression and therapeutic resistance, the immunological modulation in AML has gained interest recently.[4] Immune surveillance of tumor cells is the key defense point against tumor development. However, successful immune evasion of complex hematological malignancies (AMLs) is a hallmark of cancer development, though AML blasts and leukemic stem cells suppress the host immune response.[5] Natural killer T (NKT) cells are a professional and unique subset of T-lymphocytes expressing both T-cell markers (CD3) and natural killer markers (CD56), influencing a rapid antitumor immune response through the production of pro-inflammatory cytokines and cytolytic activity, and positioned as essential players and targets for immunotherapies.[6] A reduced number of functional phenotypes is associated with poor prognosis, supporting highlighting the data on NKT cells in distinct AML subtypes, such as M4 and M5.[7]

Interleukin-35 (IL-35) is a cytokine that belongs to the IL-12 family and is considered an immunosuppressive mediator with two subunits of p35 and Epstein–Barr virus-induced gene 3, contributing to the regulatory milieu through T regulatory (reg) cells induction and encouraging pro-tumor microenvironments. The primary secretion was implicated by both T reg and B reg cells, leading to the downregulation of effector T-cell response, enhancing tumor evasion.[8,9] Investigating the secretion of this cytokine in AML patients could help explain its role in disease prognosis and is associated with high blast burden, chemoresistance, or relapse.[10,11] Previous studies have reported altered cytokine profiles in gastrointestinal malignancies, highlighting the role of Th17-related cytokines in local immune dysregulation and disease progression, suggesting a significant role for these cytokines in disease burden and treatment responses.[12] The interplay between IL-35 levels and the frequency of CD3+ CD56+ circulating lymphocytes in AML patients remains poorly understood. Furthermore, the impact of disease status, specifically the distinction between newly diagnosed and treated patients, as well as AML subtyping for understanding remission achievement, has not been thoroughly characterized. This study aimed to analyze the percentage of CD3+ CD56+ lymphocytes cells and the serum concentration of IL-35, reflecting complementary immunological biomarkers, in a well-defined group of AML patients (newly diagnosed and patients on treatment). This analysis may elucidate the prognostic relevance of these biomarkers, considering their potential correlations as immunotherapeutic targets in AML.

Materials and Methods

Study population and design

This is a case–control study conducted at the National Center of Hematology, Mustansiriyah University, between February 2025 and June 2025. A total of 50 patients diagnosed by expert hematologists with AML were enrolled. The study consisted of 31 males and 19 females, of whom 25 were newly diagnosed patients and 25 patients who had undergone induction therapy. A control group of 20 healthy individuals was matched to the patient group. The eligibility criteria required patients between 20 and 60 years of age, diagnosed with AML, with pretreatment bone marrow aspirate (BMA) samples available for immunophenotypic profiling. Individuals younger than 20 years or receiving alternative treatment protocols were excluded.

Diagnostic and hematological evaluation

Clinical records were reviewed to extract baseline diagnostic data, including complete blood count (CBC), peripheral blood smear, and BMA morphology. Multicolor flow cytometry was carried out for immunophenotyping targeting a panel of myeloid-associated markers, including: CD7, CD11c, CD13, CD14, CD19, CD33, CD34, CD45, CD64, CD117, and myeloperoxidase. Molecular and cytogenetic analyses, including NPM1 and FLT3 mutation tests, were performed.

Sample collection and flow cytometry

Peripheral blood (5 mL) was collected from each participant using standard sterile venipuncture technique and divided equally into two ethylenediaminetetraacetic acid-treated tubes. One aliquot was for CBC, and the second for flow cytometric analysis. CD3+ CD56+ lymphocytes were quantified using an 8-color BD FACSCanto™ II cytometer. The antibody panel included CD45 (V500), CD3 (V450), and CD56 (APC), from Santa Cruz Biotechnology, UK.

The protocol of sample preparation adhered to the stain-lyse-wash. Briefly, 100 µL of whole blood was incubated with 5 µL of each antibody for 15 min at room temperature in the dark. The lysis of red cells was achieved using 2 mL of 1X RBC lysis buffer for 10 min, followed by two washes (2 mL wash buffer for 2300 rpm, 5 min). Resuspension of the cell pellet was done in 0.5 mL of 1X buffer for fixation to be analyzed immediately. A minimum of 100000 events were acquired per sample. Sequential selection of a viable $CD45^{+}$ is a gating strategy, followed by identification of the CD3+ CD56+ cell subset within the lymphocyte population [Figures 1-4].

Quantification of interleukin-35 levels

Serum concentrations of IL-35 were measured using a commercially available enzyme-linked immunosorbent

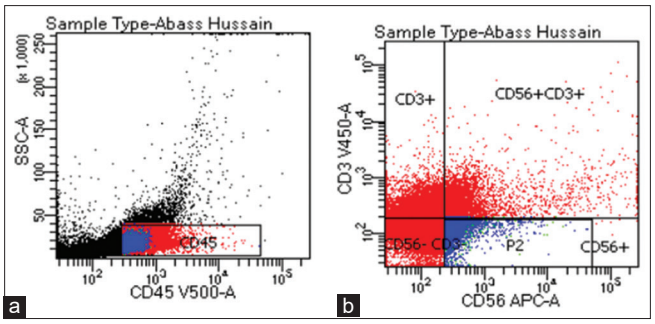

Figure 1: Flow cytometry analysis of a newly diagnosed acute myeloid leukemia patient: (a) Dot plot to identify CD45+, (b) dot plot to identify CD3+ CD56+ population

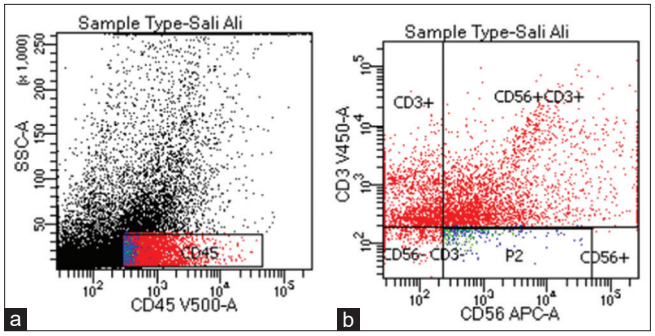

Figure 3: Flow cytometry analysis of acute myeloid leukemia patients on treatment: (a) Dot plot to identify CD45+, (b) dot plot to identify CD3+ CD56+ population

assay kit (Sunlong Biotech, China), according to the manufacturer's instructions. Serial dilutions of the standard were added to the designated wells, while test samples were diluted 1:5 using sample buffer. Plates were incubated at 37°C for 30 min, washed five times, and incubated with horseradish peroxidase (HRP)-conjugated reagent. Chromogenic substrate was added, and after a final 15-min incubation in the dark, the reaction was terminated with the stop solution, and the absorbance was read at 450 nm using a microplate reader.

Ethical approval

This study was conducted in accordance with the principles outlined in the Declaration of Helsinki. Before specimen collection, all participants provided verbal consent and analytical approval. The protocol was reviewed and approved by the local ethics committee of the Microbiology Department at the Medical College of Mustansiriyah University, numbered 46 for the academic year 2024.

Statistical analysis

Statistical analysis was conducted using the SPSS software package (IBM Corp., 2021). IBM SPSS Statistics for Windows, Version 26.0. (IBM Corp., Armonk, NY, USA). Demographic data were characterized using descriptive statistics, mean, standard deviation, ANOVA

Population	#Events	%Parent	%Total
All Events	100,000	####	100.0
CD45	53,928	53.9	53.9
CD3+	16,923	31.4	16.9
CD56+CD3+	6,273	11.6	6.3
CD56- CD3-	25,585	47.4	25.6
CD56+	5,147	9.5	5.1

Figure 2: Hierarchy analysis data from cells stained with anti-CD45, anti-CD3, and anti-CD56 for acute myeloid leukemia patients on treatment

Population	#Events	%Parent	%Total
All Events	56,825	####	100.0
CD45	5,527	9.7	9.7
CD3+	2,024	36.6	3.6
CD56+CD3+	2,716	49.1	4.8
CD56- CD3-	446	8.1	0.8
CD56+	341	6.2	0.6

Figure 4: Hierarchy analysis data from cells stained with anti-CD45, anti-CD3, and anti-CD56 for newly diagnosed acute myeloid leukemia patients

test, independent *t*-test, ratio, and Pearson correlation (*r*). Estimated $P < 0.05$ was considered statistically significant.

Results

The study included 50 AML patients, forming two equal groups: one group of 25 patients was newly diagnosed and treatment-naive, and the other 25 patients were already on treatment, specifically the (3 + 7) regimen protocol.

Age and sex distribution

The mean age of the newly diagnosed AML patient group was 40.4 ± 15.4 years, whereas the mean age of the treated AML patients was 37.1 ± 13.5 years. The control group had a mean age of 40.6 ± 13.4 years. The difference in age between the two groups was not statistically significant, as indicated by $P = 0.629$. In terms of sex distribution, the patient group consisted of 31 males and 19 females, whereas the control group included 13 males and seven females [Table 1].

In the current study of 25 newly diagnosed AML patients, the average white blood cell (WBC) count was, with a mean hemoglobin (Hb) of and a mean platelet count of. Blast cells were detected in 59.7% of these patients. In contrast, AML patients undergoing treatment had a WBC count of, a mean Hb of, and a mean platelet count of, with blast cells at 3.9%. The comparison of hematological parameters among newly diagnosed AML patients, treated AML patients, and healthy controls revealed statistically significant differences across all groups (for all parameters), as shown in Table 2.

The study compared parameters between AML patients and a control group. The results showed significant differences in the percentages of CD3+ CD56+ lymphocytes and IL-35 levels across the groups. For the percentages

of CD3+ CD56+ lymphocytes, the newly diagnosed AML patients had a mean percent of 28 ± 18.1, which increased to 52.3 ± 21.4 in the on-treatment group, while the control group had a significantly lower mean of 15.01 ± 7.7 (P = 0.001). Similarly, IL-35 serum levels were highest in newly diagnosed AML patients (320 ± 102.7 pg/mL), decreased in the on-treatment group (263.4 ± 58.7 pg/mL), and were lowest in the control group (208.2 ± 47.6 pg/mL), with the differences being statistically significant (P = 0.001). These findings indicate that both the percentages of CD3+ CD56+ lymphocytes and IL-35 levels vary significantly between AML patients and controls, as well as between newly diagnosed AML and patients on treatment [Table 3].

Patients in remission exhibited higher percentages of CD3+ CD56+ lymphocytes (58.0 ± 18.4%) compared to those not in remission (39.7 ± 23.3%). Conversely, IL-35 levels were significantly lower in the remission group (241.1 ± 37.7 pg/mL) versus nonremission patients (308.8 ± 72.1 pg/mL) [Table 4].

The analysis revealed significant correlations between key parameters in AML patients. Percentages of CD3 + CD56 + lymphocytes showed a negative correlation with blast cell count (R = −0.267, P = 0.028), suggesting that higher percentages of CD3+ CD56+ lymphocytes were associated with lower blast cell numbers. In contrast, no significant correlation was found between percentages of CD3+ CD56+ lymphocytes and IL-35 levels (R = -0.039, P = 0.75). However, IL-35 levels demonstrated a significant positive correlation with blast cell count (R = 0.349, P = 0.004), indicating that higher IL-35 concentrations were associated with increased blast cell numbers. These findings highlight distinct relationships between immune markers (percentages of CD3+ CD56+ lymphocytes and IL-35) and disease burden (blast cells) in AML [Table 5].

Discussion

The current study demonstrated that CD3+ CD56+ circulating lymphocytes and IL-35 serum levels are significantly modulated in patients with AML. Their levels reflect both disease activity and response to treatment. This addresses the point towards the association between these immunological markers and treatment status and blast burden, making them potential prognostic values.

The altered immunological response in AML is profound, including impaired T-cell proliferation and cytokine profile, which affects the ratio of immune cell population toward an increased suppressive landscape.[13] This effect is represented by the suppression of effector T-cell subsets and aberrant CD3+ CD56+ lymphocytes, which are needed for tumor surveillance and immune homeostasis.[14] In particular, CD3+ CD56+ lymphocytes, which have been categorized as cytokine-induced killer cells (CIKs), serve as a key player in the anti-tumor immune response through their ajor Histocompatibility Complex non- MHC-restricted cytotoxicity, bridging

Table 1: Age and sex distribution between patients with acute myeloid leukemia groups and control group

Parameters	AML patients (*n*=50)		Controls (*n*=20), *n* (%)	*P*
	Newly diagnosed (*n*=25), *n* (%)	On treatment (*n*=25), *n* (%)		
Age, mean±SD	40.4±15.4	37.1±13.5	40.6±13.4	0.629
Sex				
Male	15 (60)	16 (64)	13 (65)	0.84
Female	10 (40)	9 (36)	7 (35)	

AML=Acute myeloid leukemia, SD=Standard deviation

Table 2: Differences in hematologic profiles of acute myeloid leukemia patients versus the control group

Parameters	Patients (*n*=50)		Controls (*n*=20)	*P*
	Newly diagnosed (*n*=25)	On treatment (*n*=25)		
WBC (×10^9/L), mean±SD	55.4±53.2	1.6±1.5	6.6±0.75	<0.001
Platelets (×10^9/L), mean±SD	41.3±24.5	37.3±28.5	246.6±56.3	<0.001
Hb (g/dL), mean±SD	8.2±1.8	7.8±1.4	13.1±1.4	<0.001
Blast cells	59.7±31.5	3.9±4.7	0	<0.001

ANOVA test significant at the 0.01. WBC=White blood cell, SD=Standard deviation, Hb=Hemoglobin

Table 3: Comparison of CD3+ CD56+ lymphocytes % and interleukin-35 levels among acute myeloid leukemia patient groups and control group

Parameters	AML patients (*n*=50)		Control (*n*=20), mean±SD	*P*
	Newly diagnosed (*n*=25), mean±SD	On treatment (*n*=25), mean±SD		
CD3+ CD56+ lymphocytes (%)	28±18.1	52.3±21.4	15.01±7.7	0.001**
IL-35 (Pg/mL)	320±102.7	263.4±58.7	208.2±47.6	0.001**

**Significant at the 0.01 level (two-tailed). AML=Acute myeloid leukemia, SD=Standard deviation, IL - 35=Interleukin-35

Table 4: Comparison of CD3+ CD56+ lymphocytes % and interleukin-35 levels between acute myeloid leukemia patients on treatment

Parameters	AML-treated patients (*n*=25)	
	Remission (*n*=17), mean±SD	Not in remission (*n*=8), mean±SD
CD3+ CD56+ lymphocytes (%)	58.0±18.4	39.7±23.3
IL-35 (Pg/mL)	241.1±37.7	308.8±72.1

AML=Acute myeloid leukemia, SD=Standard deviation, IL - 35=Interleukin-35

Table 5: Correlation between CD3+ CD56+ lymphocytes %, interleukin-35, and blast cells

Parameters	Blast cells	IL-35
CD3+ CD56+ lymphocytes (%)		
r	−0.267	−0.039
P	0.028*	0.75
IL-35 (Pg/mL)		
r	0.349	
P	0.004**	

*Correlation is significant at the 0.05 level (two-tailed), **Correlation is significant at the 0.01 level (two-tailed). *r*=Person correlation, IL - 35=Interleukin-35

the gap between the innate and adaptive immune responses, via activating NKG2D and DNAM-1 receptors and releasing tumor necrosis factor-α and interferon-γ, thereby modulating the tumor microenvironment toward an anti-tumor response.[15] The present study demonstrated that the newly diagnosed had decreased CD3+ CD56+ circulating lymphocytes compared to healthy controls, while treated individuals had recovered percentages of these cells, which is in agreement with others who found that the remitted patients had a restoration in the NKT cells population, indicating their potential role as an antitumor effect.[16] An engineered CAR-iNKT cell has been studied as a potent therapy in preclinical trials for anti-AML activity, showing massive cytotoxicity, reshaping the bone marrow microenvironment, and achieving remission.[17] Prior studies confirmed that AML patients exhibit reduced CD3+ CD56+ populations with compromised function compared to healthy controls.[18] Our findings are consistent with previous studies and demonstrate a significant restoration of CD3+ CD56+ lymphocytes during remission, suggesting that this recovery mirrors findings from treatment contexts in other cancers, where reconstitution of effector populations correlates with improved prognosis.

Regarding the therapeutic implications of CIKs, a novel subgroup of immune effector cells consisting of CD3+ CD56+ NKT cells has gained attention in immunology. An *in vitro* study demonstrated that these cells exhibited potent cytotoxicity and a low risk of ocular graft-versus-host disease, making them a potential target for allogeneic application.[19] In other studies, these cells have shown potent anti-leukemic activity, enhanced bone marrow homing, and modulating suppressive niches in AML models.[15]

IL-35, produced primarily by regulatory T-cells, suppresses immune effector function through the inhibition of Th1 responses, inducing Treg expansion, and downregulation of cytotoxic lymphocyte function through the signaling of 12Rβ2/gp130 heterodimer and activation of STAT1 and STAT3 pathway predisposing for anti-inflammatory feedback meili which augment the pro-tumor microenvironment facilitating tumor escape,[20,21] and is elevated in various cancers, where it correlates with disease severity. Increased serum IL-35 levels in AML cases have been shown to correlate with higher blast counts, chemoresistance, and a poor prognosis.[11] Moreover, IL-35 enhances the immunosuppressive networks in the leukemic microenvironment through the promotion and recruitment of myeloid-derived suppressor cells and regulatory B-cells.[21,22] The findings of this study align with these observations, which showed an elevated IL-35 serum level at diagnosis, followed by a decrease posttreatment, and a positive correlation with blast percentages, supporting IL-35's role as a biomarker that reflects immunosuppressive effect and contributes to AML pathophysiology by promoting Treg expansion leading to cytotoxic lymphocytes suppression. The inverse correlation of the frequency of CD3+ CD56+ lymphocytes and the positive correlation of IL-35 with blast count underscore the dynamic immunological balance as the leukemic burden decreases, immune surveillance is activated, and suppressive cytokines are diminished, providing these markers with a tracking effect for disease progression and treatment responses.

Conclusion

This study demonstrates that CD3+ CD56+ lymphocytes and IL-35 can serve as critical immunological biomarkers in AML, reflecting the balance between anti-tumor immunity and immune suppression. The inverse relationship between these markers and disease burden highlights their potential prognostic value, with CD3+ CD56+ depletion indicating impaired tumor surveillance and elevated IL-35 signifying a suppressive microenvironment.

Study limitations

This study is limited by its sample size, particularly for the remission subtype group of patients, which may affect its generalizability. A longitudinal follow-up is recommended for measuring IL-35. Evaluating immune checkpoint molecules was not assessed in this study, which are the key regulators of immune exhaustion in AML. Future studies could improve these points and

clarify the mechanistic role of CD3+ CD56+ lymphocytes and IL-35 in the pathogenesis of AML.

Acknowledgment

We sincerely thank the physicians and laboratory staff of the Baghdad Medical City, National Center of Hematology, for their invaluable support and contributions, which were instrumental in the successful completion of this study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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