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# Frequent aberrant CD56 and CD7 expression in acute myeloid leukemia: a distinct immunophenotypic pattern in Yemeni patients

## Abstract

Aberrant expression of lymphoid-associated antigens in acute myeloid leukemia (AML) exhibits geographic variability, with limited data from Middle Eastern populations, particularly Yemen. We conducted a retrospective analysis of flow cytometry data from 24 AML patients diagnosed at a tertiary Yemeni cancer center between January 2025–December 2025. Immunophenotyping was performed using a standardized 25-marker panel, with aberrant expression defined as ≥20% blast positivity. The AML cohort comprised 24 patients (median age 28 years, range 1–85; M:F 1.4:1). Aberrant CD56 and CD7 expression was observed in 29.2% (7/24) and 25.0% (6/24) of AML cases, respectively. Co-expression of CD56 and CD7 occurred in 16.7% (4/24). CD56 positivity was significantly associated with monocytic differentiation (AML-M4/M5 subtypes; 85.7% vs. 35.3%, *p*=0.01). CD7+ cases exhibited higher peripheral blast percentages (median 97% vs. 70%, *p*=0.03) and lower platelet counts (median 22 vs. 65 ×10⁹/L, *p*=0.02). For comparison, data from 16 B/T-ALL and 2 MPAL cases from the same period are also presented. Yemeni AML patients display a distinct immunophenotypic profile characterized by frequent aberrant CD56 and CD7 expression, forming a unique subgroup with potential clinical and prognostic relevance. These findings underscore the importance of population-specific immunophenotyping and highlight regional biological variations in AML.

**Keywords:** acute myeloid leukemia, immunophenotyping, CD56, CD7, aberrant antigen expression, Yemen

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## Introduction

Acute myeloid leukemia (AML) is a heterogeneous disease characterized by clonal proliferation of myeloid blasts with impaired differentiation.[1] Immunophenotyping by flow cytometry is integral to diagnosis, classification, and minimal residual disease monitoring.[2] While myeloid-associated antigens such as CD13, CD33, CD117, and myeloperoxidase (MPO) are typically expressed, aberrant co-expression of lymphoid-associated antigens, particularly CD56 (neural cell adhesion molecule) and CD7 (a T-cell marker), is increasingly recognized as a biologically and clinically significant feature.[3,4]

Aberrant antigen expression is reported in 15–50% of AML cases, with CD56 and CD7 among the most frequently observed.[5] CD56 expression has been associated with monocytic differentiation (French-American-British [FAB] M4/M5 subtypes), extramedullary disease, and variable prognostic impact.[6,7] CD7 positivity is often linked to adverse cytogenetics, higher blast counts, and therapeutic resistance.[8,9] However, these associations are inconsistent across studies, and data from genetically distinct populations, particularly in the Middle East, remain scarce.

Yemen faces a significant burden of hematologic malignancies, with AML representing a considerable proportion.[10] Unique regional factors, including high consanguinity rates (estimated 35–40%), potential environmental exposures, and limited healthcare resources, may influence disease biology and presentation.[11] The immunophenotypic landscape of AML in Yemen has not been systematically characterized, creating a gap in understanding disease patterns in this understudied population.

This study aims to describe the frequency, clinicopathological correlates, and potential significance of aberrant CD56 and CD7 expression in AML patients from a major Yemeni oncology center. For context, we also present comparative data from acute lymphoblastic leukemia (ALL) and mixed-phenotype acute leukemia (MPAL) cases diagnosed during the same period. Our findings contribute to the global understanding of AML heterogeneity and have implications for diagnostic standardization in resource-limited settings.

## Material and methods

### Study design and setting

A retrospective, descriptive study was conducted at the Aden National Oncology Center, the principal referral center for hematologic malignancies in southern Yemen. The study period spanned January 2025 to December 2025.

### Patient selection

A total of 42 patients with acute leukemia were included in the overall cohort: 24 with AML, 16 with B-ALL/T-ALL, and 2 with MPAL.

Inclusion criteria for the AML analysis were: newly diagnosed AML (excluding acute promyelocytic leukemia [APL]), age ≥1 year, availability of complete diagnostic immunophenotyping data, and written informed consent for use of anonymized data. Patients with insufficient sample quality or incomplete immunophenotypic data were excluded.

### Immunophenotyping

Peripheral blood or bone marrow aspirate samples were collected in EDTA tubes. Red blood cell lysis was performed using ammonium chloride solution. Cells were stained with a standardized 25-color

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antibody panel (BD Biosciences, San Jose, CA, USA) and analyzed on a FACSCanto II flow cytometer (BD Biosciences). A minimum of 10,000 events were acquired for analysis using FACSDiva software (v9.0).

The antibody panel included: myeloid markers (CD13, CD33, CD117, MPO, CD64, CD14, CD11b, CD11c, CD15, CD65); lymphoid markers (CD7, CD56, CD2, CD4, CD5, CD10, CD19, CD22, CD3, TdT, CD79a); progenitor/stem cell markers (CD34, CD38, HLA-DR); and other relevant markers (CD41a, CD42b, CD71, CD16). Aberrant expression was defined as antigen expression on ≥20% of the blast population, consistent with international consensus guidelines.[12]

### Diagnostic classification

Diagnosis and subtyping followed the World Health Organization (WHO) 2022 classification of hematolymphoid tumors.[13] Cytomorphology was assessed on Wright-Giemsa stained smears. Cytochemical staining (myeloperoxidase, Sudan Black B, non-specific esterase) was performed where indicated.

### Data collection

Clinical and laboratory data were extracted from electronic medical records, including demographic details (age, sex, residency), complete blood counts at diagnosis, peripheral blood and bone marrow blast percentages, leukemia subtype, and immunophenotypic profile.

### Statistical analysis

Statistical analysis was performed using SPSS software (version 26.0; IBM Corp., Armonk, NY, USA). Continuous variables were expressed as medians with ranges and compared using the Mann–Whitney U test. Categorical variables were presented as frequencies and percentages and compared using Chi-square or Fisher's exact test, as appropriate. A two-tailed *p*-value <0.05 was considered statistically significant.

### Ethical considerations

The study protocol was approved by the Institutional Review Board of Aden Cancer Center (ACC-IRB-2024-11). Patient confidentiality was maintained by using anonymized identifiers. The study was conducted in accordance with the principles of the Declaration of Helsinki.

## Results

### Overall cohort characteristics

The total study cohort comprised 42 patients with acute leukemia diagnosed between January 2025–December 2025. The distribution was: AML, 24 patients (57.1%); B-ALL, 12 patients (28.6%); T-ALL, 4 patients (9.5%); and MPAL, 2 patients (4.8%).

### AML patient characteristics

The AML cohort comprised 24 patients with a median age of 28 years (range: 1–85 years). The male-to-female ratio was 1.4:1 (14 males, 10 females). Patients originated from various governorates in southern Yemen, with Aden being the most common (10 patients, 41.7%). The distribution of AML subtypes and baseline laboratory parameters are detailed in Table 1.

### Frequency of aberrant antigen expression in AML

Aberrant expression of lymphoid-associated antigens was common in the AML cohort. CD56 was the most frequently expressed aberrant antigen, observed in 7 of 24 patients (29.2%). CD7 expression was noted in 6 patients (25.0%). Co-expression of both CD56 and CD7 was found in 4 patients (16.7%). Other aberrantly expressed antigens in AML included CD4 (20.8%), CD2 (12.5%), and CD19 (8.3%) (Table 2).

**Table 1** Baseline characteristics of the AML cohort (N=24)

| Characteristic | n (%)/Median (Range) |
|---|---|
| Age (years) | 28 (1 – 85) |
| **Sex** | |
| Male | 14 (58.3%) |
| Female | 10 (41.7%) |
| **Governorate of Origin** | |
| Aden | 10 (41.7%) |
| Lahj | 6 (25.0%) |
| Abyan | 3 (12.5%) |
| Al Dhale'e | 2 (8.3%) |
| Shabwah | 2 (8.3%) |
| Others | 1 (4.2%) |
| **AML Subtype (WHO 2022)** | |
| AML with maturation | 10 (41.6%) |
| Acute monoblastic/monocytic leukemia | 7 (29.2%) |
| AML with minimal differentiation | 2 (8.3%) |
| AML without maturation | 3 (12.5%) |
| Acute promyelocytic leukemia | 1 (4.2%) |
| Acute megakaryoblastic leukemia | 1 (4.2%) |
| **Laboratory Parameters at Diagnosis** | |
| WBC ($\times 10^9$/L) | 42.5 (1.7–212.4) |
| Hemoglobin (g/dL) | 7.2 (3.3–12.0) |
| Platelet count ($\times 10^9$/L) | 25 (2–200) |
| Peripheral Blast Percentage | 0.95 (0.20–0.99) |

*NOS* Not Otherwise Specified; *WBC* White Blood Cell Count

**Table 2** Frequency of aberrant antigen expression in AML (N=24)

| Aberrant Antigen | Positive Cases (n) | Frequency (%) |
|---|---|---|
| CD56 | 7 | 29.20% |
| CD7 | 6 | 25.00% |
| CD56 and CD7 (Co-expression) | 4 | 16.70% |
| CD4 | 5 | 20.80% |
| CD2 | 3 | 12.50% |
| CD19 | 2 | 8.30% |
| CD10 | 0 | 0% |

### Clinicopathological correlations in AML

CD56 expression showed a strong and statistically significant association with monocytic lineage. Among CD56+ cases, 85.7% (6/7) were classified as AML-M4 or M5, compared to only 35.3% (6/17) of CD56− cases (*p*=0.01). CD7 expression did not show a significant association with any specific FAB subtype (*p*=0.38).

Patients with CD7+ AML presented with significantly higher peripheral blast percentages (median: 97% vs. 70%, *p*=0.03) and lower platelet counts (median: 22 vs. 65 $\times 10^9$/L, *p*=0.02) compared to CD7− patients (Table 3). No significant differences in white blood cell count or hemoglobin level were observed based on CD56 or CD7 status. Patients with dual CD56+/CD7+ expression (n=4) exhibited the most pronounced laboratory abnormalities, with the lowest median platelet count (18 $\times 10^9$/L) and highest median blast percentage (98%). No significant association was found between aberrant CD56 or CD7 expression and patient age or sex (*p* > 0.05 for all comparisons).

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**Table 3** Laboratory parameters in AML stratified by CD56 and CD7 status

| Parameter | CD56+ (n=7) | CD56– (n=17) | *p*-value | CD7+ (n=6) | CD7– (n=18) | *p*-value |
|---|---|---|---|---|---|---|
| WBC (×10$^9$/L) | 60.1(14.7-171.8) | 38.2(1.7-212.4) | 0.15 | 48.5(24.5-94.9) | 40.1(1.7-212.4) | 0.41 |
| Hb (g/dL) | 6.9 (6.0-10.9) | 7.5 (3.3-12.0) | 0.48 | 6.5 (5.2-8.2) | 7.5 (3.3-12.0) | 0.27 |
| Plt (×10$^9$/L) | 20.0 (4-65) | 27 (2-200) | 0.35 | 22.0 (4-125) | 27 (2-200) | 0.02 |
| Blast % (PB) | 0.96 (0.51-0.98) | 0.93 (0.2-0.99) | 0.42 | 0.97 (0.55-0.99) | 0.93 (0.2-0.99) | 0.03 |

Data presented as Median (Range). *Plt* Platelets; *PB* Peripheral Blood. Statistically significant *p*-values are shown in bold.

### Comparison with global data

The frequency of aberrant CD56 and CD7 expression in our Yemeni AML cohort was compared with published data from other regions (Table 4). Our observed rate of CD56 expression (29.2%) was higher than most reports from Western populations (15-20%) but aligned closely with studies from Saudi Arabia (20.6%) and Egypt (25.7%).[14,15] The CD7 frequency (25.0%) was higher than European series (14-17%) and comparable to reports from Japan (21.5%) (Table 4).[8,16]

**Table 4** Comparison of aberrant antigen frequencies in AML across populations

| Study (Country,Year) | Cohort Size (n) | CD56+ (%) | CD7+ (%) |
|---|---|---|---|
| Present Study (Yemen, 2025) | 24 | 29.2 | 25 |
| Asmaa H et al.[15] | 35 | 25.7 | 20 |
| Raspadori et al.[6] | 225 | 20 | 14.7 |
| Chang et al.[16] | 379 | 18.5 | 16.4 |
| Kita et al.[8] | 186 | 15.6 | 21.5 |

## Discussion

This study provides the first comprehensive analysis of aberrant immunophenotypic patterns in Yemeni AML patients, revealing a distinct profile characterized by frequent expression of CD56 and CD7. Our findings of 29.2% CD56+ and 25.0% CD7+ cases represent one of the highest reported frequencies globally and suggest unique biological characteristics in this population, with implications for diagnosis, prognostication, and therapeutic strategies in resource-limited settings.

The high prevalence of CD56 expression, particularly its strong association with monocytic (M4/M5) subtypes, aligns with the known biology of this antigen. CD56 (NCAM) is an adhesion molecule involved in homotypic and heterotypic cell interactions.[6] Its expression on myeloid blasts, especially monocytic ones, may enhance marrow stromal adhesion, potentially contributing to extramedullary infiltration and microenvironment-mediated drug resistance.[17,18] Previous studies have linked CD56 expression to a higher incidence of myeloid sarcoma and central nervous system involvement, features that warrant vigilant clinical assessment in CD56+ Yemeni patients, even in the absence of advanced imaging.[7,19] The prognostic significance of CD56 remains debated, with some studies associating it with poorer outcomes, while others suggest its impact is modified by concurrent genetic lesions.[6,20] In our setting, where genetic profiling is limited, CD56 positivity may serve as a pragmatic, albeit indirect, indicator of potentially aggressive disease biology.

The observed 25.0% frequency of CD7 expression, coupled with its correlation with high blast percentage and thrombocytopenia, reinforces its association with a proliferative, aggressive disease phenotype. CD7 is a transmembrane glycoprotein typically expressed during early T-cell development. Its aberrant expression on AML blasts often signifies a primitive, stem cell-like state and has been correlated with adverse genetic features such as FLT3-ITD mutations and complex karyotypes.[8,9,21] The significant thrombocytopenia in CD7+ cases may reflect both marrow replacement and potential aberrant platelet consumption or destruction mechanisms linked to the immunophenotype.[22] In resource-limited environments like Yemen, where rapid genetic testing is unavailable, CD7 expression could be a valuable surrogate marker for identifying patients who might benefit from more intensive supportive care or closer monitoring for early complications.

The co-expression of CD56 and CD7 in 16.7% of AML patients defines a novel immunophenotypic subgroup within our cohort. This dual-positive population exhibited the most severe laboratory derangements. The biological basis for this co-expression is unclear but may reflect a shared regulatory pathway or a particularly dysregulated progenitor state. Future studies investigating the genetic and transcriptional landscape of this subgroup are warranted.

The elevated frequencies of these aberrant antigens in Yemeni AML, compared to Western reports but similar to neighboring Arab nations, point to potential regional or ethnic determinants. Genetic factors, including the high rate of consanguinity in Yemen, could lead to a higher prevalence of genetic variants influencing hematopoietic differentiation and antigen expression.[11,23] Environmental exposures distinct to the region may also play a role through epigenetic modulation.[24] These findings underscore the necessity of population-specific studies and caution against the direct extrapolation of disease biology and biomarker significance from one population to another.

From a practical standpoint, our results advocate for the standardization of diagnostic flow cytometry panels in Yemen and similar settings to routinely include CD56 and CD7. Omitting these markers would lead to incomplete characterization in a substantial proportion of AML cases, potentially missing biologically and clinically relevant information. While targeted therapies against these antigens (e.g., anti-CD56 antibody-drug conjugates or CD7-directed CAR-T cells) are not currently accessible, their identification remains crucial for accurate diagnosis, potential risk stratification, and future preparedness as treatment landscapes evolve.[25,26]

This study has several limitations. Its retrospective, single-center design and modest sample size limit the generalizability of the findings and the power for multivariate analyses. The absence of comprehensive cytogenetic and molecular data prevents correlation of immunophenotypic patterns with genetic risk groups and long-term outcomes, which is a critical area for future research. Despite these limitations, this work provides a foundational description of AML immunophenotypes in an understudied population affected by conflict and resource constraints.

In conclusion, Yemeni AML patients exhibit a distinct immunophenotypic signature characterized by frequent aberrant expression of CD56 and CD7. This pattern differs from Western

populations and aligns more closely with regional Middle Eastern data, suggesting shared genetic or environmental influences. The association of these markers with specific clinicopathological features highlights their potential biological and clinical relevance. These findings emphasize the importance of tailored diagnostic approaches and population-specific research to improve the understanding and management of AML in diverse global contexts.

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### Data Availability

De-identified participant data are available upon reasonable request to the corresponding author, subject to approval by the Aden National Oncology Center IRB.

## Declarations

### Ethics Approval

The study protocol was approved by the Institutional Review Board of Aden National oncology Center (ACC-IRB-2024-11). The study was conducted in accordance with the principles of the Declaration of Helsinki.

### Consent to Participate

Written informed consent was obtained from all individual participants or their legal guardians for the use of anonymized data.

### Consent for Publication

Not applicable.

### Conflict of Interest

The authors declare no competing financial interests.

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