Clinical Characteristics and Outcome of Acute Myeloid Leukemia Patients: Correlation to CD200 and CD56 Expression

Running Title: CD200 and CD56 in Acute Myeloid Leukemia.

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Abstract

Background and Aim: The expression of CD56 and CD200 has emerged as novel biomarkers for predicting the prognosis of individuals with acute myeloid leukemia. The study aims to examine CD200 and CD56 expression among patients with AML.

Patients and Methods: We enrolled 51 recently diagnosed with (non-M3-denovo) AML. Baseline demographic, clinical, and laboratory information was collected. The expression of CD200 and CD56 was measured by flow cytometry.

Results: The average age of the patients was 49.23. Fifteen (29.4%), ten (19.6%), and ten (19.6%) patients had CD200, CD56, and CD200/CD56 expression, respectively. Overall survival was significantly better among patients with negative CD200 expression (9.11 vs. 3.22 (months); $p < 0.001$). Also, patients with negative CD200 expression had significantly better DFS (10.11 vs. 5.56 (months); $p= 0.01$). Also, overall survival was significantly better among those with negative CD56 expression (8.80 vs. 2.65 (months); $p < 0.001$) and better DFS (10.04 vs. 6.11 (months); $p= 0.02$).

Conclusion: Overall, our findings suggest that high levels of CD200 and CD56 expression are associated with a poor prognosis in newly diagnosed AML patients. These findings indicate that CD200 and CD56 could be targets for targeted AML therapy, particularly in patients with CD200 and CD56 overexpression. More clinical and experimental evidence will be required to confirm these findings.

Keywords: CD200, CD56, prognosis, leukemia.

Introduction:

Acute myeloid leukemia (AML) is a clonal malignant disease of the hematopoietic tissue. The diversity of the clinical, hematological, and genetic features among patients with AML has been recognized. Considerable progress has been made in defining new diagnostic and prognostic markers in AML treatment [1]. Possible immunological indications have lately emerged, showing a plethora of possible therapeutic targets.

CD200 is a trans-membrane cell surface glycoprotein in the type1 immunoglobulin superfamily. Expression of CD200 is normally seen in some populations of T and B-lymphocytes, neurons, and endothelial cells [2]

CD200 abnormal overexpression in acute myeloid leukemia (AML) has been put forward as a bad predictive factor due to the reduction of natural killer activity; its overexpression is linked to an adverse outcome even in the presence of advantageous biological markers, such as Flt3 wild-type, mutated nucleolar protein nucleophosmin, and negative expression of CD34 and CD56 [3,4].

CD56, also known as neural cell adhesion molecule 1 (NCAM1), is a 180 kD glycoprotein that mediates hematopoietic cell adhesion and is involved in cytotoxicity [5]

The current study aimed to evaluate the clinical characteristics and outcomes of adult de-novo AML patients before and after induction with conventional chemotherapy (3 and 7), examining the correlation with CD200 and CD56 expression to assess the prognostic significance of these markers.

Patients and Methods

Study Design and Setting

A hospital-based observation study was conducted at the Clinical Hematology Unit in the Internal Medicine Department, Assiut University Hospitals.

The study approval was obtained from the Assiut University Academic and Ethical Committee, and the IRB number was 17101799 on 28/6/2022. This work has been carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans. ClinicalTrials.gov Identifier: NCT05512104. In the current study, the diagnosis of AML was applied according to the WHO criteria, showing AML mainly AML 4, AML5, AML1, and AML2(29.4%,19.5%,15.7%, and 15.7%, respectively).

Another Egyptian study showed the main types AML 5, AML4, and AML2 (30%, 25%, and 22.5%, respectively) [6].

Selection Criteria

The current trial included newly diagnosed de-novo AML patients aged 18 to 60 who were treated with the 3+7 protocol, which consisted of 3 days of doxorubicin (45mg/m2) and 7 days of cytarabine (100-200 mg/m2 with intravenous infusion over 24 hours). Exclusion criteria were age over 60 or under 18 years, promyelocytic leukemia (M3), and/or ultimate organ failure.[7]

Sample Size

A total coverage sample technique was used here, where newly diagnosed patients with AML and eligible for the 3+7 protocol from October 1st,2022, to May 30th, 2023, were enrolled in the study. A total of 51 patients with AML were recruited.

Methodology

All patients underwent a thorough medical history review and a comprehensive clinical examination. Laboratory investigations were conducted using blood samples collected in EDTA and citrate tubes. These investigations included a complete blood count (CBC) performed with ADVIA 2120i Siemens machines, providing a full differential cell count and blast percentage. Coagulation studies were carried out using Sysmex 2500. Bone marrow aspiration was performed, followed by smear interpretation and cytochemical testing. Additionally, cytogenetic analysis and molecular studies were conducted.

Immunophenotyping (IPT) was performed using a comprehensive panel of monoclonal antibodies with BD FACS Calibur systems (Becton Dickinson Company, California, USA) and fluorochrome-labeled monoclonal antibodies (MoAbs) from Becton Dickinson (Franklin Lakes, New Jersey, USA) and Immunostep (ES).

Minimal residual disease (MRD) was assessed on day 28 post-induction. Patients

with AML-M3 were excluded from the study as they were managed using a distinct therapeutic approach.

CD56 and CD200 Expression by Flow Cytometry

Bone marrow samples were subjected to flow cytometric analysis for immunophenotyping. The panel of monoclonal antibodies included markers such as CD45, CD14, CD33, CD64, CD13, MPO, HLA-DR, CD4, CD3, CD19, CD22, CD10, CD34, CytoCD61, CytoCD41, CD36, CD235a, and CD117.

For the evaluation of CD56 and CD200 expression, Anti-CD56-FITC (Clone 7G3, Fluorescein isothiocyanate-labeled) antibodies from Beckman Coulter (USA) and Anti-CD200-PE (Phycoerythrin-labeled) antibodies from Immunostep (ES) were used. These markers were assessed at diagnosis, during MRD detection, and upon relapse. Markers were considered positive when expressed on ≥ 20% of the analyzed cells.

Study Outcomes

Complete remission (CR) was defined as the complete peripheral hematological recovery and the absence of bone marrow disease (at morphological, immunophenotypic, or molecular evaluation) **[8]**. Overall survival (OS) was calculated from diagnosis to death (irrespective of the cause). Disease-free survival (DFS) is the time between CR and relapse **[9]**. Patients lost to follow-up were censored at the time they were last seen alive.

Statistical Analysis

Statistical analyses were performed using the SPSS software package. Data were statistically described in terms of mean with range and mean ± SD. Quantitative parametric variables were compared between studied groups using the students' t-test, Chi-square, and correlation coefficient study.

The correlation of peripheral blood indices with other variables was determined by Pearson correlation. Overall survival (OS) was calculated from the date of first diagnosis to death from any cause. Meanwhile, remission duration was calculated from the time of complete remission (CR) achievement to the time of relapse or death in CR. *A p-value of* less than 0.05 was considered statistically significant.

Results

Baseline data of the studied patients

The mean age was 49.23 years old, and the most frequent presentations among the studied patients were fever (88.2%) and splenomegaly (68.6%). Also, the most frequent subtypes were AML-M4 (29.4%) and AML-M5 (19.5%).

Complete response and outcome among the studied patients:

26 (51%) patients achieved CR, and 25 (49%) patients failed to achieve CR. Also, the majority 31(60.8%) of patients deteriorated and died, (7 %) from them died during the induction period due to uncontrolled infection (bacterial, viral, and/or fungal) (69 %), hemorrhage (11 %), shock (10 %), pulmonary embolism (P.E) (7 %), others(Ludwig angina) (3 %) and twenty 20 (39.2%) patients were alive.

CD200 and CD56 expression among the studied patients:

15 (29.4%) and 10 (19.6%) patients had positive CD200 and CD56 expression, respectively. All patients with positive CD56 expression had positive CD200 expression. After induction, there was an insignificant difference as regards the expression of CD200 [35 (2.9-90) *vs.* 23 (2-80); p= 0.45] and CD56 [22 (3-60.66) *vs.* 21 (1-59); p 0.54] in comparison to baseline expression.

Characteristics of patients based on the expression of CD200 (Table 1):

Both groups with positive CD200 and negative expression had insignificant differences regarding different data (p > 0.05).

Table 1: Characteristics of the studied patients based on expression of CD200

	CD200 expression		*P* value
	Positive (n=15)	Negative (n= 36)	
Age (years)	48.11 ± 9.11	50.11 ± 10.18	0.44
Sex			0.34
Male	8 (53.3%)	23 (63.9%)	
Female	7 (46.7%)	13 (36.1%)	
Clinical manifestations			
Fever	13 (86.7%)	32 (88.9%)	0.57
Splenomegaly	10 (66.7%)	25 (69.4%)	0.54
Hepatomegaly	7 (46.7%)	18 (50%)	0.53
Lymphadenopathy	4 (26.7%)	10 (27.8%)	0.16
Bleeding	3 (20%)	9 (25%)	0.50
Laboratory data			
Haemoglobin (g/dl)	7.09± 1.22	7.90 ± 1.27	0.34
Platelets (x 10^3/ml)	50.56 ± 8.88	68.88 ± 8.10	0.09
Leucocytes (x 10^3/ml)	55.76 ± 15.34	61.11 ± 15.90	0.22
Peripheral blast (%)	50.45 ± 9.11	53.34 ± 10.22	0.87
Bone marrow blast (%)	58.98 ± 12.34	59.22 ± 8.12	0.45
Total bilirubin (mg/dl)	2.89 ± 1.21	2.96 ± 1.98	0.21
Albumin (mg/dl)	33.01 ± 2.11	34 ± 2.77	0.18
Urea (mg/dl)	4.30 ± 2.09	4.42 ± 2.44	0.49
Creatinine (mg/dl)	0.74 ± 0.13	0.77 ± 0.23	0.15
LDH (U/L)	922.34 ± 40.56	937.66 ± 60.6	0.07
INR	1.10 ± 0.10	1.13 ± 0.14	0.39
Serum calcium (mg/dl)	8.62 ± 0.32	8.65± 0.87	0.88
Neutrophil/lymphocyte ratio	0.93 ± 0.10	0.97 ±0.14	0.30
Platelets/lymphocytes ratio	3.99 ± 1.80	4.55 ± 1.87	0.08
Lymphocytes/monocyte ratio	1.68 ± 0.20	1.71 ± 0.44	0.44
FAB classification			0.89
M0	1 (6.7%)	1 (2.8%)	
M1	2 (13.3%)	6 (16.7%)	
M2	2 (13.3%)	6 (16.7%)	
M4	4 (26.7%)	11 (30.6%)	
M5	3 (20%)	7 (19.4%)	
M6	2 (13.3%)	3 (8.3%)	
M7	1 (6.7%)	2 (5.6%)	

Outcome and survival analysis based on the expression of CD200 (Figure 1,2):

Patients with positive CD200 expression had a significantly lower frequency of CR (13.3% *vs.* 66.7%; $p < 0.001$).

Overall survival (OS) was significantly longer among those with negative CD200 expression (9.11 *vs.* 3.22 (months); $p < 0.001$). Also, patients with negative CD200 expression had significantly longer DFS (10.11 *vs.* 5.56 (months); $p= 0.01$).

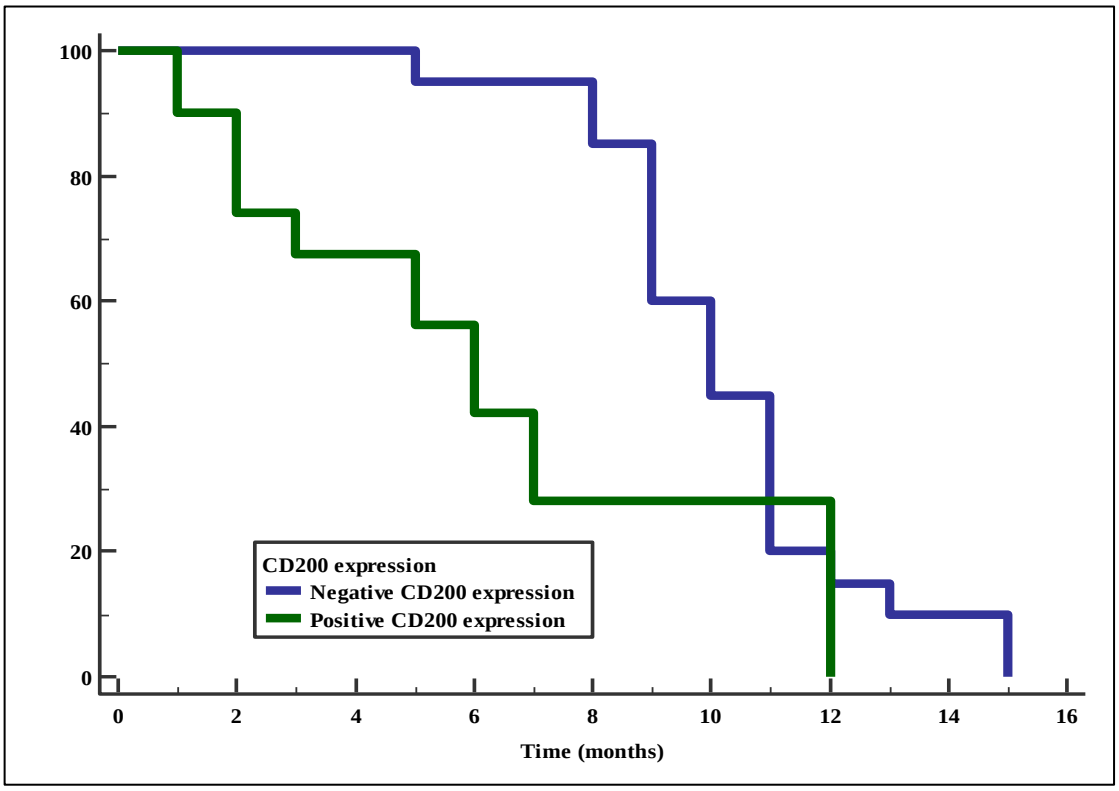

Figure 1: Overall survival in patients based on expression of CD200.

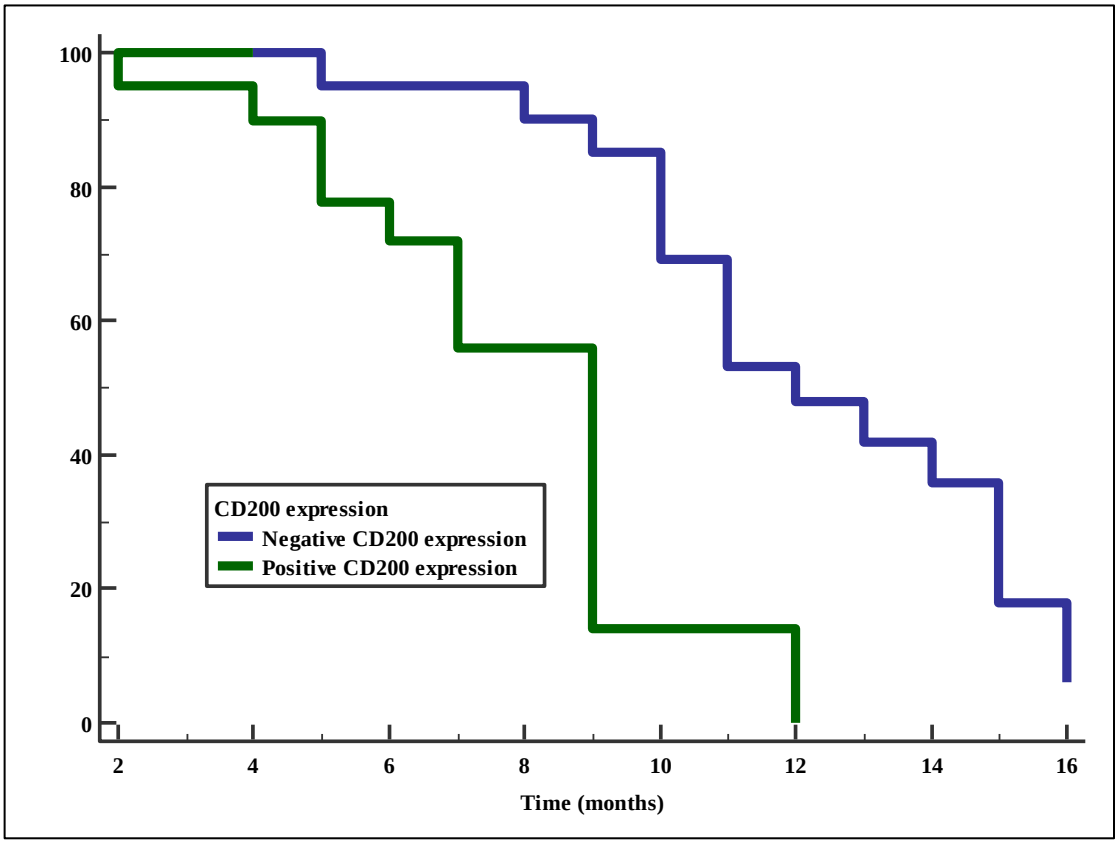

Figure 2: Disease-free survival in patients based on the expression of CD200

Characteristics based on expression of CD56 (Table 2):

Patients with positive CD56 expression and those with negative expression had insignificant differences regarding different characteristics ($p > 0.05$). All patients with positive CD56 expression were found to have positive CD200 expression.

Table 2: Characteristics of the studied patients based on expression of CD56

	CD56 expression		*P* value
	Positive (n=10)	Negative (n= 41)	
Age (years)	50.01 ± 13.33	49.01 ± 6.99	0.10
Sex			0.15
Male	8 (80%)	23 (56.1%)	
Female	2 (20%)	18 (43.9%)	
Clinical manifestations			
Fever	10 (100%)	35 (85.4%)	0.25
Splenomegaly	9 (90%)	26 (63.4%)	0.10
Hepatomegaly	7 (70%)	18 (43.9%)	0.13
Lymphadenopathy	6 (60%)	31 (75.6%)	0.26
Bleeding	3 (30%)	9 (22%)	0.43
Laboratory data			
Haemoglobin (g/dl)	7.90 ± 1.11	7.55 ± 1.17	0.11
Platelets (x 10^3/ml)	68.97 ± 8.90	68.12 ± 8.40	0.07
Leucocytes (x 10^3/ml)	61.10 ± 12.98	59.01 ± 15.11	0.23
Peripheral blast (%)	54.66 ± 10.12	52.52 ± 7.77	0.18
Bone marrow blast (%)	60.87 ± 14.31	57.98 ± 8.54	0.39
Total bilirubin (mg/dl)	2.92 ± 1.11	2.88 ± 2.01	0.08
AST (U/L)	42 ± 11.67	41.40 ± 8.10	0.34
ALT (U/L)	45.56 ± 8.45	45 ± 8.34	0.09
Albumin (mg/dl)	33.90 ± 1.78	23.91 ± 2.11	0.22
Creatinine (mg/dl)	0.76 ± 0.12	0.74 ± 0.17	0.45
LDH (U/L)	960 ± 79.87	944.34 ± 71.6	0.40
Prothrombin time (second)	13.48 ± 2.11	13.33 ± 1.45	0.21
PC (%)	80.87 ± 12.78	79.45 ± 12.11	0.19
INR	1.14 ± 0.10	1.16 ± 0.13	0.56
Serum calcium (mg/dl)	8.68 ± 0.20	8.55± 0.17	0.80
Neutrophil/lymphocyte ratio	0.91 ± 0.18	0.95 ±0.14	0.10
Platelets/lymphocytes ratio	4.01 ± 1.31	5.88 ± 1.31	0.10
Lymphocytes/monocyte ratio	1.78 ± 0.87	1.66 ± 0.40	0.59
FAB classification			0.16
M0	1 (10%)	1 (2.4%)	
M1	2 (20%)	6 (14.6%)	
M2	2 (20%)	6 (14.6%)	
M4	4 (40%)	11 (26.8%)	
M5	1 (10%)	9 (22%)	
M6	0	5 (12.2%)	
M7	0	3 (7.3%)	

Outcome and survival analysis based on the expression of CD56 (Figure 3,4):

Patients with positive CD56 expression had a significantly lower frequency of CR (20% *vs.* 58.5%; $p < 0.001$) than those with negative CD56 expression.

Overall survival was significantly longer among those with negative CD56 expression [(8.80 *vs.* 2.65 (months); $p < 0.001$)]. Also, patients with negative CD56 expression had significantly longer DFS [(10.04 *vs.* 6.11 (months); $p= 0.02$].

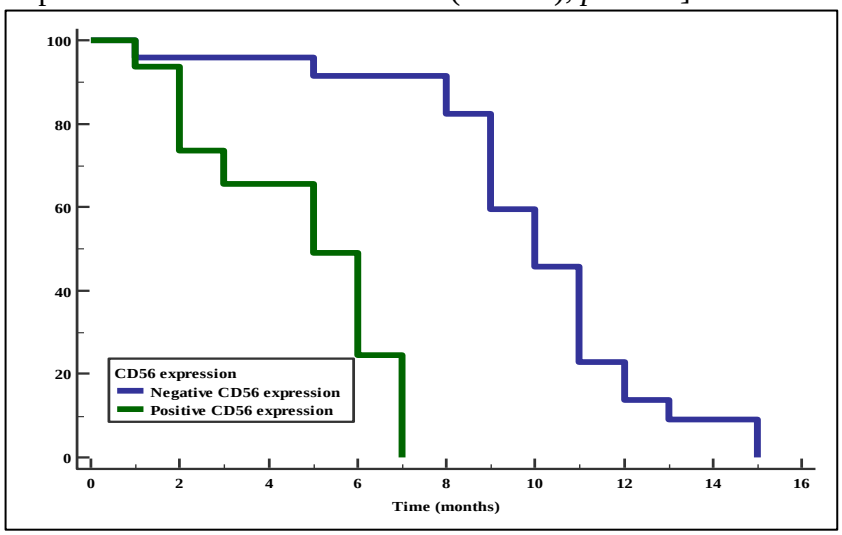

Figure 3: Overall survival in patients based on expression of CD56.

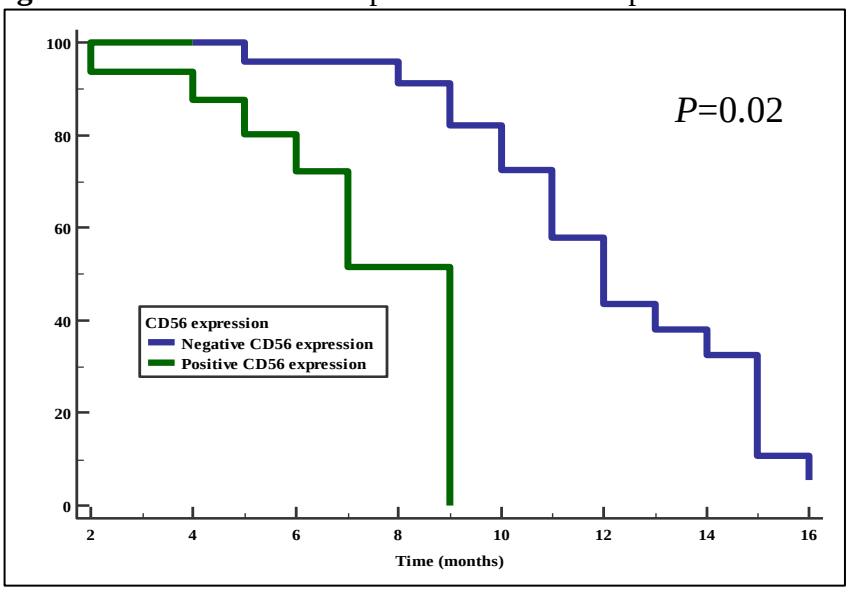

Figure 4: Disease-free survival in patients based on expression of CD56.

Peripheral blood indices based on complete response (Table 3):

Patients who failed to achieve CR had significantly higher platelets/lymphocytes ratio (15.43 ± 1.20 *vs.* 3.09 ± 0.16; $p < 0.001$).

Table 3: Peripheral blood indices based on complete response

	Complete response		*P* value
	Yes (n=26)	No (n= 25)	
Neutrophil/lymphocyte ratio (NLR)	0.90 ± 0.32	0.98 ± 0.60	0.78
Platelets/lymphocytes ratio (PLR)	3.09 ± 0.16	15.43 ± 1.20	**< 0.001**
Lymphocytes/monocyte ratio (LMR)	1.60 ± 0.39	1.88 ± 0.51	0.41

Data expressed as mean (SD). *P* value was significant if < 0.05.

Peripheral blood indices based on the outcome (Table 4):

Died patients had a significantly higher platelets/lymphocytes ratio than alive patients (2.45 ± 0.56 *vs.* 14.45 ± 1.34; $p < 0.001$).

Table 4: Peripheral blood indices based on the outcome of the studied patients

	Outcome		*P* value
	Alive (n=20)	Died (n= 31)	
Neutrophil/lymphocyte ratio (NLR)	0.99 ± 0.40	1.07 ± 0.67	0.32
Platelets/lymphocytes ratio (PLR)	2.45 ± 0.56	14.45 ± 1.34	**< 0.001**
Lymphocytes/monocyte ratio (LMR)	1.68 ± 0.70	1.90 ± 0.40	0.56

Data expressed as mean (SD). *P* value was significant if < 0.05

Correlation of peripheral blood indices with other variables (Table 5):

Different blood indices had insignificant correlations with other variables, including CD200 and CD56 expression, except for a negative correlation between PLR with overall survival (r= -0.34, p= 0.02) and disease-free survival (r= -0.39, p=0.01).

Table 5: Correlation of peripheral blood indices with other variables

	NLR	**PLR**	**LMR**
Age (years)	0.04 (0.98)	0.11 (0.87)	0.21 (0.40)
Haemoglobin (g/dl)	0.10 (0.45)	0.10 (0.06)	0.04 (0.22)
Platelets (x 10^3/ml)	-0.05 (0.62)	-0.08 (0.47)	0.09 (0.55)
Leucocytes (x 10^3/ml)	-0.19 (0.09)	-0.09 (0.39)	0.12 (0.26)
Peripheral blast (%)	-0.06 (0.56)	-0.02 (0.84)	0.03 (0.78)
Bone marrow blast (%)	-0.1 (0.93)	0.03 (0.76)	-0.04 (0.69)
Total bilirubin (mg/dl)	0.07 (0.54)	-0.03 (0.74)	-0.02 (0.80)
AST (U/L)	0.14 (0.21)	0.24 (0.40)	-0.03 (0.79)
ALT (U/L)	-0.13 (0.23)	0.01 (0.99)	0.17 (0.12)
Albumin (mg/dl)	0.21 (0.06)	0.06 (0.58)	0.15 (0.16)
Urea (mg/dl)	0.21 (0.06)	0.11 (0.33)	0.06 (0.56)
Creatinine (mg/dl)	0.04 (0.69)	0.01 (0.90)	-0.01 (0.67)
LDH (U/L)	-0.01 (0.87)	-0.21 (0.06)	-0.04 (0.69)
INR	0.05 (0.65)	0.14 (0.20)	-0.08 (0.43)
Serum calcium (mg/dl)	0.12 (0.27)	0.06 (0.55)	0.05 (0.60)
Overall survival	0.07 (0.20)	**- 0.34 (0.02)**	0.19 (0.98)
Disease free survival	0.19 (0.47)	**- 0.39 (0.01)**	0.18 (0.29)

Data expressed as *r* value (*p* value). *P* value was significant if < 0.05. **NLR:** neutrophil/ lymphocyte ratio; **PLR:** platelets/lymphocytes ratio; **LMR;** lymphocytes/monocyte ratio; **LDH:** Lactate dehydrogenase; **INR:** International randomized ratio.

Discussion

In the current study, the patient's mean age was 49.23 years old, with male predominance. Similarly, a previous study of 30 patients with AML reported that the mean age and range of AML patients were 40.93 ± 15.63 (mean ± SD) years with an M: F ratio of 3:2 **[7]** Also, another Egyptian study showed mean age of patients of 49 years and slight male predominance[**6,11]**.

The current study also revealed that fever (88.2%) and splenomegaly (68.6%) were the most common presentations, followed by

hepatomegaly (49.1%). Previous research has found that fever is the most prevalent presenting sign of adult AML, while lymphadenopathy and gingival enlargement are the least common [**12,13]**.

A total of 15 (29.4%) patients had positive CD200, 10 (19.6%) patients had positive CD56, and 10 (19.6%) had co-expression. Muhsin et al. (2018) discovered that CD200 and CD56 were abnormally

expressed in 53.3% and 20.0%, respectively, while co-expression of both markers was seen in 13.3% **[6]**.

Meanwhile, **El-Sissy et al. (2006)** reported that CD56 was expressed in 20.3% of Sudanese patients with AML**[14]**. These variations in the frequency of positive expression in different studies may be attributed to different studied populations, different sample sizes, and selection bias.

It came out that both patient subgroups based on CD200 and CD56 expression showed no significant differences in terms of distinct features (P> 0.05). In contrast, a prior study indicated that patients with positive CD200 expression had a considerably higher fever and bleeding tendency with raised LDH than those with negative CD200 expression **[15]**. These differences are mainly attributed to different sample sizes and studied populations.

Also, patients with positive CD200 expression had a significantly lower frequency of CR (13.3% *vs.* 66.7%; *p*< 0.001). Also, the majority (50%) of patients with negative expression were alive, and the majority (86.7%) of those with positive CD200 expression died.

In line with the current study, Kandeel et al. (2021) discovered that positive CD200 expression was associated with poor outcomes, as all patients who did not achieve CR had positive CD200 expression. Furthermore, positive expression of CD200 was associated with MRD, which was observed in 62 out of 71 individuals (87.3%) **[16]**.

The study found that individuals with positive CD56 expression had a considerably lower frequency of CR (20% vs. 58.5%; P < 0.001) compared to those with negative CD56 expression. This agrees with several earlier studies that indicated poor treatment response among patients with positive expression of CD56 **[15].**

A further investigation discovered that CR after regular chemotherapy had a comparable proportion in groups classified according to different levels of CD56 expression, demonstrating no difference in treatment response between the two groups based on CD56 expression [17**]**.

The current study's most notable finding was that those with negative CD200/CD56 expression had a considerably longer OS/DFS. In keeping with the current findings, Aref et al. (2020) said that OS was considerably shorter in those having positive expression of CD200, with mean OS being 8.047 months for those with negative CD200 expression compared to 3.224 months for patients with positive expression (*P* = 0.049) **[15]**.

A prior study found that positive CD200 cases had an OS rate of 14.3% at 6 months and 9.5% at 1 year, whereas negative CD200 cases had an OS rate of 92.0% at 6 months and 69.7% at 1 year (P < 0.001). DFS was significantly lower in positive CD200 patients compared to negative CD200 patients at 6 months (75% *vs.* 100%, *P* < 0.0001)[**16]**.

Previous studies suggested that NLR, LRM, PLR, RDW-CV, and RDW-SD could be simple, easily available, and cost-effective prognostic tests that may be clinically useful to help risk-stratify patients with AML to adjust the treatment intensity better. The authors identified higher NLR, RDW-SD, RDW-CV, and lower LMR and PLR as poor prognostic factors **[18]**. Different blood indices had insignificant correlations with other variables, including CD200 and CD56 expression.

The current study had some limitations, including being conducted in a single center with a relatively small sample size, a control group of healthy people not enrolled, and the short-term duration of the studied patients didn't allow for assessing the long-term effect of CD56 and CD200 expression. Yet, to our knowledge, the current study is the first to discuss such an issue in our locality.

Conclusion: based on the current study, our findings indicate that patients with high CD200 and CD56 expression levels had poor outcomes in newly diagnosed AML patients. These results suggest that CD200 and CD56 may be potential targets for targeted AML therapy, particularly in patients with CD200 and CD56

overexpression. Multi-center studies with many patients are warranted to confirm such findings

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