The Impact of CD200 and CD56 Expression on The Prognosis of Acute Myeloid Leukemia Patients at Ain Shams University Hospitals

Original Article

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ABSTRACT

Background: Acute myeloid leukemia (AML) is a clonal malignant disease of hematopoietic tissue which results from a block of normal differentiation of hematopoietic progenitor cells along with uncontrolled proliferation of cells of myeloid origin with maturation arrest leading to infiltration of bone marrow and other tissues by myeloblasts. It escapes from immunosurveillance by induction of immunosuppression through expression of specific cell surface molecules with immune modulatory function. Novel immune-directed therapeutic approaches form a major focus of current and clinical research.

Objective: To evaluate the expression levels of CD200 and CD56 in newly diagnosed acute myeloid leukemia (AML) patients (classified according to FAB classification) and assess the prognostic significance of their positive expression in AML cases.

Methods: This Cohort study was conducted at Ain Shams University Hospitals, on 51 newly diagnosed adult AML patients attending the Hematology Oncology Unit of Ain-Shams University Hospitals from February 2022 until June 2023.

Results: The CD200+ expression was reported in 74.5% of patients while 9.8% of patients showed CD56+ expression. The M1-M2 were found to be the most common FAB subtypes. CD200+ was higher among female patients (p= 0.045). On the other hand, CD56+ patients were younger in comparison to CD56- patients (p= 0.002). Total death was higher among CD200+ patients than CD200- patients (p= 0.037).

Conclusion: Our study indicates that CD200 expression is linked to a higher mortality rate, suggesting a negative effect on survival, whereas CD56 expression does not show a significant association with mortality.

Key Words: FAB classification, immune evasion, immunomodulatory markers, survival.

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INTRODUCTION

Acute myeloid leukemia is a heterogeneous disorder characterized by the impaired differentiation of hematopoietic progenitor cells, accompanied by the uncontrolled proliferation of myeloid-origin cells with maturation arrest. This results in the infiltration of bone marrow (BM) and other tissues by myeloblasts[1]. Among patients with AML, the genetic features, clinical and hematological variability has been identified. Concerning AML treatment, identifying new diagnostic and prognostic markers has achieved marked progress, Therefore, the detection of specific molecules in leukemic cells is crucial and essential for identifying certain subtypes of myeloid neoplasms[2].

The CD200 is a transmembrane cell surface glycoprotein belonging to the type I immunoglobulin superfamily. It is typically expressed in certain subsets of T and B lymphocytes, as well as in endothelial cells and neurons[3]. Immunosuppression is triggered when CD200 binds to its receptor, CD200R, a homologous cell-surface receptor expressed on leukocytes of the myeloid lineage, including mast cells, macrophages, basophils, dendritic cells, as well as certain T-cell populations[4]. The CD200 is frequently overexpressed in AML blasts and promotes the formation of CD4+CD25+FoxP3+ regulatory T cells (Tregs), an immunosuppressive T-cell subset that may contribute to poor prognosis in AML[5].

The CD56 is a cell surface glycoprotein identified as an isoform of the neural cell adhesion molecule (NCAM),

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which plays a role in mediating cell-to-cell interactions[6]. Initially recognized as a marker for NK cells, CD56 is also found in various hematopoietic malignancies, including AML. However, the prognostic significance of its expression in AML remains a subject of controversy[7].

AIM OF THE WORK

The aim of this study is to evaluate the expression levels of CD200 and CD56 in newly diagnosed acute myeloid leukemia patients and to assess the prognostic significance of their positive expression in AML patients.

PATIENTS AND METHODS

Study design: Cohort study.

Study settings: This Cohort study was conducted at Ain Shams University Hospitals Laboratories and the Hematology Oncology Unit of Ain Shams University Hospitals from February 2022 until June 2023.

Sample size: The study included 51 newly diagnosed adult AML patients attending the Hematology Oncology Unit of Ain Shams University Hospitals. Exclusion criteria were patients under 18 years of age, those with a history of myelodysplastic syndrome (MDS) or myeloproliferative neoplasms (MPN), leukopenia and individuals who had been exposed to leukemogenic therapies or agents.

Sample collection: Five milliliters of peripheral blood (PB) were collected aseptically from each patient and Two milliliters transferred into K2 EDTA-coated vacutainer tubes for complete blood count (CBC) analysis. Additionally, three milliliters were dispensed into sterile plain vacutainer and were left to clot for 30 minutes. Serum was separated by centrifugation at 4000 RPM for 10 minutes for uric acid, CRP and LDH, two milliliters of bone marrow (BM) aspirate were obtained in K2 EDTA-coated sterile vacutainer tubes for immunophenotyping (IPT) to assess CD200 and CD56 levels. Furthermore, one milliliter of BM aspirate was collected in a sterile lithium heparin-coated vacutainer tube for cytogenetic analysis.

ETHICAL CONSIDERATIONS

Informed consent was obtained from all enrolled patients prior to the study's commencement. Data were collected from medical records and handled with strict confidentiality. The information was used solely for research purposes. The study was approved by the Ain Shams University Institutional Ethics Committee (REC). FMASU MS 95/2022

All patients underwent the following: comprehensive history taking and a thorough clinical examination, with particular emphasis on: weight loss, organomegaly, lymphadenopathy, bleeding tendency, fever and bony aches, routine diagnostic work up for acute myeloid leukemia that includes: Complete blood count and microscopic examination of Leishman- stained peripheral blood (PB) smear, uric acid, LDH, CRP, BM aspiration and examination of Leishman stained smears for proper enumeration of blast cells, followed by cytochemical analysis using myeloperoxidase stain, flowcytometric analysis performed on BM samples using an extended panel of monoclonal antibodies (MoAbs) on 6 Color NAVIOS flow cytometer [Beckman Coulter, USA] for routine diagnosis and lineage determination of leukemia patients with determination of CD200 – CD56 expression and cytogenetic analysis [t(8,22)- (inv.16)- t (16;16)- t(8;21)-t(15;17) -t(9.22)] performed on Leica scan using fluorescence in situ (FISH) technique.

Statistical Analysis:

Data were reviewed, coded, and analyzed using the Statistical Package for Social Sciences (SPSS), version 25. Parametric numerical data were summarized as mean ± standard deviation (SD) and range, while non-parametric numerical data were expressed as median and interquartile range (IQR). Categorical data were presented as frequencies and percentages.

Comparisons of quantitative variables were performed using the non-parametric Kruskal-Wallis and Mann-Whitney tests. For categorical data, the Chi-square test was utilized. A receiver operating characteristic (ROC) curve was generated to assess the sensitivity and specificity of prognostic measures. A *p-value* of less than 0.05 was considered statistically significant.

RESULTS

The study was carried out on 51 adult patients with de-novo AML; their baseline characteristics are shown in (Table 1). The results of the present study are shown in (Tables 2-11) and (Figures 1-3).

Descriptive statistics:

A. Patients' characteristics

As seen in (Table 1), the ages of the studied patients ranged from 18 to 71 years with mean of 44.08 ± 16.24 years. They were 27 (52.9%) males and 24 (47.1 %) females. According to FAB classification, 29 patients (56.9%) showed (M1-M2) subcategory,11patients (21.6%) were (M4-M5),6 patients (11.8%) were M0 while 3 patients (5.9%) were AML not classified and 2 patients (3.9%) were M3.

Table 1: Patients' characteristics.

Characteristic	Mean ± SD Range
Age (years)	44.08 ± 16.21 18-71
Gender Female Male	 24 (47.1.0%) 27 (52.9%)
FAB Classification: AML unclassified (M0) (M1-M2) (M3) (M4-M5)	 3 (5.9%) 6 (11.8%) 29 (56.9%) 2 (3.9%) 11 (21.6%)
CD200: + -	 38 (74.5%) 13 (25.5%)
CD56 + -	 5 (9.8%) 46 (90.2%)
Double negative (CD200- CD56-) Yes No	 13 (25.5%) 38 (74.5%)

B. Analytical statistics: The demographic and clinical data of CD200+ patients were compared to those of CD200– patients, as presented in (Table 2) and (Figure 1). A statistically significant difference was observed between the CD200+ and CD200– groups concerning sex (p = 0.045). In contrast, CD56+ expression showed no significant impact on demographic or clinical data, except for age, which was higher in CD56– patients, as illustrated in (Table 3) and (Figure 2).

Table 2: The difference between CD200+ and CD200- regarding demographic and clinical data.

Characteristics		CD200		Test of significance		
		Negative	Positive			
		Mean ± SD N (%)	Mean ± SD N (%)	Value	*p-Value*	Sig.
Age		47.54 ± 15.83	42.89 ± 16.41	t= 0.888	0.379	NS
Sex	Male	10 (76.92%)	17 (44.74%)	X^2= 4.028	0.045	S
	Female	3 (23.08%)	21 (55.26%)			
Weight Loss	No	7 (53.85%)	16 (42.11%)	X^2= 0.539	0.463	NS
	Yes	6 (46.15%)	22 (57.89%)			
Fever	No	10 (76.92%)	20 (52.63%)	X^2= 2.36	0.125	NS
	Yes	3 (23.08%)	18 (47.37%)			
Lymphadenopathy	No	10 (76.92%)	24 (63.16%)	FE	0.502	NS
	Yes	3 (23.08%)	14 (36.84%)			
Hepatomegaly	No	6 (46.15%)	20 (52.63%)	X^2= 0.163	0.687	NS
	Yes	7 (53.85%)	18 (47.37%)			
Splenomegaly	No	5 (38.46%)	22 (57.89%)	X^2= 1.468	0.226	NS
	Yes	8 (61.54%)	16 (42.11%)			
Bleeding tendency	No	8 (61.54%)	27 (71.05%)	FE	0.73	NS
	Yes	5 (38.46%)	11 (28.95%)			
Bone aches	No	7 (53.85%)	21 (55.26%)	X^2= 0.008	0.929	NS
	Yes	6 (46.15%)	17 (44.74%)			

*Student t-test of significance (t); *Fisher's Exact test of significance (FE); *Chi-Square test of significance (X^2); Non-significant (NS). Significant (S).

Table 3: The difference between CD56+ and CD56- regarding demographic and clinical data.

Characteristics		CD56		Test of significance		
		Negative	Positive			
		Mean ± SD N (%)	Mean ± SD N (%)	Value	*p-Value*	Sig.
Age		46.28 ± 15.32	23.8 ± 9.18	t= 3.201	0.002	S
Sex	Male	25 (54.35%)	2 (40%)	FE	0.656	NS
	Female	21 (45.65%)	3 (60%)			
Weight Loss	No	22 (47.83%)	1 (20%)	FE	0.362	NS
	Yes	24 (52.17%)	4 (80%)			
Fever	No	26 (56.52%)	4 (80%)	FE	0.391	NS
	Yes	20 (43.48%)	1 (20%)			
Lymphadenopathy	No	31 (67.39%)	3 (60%)	FE	1.00	NS
	Yes	15 (32.61%)	2 (40%)			
Hepatomegaly	No	23 (50%)	3 (60%)	FE	1.00	NS
	Yes	23 (50%)	2 (40%)			
Splenomegaly	No	24 (52.17%)	3 (60%)	FE	1.00	NS
	Yes	22 (47.83%)	2 (40%)			
Bleeding tendency	No	30 (65.22%)	5 (100%)	FE	0.167	NS
	Yes	16 (34.78%)	0 (0%)			
Bone aches	No	24 (52.17%)	4 (80%)	FE	0.362	NS
	Yes	22 (47.83%)	1 (20%)			

*Student t-test of significance (t); *Fisher's Exact test of significance (FE); Significant (S); Non-significant (NS).

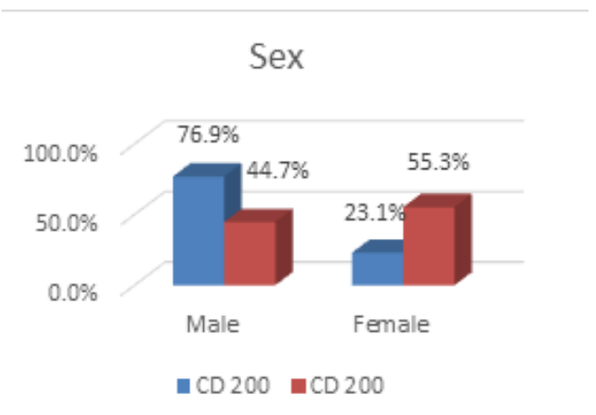

Fig. 1: Difference between CD200+ and CD200- patients' groups regarding sex.

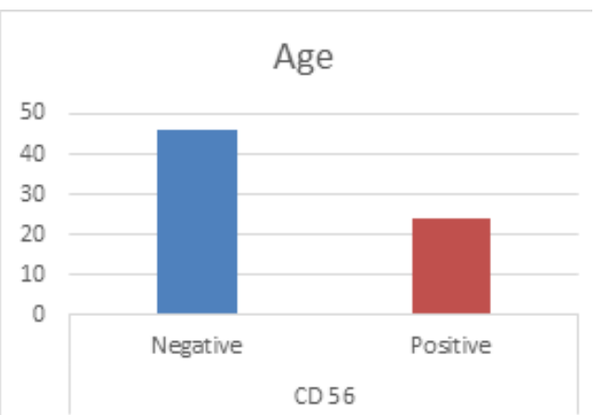

Fig. 2: Difference between CD56+ and CD56- patients' groups regarding age.

Regarding laboratory data, only CRP showed significant difference when comparing between CD56+ and CD56- patients' groups, being higher in CD56- patients (p= 0.031) as shown in (Table 5). On the other hand, there was no significant difference between CD200+ and CD200- patients' groups regarding laboratory data as presented in (Table 4).

Table 4: The difference between CD200+ and CD200- regarding laboratory data.

		CD200		Test of significance		
		Negative	Positive			
		Median (IQR) Mean ± SD	Median (IQR) Mean ± SD	Value	*p-Value*	Sig.
WBCS (10^3 / µL)		13.7 (9.8 - 52.2)	25.55 (5.7 - 76.1)	z= -0.324	0.746	NS
Hb (g/dL)		6.94 ± 1.54	7.16 ± 1.61	t= -0.433	0.667	NS
PLT (10^3 / µL)		50 (25 - 129)	31.5 (17 - 43)	z= -1.665	0.096	NS
P.B Blast (%)		42% (39% - 70%)	65% (31% - 78%)	z= -0.595	0.552	NS
B.M Blast (%)		73% (60% - 90%)	80% (62% - 90%)	z= -0.208	0.835	NS
Uric acid (mg/dL)		5.5 (3.3 - 7)	4.55 (3.3 - 7.6)	z= -0.173	0.863	NS
Uric acid	Normal	6 (46.15%)	18 (47.37%)	X^2= 0.006	0.94	NS
	Increased	7 (53.85%)	20 (52.63%)			
LDH (U/L)		460 (291 - 670)	396 (232 - 652)	z= -0.757	0.449	NS
LDH	Normal	3 (23.08%)	12 (31.58%)	FE	0.73	NS
	Increased	10 (76.92%)	26 (68.42%)			
CRP (mg/L)		101 (55.3 - 110)	50.65 (29.6 - 120)	z= -0.800	0.424	NS
CRP	Normal	0 (0%)	0 (0%)			
	Increased	13 (100%)	38 (100%)			
Cytogenetics						
Cytogenetics	Unfavorable	0 (0%)	1 (2.6%)			
	Favorable	4 (30.8%)	4 (10.5%)	X^2= 3.211	0.230	NS
	Intermediate	9 (69.2%)	33(86.8%)			

*Mann-Whitney test of significance (z); *Fisher's Exact test of significance (FE); *Chi-Square test of significance (X^2); *Student t-test of significance (t); Non-significant (NS).

Table 5: The difference between CD56+ and CD56- regarding laboratory data.

		CD56		Test of significance		
		Negative	Positive			
		Median (IQR) Mean ± SD	Median (IQR) Mean ± SD	Value	*p-Value*	.Sig
WBCS (10^3 / µL)		23.4 (6.8 - 66)	24.5 (3.6 - 58)	z= -0.570	0.569	NS
Hb (g/dL)		7.08 ± 1.6	7.32 ± 1.6	t= -0.319	0.751	NS
PLT (10^3 / µL)		36 (21 - 76)	30 (26 - 33)	z= -0.840	0.401	NS
P.B Blast (%)		61.5% (34% - 77%)	56% (30% - 72%)	z= -0.349	0.727	NS
B.M Blast (%)		80% (60% - 90%)	70% (65% - 80%)	z= -0.562	0.574	NS
Uric acid (mg/dL)		5.2 (3.5 - 7.6)	3.1 (2.3 - 4.4)	z= -1.283	0.199	NS
Uric acid	Normal	23 (50%)	1 (20%)	FE	0.354	NS
	Increased	23 (50%)	4 (80%)			
LDH (U/L)		418.5 (256 - 652)	390 (224 - 675)	z= -0.032	0.975	NS
LDH	Normal	13 (28.26%)	2 (40%)	FE	0.624	NS
	Increased	33 (71.74%)	3 (60%)			
CRP (mg/L)		77.25 (38.4 - 111.9)	14.9 (12.8 - 44.4)	z= -2.154	0.031	S
CRP	Normal	0 (0%)	0 (0%)			
	Increased	46 (100%)	5 (100%)			
Cytogenetics						
Cytogenetics	Unfavorable	0 (0%)	1 (20%)	X^2= 5.378	0.122	NS
	Favorable	8 (17.4%)	0 (0%)			
	Intermediate	38 (82.6%)	4 (80%)			

*Mann-Whitney test of significance (z); *Fisher's Exact test of significance (FE); Significant (S); *Student t-test of significance; Non-significant (NS).

As regard different FAB subtypes, we observed a significant difference between CD200 positive and negative patients' groups (p=0.006); CD200 positive expression was higher among M1-M2 subtypes as shown in (Table 6). On the other hand, CD56 antigen expression was higher among M1-M2 but with no significance (Table 7).

Table 6: The difference between CD200+ and CD200- regarding FAB classification.

Characteristics		CD200		Test of significance		
		Negative	Positive			
		(%) N	(%) N	Value	*p-Value*	Sig.
FAB class	AML unclassified	0 (0%)	3 (7.89%)	FE	0.006	S
	AML (M0)	0 (0%)	6 (15.79%)			
	AML (M1-M2)	5 (38.46%)	24 (63.16%)			
	AML (M3)	2 (15.38%)	0 (0%)			
	AML (M4-M5)	6 (46.15%)	5 (13.16%)			

*Fisher's Exact test of significance (FE); Significant (S).

Table 7: The difference between CD56+ and CD 56- regarding FAB classification.

Characteristics		CD56		Test of significance		
		Negative	Positive			
		(%) N	(%) N	Value	*p-Value*	Sig.
FAB class	AML unclassified	3 (6.52%)	0 (0%)	FE	0.889	NS
	AML (M0)	5 (10.87%)	1 (20%)			
	AML (M1-M2)	26 (56.52%)	3 (60%)			
	AML (M3)	2 (4.35%)	0 (0%)			
	AML (M4-M5)	10 (21.74%)	1 (20%)			

*Fisher's Exact test of significance (FE); Non-significant (NS).

Response to induction chemotherapy and fate

As detailed in (Table 8), five patients (38.46%) achieved complete remission in CD200– subgroup compared to seven patients (18.42%) in CD200+ subgroup, two patients (15.38%) in CD200– subgroup showed induction failure compared to 7 patients (18.42%) in CD200+ subgroup (P= 0.404). Twenty-four patients (63.16%) died during induction in CD200+ subgroup in comparison to 6 patients (46.15%) in CD200- patients (P=0.282).

Total death was higher among CD200+ (30 patients, 78.95%) patients in comparison to CD200- patients (6 patients, 46.15%) (p= 0.037).

Table 8: The difference between CD200+ and CD200- regarding response of the treatment and fate.

			CD200		Test of significance		
			Negative	Positive			
			N (%)	N (%)	Value	*p-Value*	.Sig
Remission	No (Induction Deaths)		6 (46.15%)	24 (63.16%)	FE	0.404	NS
	Yes	Partial remission (Induction Failure)	2 (15.38%)	7 (18.42%)			
		Complete remission	5 (38.46%)	7(18.42%)			
Total Death	No		7 (53.85%)	8 (21.05%)	FE	0.037	S
	Yes		6 (46.15%)	30 (78.95%)			
Induction Death	No		7 (53.8%)	14 (36.8%)	X^2= 1.156	0.282	NS
	Yes		6 (46.2%)	24 (63.2%)			

*Fisher's Exact test of significance (FE); *Chi-Square test of significance (X^2); Significant (S); Non-significant (NS).

On the other hand, Complete remission (CR) was achieved by 11 patients (23.91%) in the CD56– subgroup, compared to 1 patient (20%) in the CD56+ subgroup, Induction failure was observed in 8 patients (17.39%) in the CD56– subgroup and in 1 patient (20%) in the CD56+ subgroup (p = 1.00). Mortality during induction occurred in 3 patients (60%) in the CD56+ subgroup, compared to 27 patients (58.7%) in the CD56– subgroup (p = 1.00). Total number of deaths among CD56+ subgroup of patients was (4 patients, 80%), in comparison to (32 patients, 69.57%) in CD56- subgroup of patients (p= 1.00) as shown in (Table 9).

Table 9: The difference between CD56+ and CD56- regarding response of the treatment and fate.

			CD56		Test of significance		
			Negative	Positive			
			N (%)	N (%)	Value	*p-Value*	.Sig
Remission	No (Induction Deaths)		27 (58.7%)	3 (60%)	FE	1.00	NS
	Yes	Partial remission (Induction Failure)	8 (17.39%)	1 (20%)			
		Complete remission	11(23.91%)	1 (20%)			
Total Death		No	14 (30.43%)	1 (20%)	FE	1.00	NS
		Yes	32 (69.57%)	4 (80%)			
Induction Death		No	19 (41.3%)	2 (40%)	FE	1.00	NS
		Yes	27 (58.7%)	3 (60%)			

*Fisher's Exact test of significance (FE); Non-significant (NS).

As shown in (Table 10), some significant data were observed regarding the group of patients with double negative expression of both markers (CD200- CD56-) in comparison to the rest of patients included in the study; 76.92% of patients with double negative expression were among males (p= 0.045), with M4-M5 (46.15%) and M3 (15.38%) as the commonest FAB subtypes among them (p= 0.006) and this group had a lower incidence of mortality (p= 0.037).

Table 10: The difference between (CD200- CD56-) group of patients and the remaining patients regarding demographic and clinical data.

		Double negative		Test of significance		
		No	Yes			
		Mean ± SD N (%)	Mean ± SD N (%)	Value	*p-Value*	.Sig
Sex	Male	17 (44.74%)	10 (76.92%)	X^2= 4.028	0.045	S
	Female	21 (55.26%)	3 (23.08%)			
FAB class	AML unclassified	3 (7.89%)	0 (0%)	FE	0.006	S
	AML (M0)	6 (15.79%)	0 (0%)			
	AML (M1-M2)	24 (63.16%)	5 (38.46%)			
	AML (M3)	0 (0%)	2 (15.38%)			
	AML (M4-M5)	5 (13.16%)	6 (46.15%)			
Total Deaths	No	8 (21.05%)	7 (53.85%)	FE	0.037	S
	Yes	30 (78.95%)	6 (46.15%)			

*Fisher's Exact test of significance (FE); *Chi-Square test of significance (X^2); Significant (S).

The CD200 expression is associated with higher incidence of mortality in our study (OR 4.38, p= 0.037), while CD56 is not associated with significant mortality (p=1.00).

In our study; 12 patients have lived free from the disease for a certain time (ranges from 3 to12 months) during our study time; with a cumulative proportion surviving at 3 months represents 83.3% (10/12 cases), at 5 months represents 72.9% (7/12 cases), and at 7 months represents 60.8% (5/12 cases) as shown in (Table 11), (Figure 3).

Table 11: Disease free survival (DFS) in the studied patients.

Time (months)	Cumulative Proportion Surviving at the Time	Numbers of remaining cases
3	83.3%	10
5	72.9%	7
7	60.8%	5

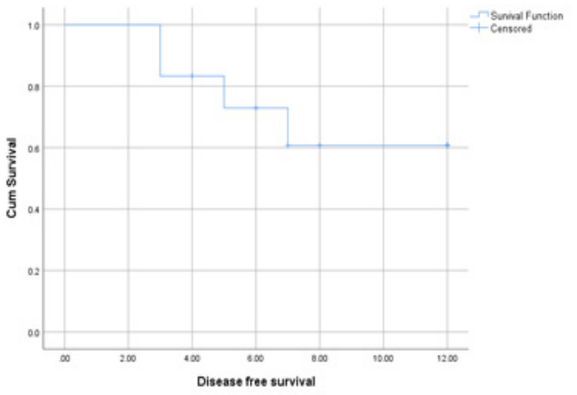

Fig. 3: Descriptive for the DFS of the whole studied patients.

DISCUSSION

Acute myeloid leukemia (AML) is a heterogenous, and complex disease characterized by rapid cellular proliferation, an aggressive clinical course, and generally high mortality[8]. Recent advances in understanding the molecular pathogenesis, prognostic markers and treatment options for AML have significantly expanded in the modern era[9].

The persistence of leukemic stem cells is considered the primary cause of relapse in acute myeloid leukemia[10]. Immune evasion by leukemic stem cells is a key factor in relapse, mediated by the expression of specific cell surface molecules that have immune-modulatory functions[11]. Novel immune-directed therapeutic approaches form a major focus of current and clinical research[12].

The CD200 is a crucial immune checkpoint protein belonging to the immunoglobulin superfamily. It exerts immunosuppressive signaling through its receptor, CD200R, which is present on immune cells[11]. Previous studies have shown that AML patients with CD200 overexpression exhibit reduced immune responses from Natural Killer cells and T cells, suggesting that CD200 may serve as an immunotherapeutic target in AML[13].

The CD56 (NCAM1), a marker for NK cells and a member of the immunoglobulin superfamily, is also expressed in AML. Previous studies suggest a functional role of NCAM1 in disease progression and contributes to resistance to therapy[14].

In this study, we examined the expression of CD200 and CD56 on a series of 51 adult patients with de novo AML at time of diagnosis; 27 (52.9%) males and 24 (47.1%) females with a male to female ratio of 1.13: 1. A similar higher incidence in males was reported by ***Zhang et al.*** (2022)[9].

All patients were diagnosed according to morphological, cytogenetic analysis and immunophenotypic criteria. Follow up of the patients was done on days 28, 60 and 90 from the beginning of the induction therapy by different parameters, CBC, peripheral blood films and BM examination. By the end of our study time, 36 (70.6%) died and 15 (29.4%) patients survived.

The clinical signs and symptoms of AML are varied and nonspecific, typically resulting from leukemic infiltration of the bone marrow, leading to cytopenia. Commonly, patients present with fatigue, hemorrhage, infections, and fever due to reductions in red blood cells, platelets, and white blood cells, respectively. Other typical symptoms include fatigue, hemorrhage or infections and fever due to decreases in red cells, platelets, and white blood cells, respectively. Pallor, dyspnea and fatigue on exertion are common. Leukemic infiltration of various tissues, including the liver (hepatomegaly), spleen (splenomegaly), skin (leukemia cutis), lymph nodes (lymphadenopathy), bone (bone pain), gingiva, and central nervous system, can produce a variety of other symptoms[15].

In this study, weight loss and hepatomegaly were the most common clinical symptoms observed in our patients' group (54.9% and 49.0% respectively) followed by splenomegaly (47.1%), bony aches (45.1%), fever (41.2%) then lymphadenopathy (39.3%) and finally bleeding tendency (28.6%).

Moreover, M1-M2 subtypes were found to be the most common FAB subtypes (56.9%) in accordance with ***Muhsin et al.*** (2018)[1] who reported M2 as the most frequent subtype (36.7%), in addition to ***Alwan et al.*** (2009)[16], who found that M2 (38%) and M1(20%) are the most frequent subtypes. No M6 and M7 due to low incidence rate.

In this study, The CD200 positive expression was observed in 38 out of 51 patients (74.5%), compared to 76.5% reported by ***Atfy et al.*** (2015)[17] and 56% reported in study by ***Damiani et al.*** (2015)[5]. While CD56 was expressed in 5 of 51 patients (9.8%), in comparison to 10%, 19.8% and 29.21% as reported by ***Jiang et al.*** (2011)[18], ***Juncà et al.*** (2014)[19] and ***Sun et al.,*** (2021)[20] respectively. In our study, low levels of CD56 expression may be attributable to small number of included patients specially with M4-M5 subtypes with consideration to the fact that CD56 antigen is constitutively expressed in normal

monocyte and monocyte-derived cells, while monoblastic leukemia is generally associated with a poorer prognosis[21], so suggesting larger numbers of patients will be required to provide more reliable data about CD56 antigen. Regarding double expression of CD200 and CD56, we found that both markers are co-expressed in only 5 (9.8%) patients representing double positive expression, and the number of patients who were negative for both markers is 13 (25.5%) patients representing double negative expression.

Regarding demographic data in patients with CD200 positive versus patients with CD200 negative: 55.26% of CD200 positive patients were among females while 76.9% of CD200 negative patients were among males and this was statistically significant. While no significant difference was found between two groups as regard age and clinical data and this data is consistent with ***Tiribelli et al.*** (2017)[22] and ***Girshova et al.*** (2023)[23] who reported no significant differences in CD200 antigen expression regarding sex and age of patients. On the other hand, our study showed a significant difference as regard age between CD56 positive and negative groups. While CD56 antigen expression has no significant difference on sex and clinical data which is similar to a study by ***Ahmed et al.*** (2015)[24] who reported no significance of CD56 antigen expression as regard demographic and clinical data.

As regard the present study lab data, we observed no significant difference between CD200 positive and negative groups as reported by ***Aref et al.*** (2020)[4] and ***Rabea et al.*** (2022)[13]. On the other hand, only CRP shows significant difference between two groups of CD56; may be due to association with other co-infections.

Concerning cytogenetic risk groups in our study, we observed no significant difference between two groups of CD200 expression in comparison to ***Damiani et al.*** (2015)[5] who found a negative impact of CD200 expression in patients with unfavorable cytogenetics and this difference could be attributed to lower number of studied groups and lack of molecular studies for identifying more risk groups.

As regard two groups of CD56, no significant difference was observed and these results are in consistent with the findings of ***Djunic et al.*** (2012)[21], ***Juncà et al.*** (2014)[19] and ***Sun et al.*** (2021)[20] who also reported no difference in CD56 positivity across cytogenetic risk groups. In contrast, ***Chang et al.*** (2004)[25] demonstrated a significant association between CD56 antigen expression and the favorable cytogenetic translocation and ***Raspadori et al.*** (2001)[26] reported that CD56 is frequently associated with unfavorable cytogenetic abnormalities.

Another notable finding in the present study was the significant difference between CD200 positive and negative patients' groups concerning the different FAB subtypes (P=0.006); CD200 positive expression was higher among M1-M2 subtypes as reported by ***Coles et al.*** (2011)[27] and ***Atfy et al.,*** (2015)[17]. On the other hand, CD56 antigen expression was higher among M1-M2 but with no significance. In comparison to a study reported by ***Junge et al,*** (2018)[6] who reported CD56 antigen expression was most frequently associated with the M5 FAB subtype of AML, while ***Raspadori et al.*** (2001)[26], who reported CD56 positive expression as 24% (37/152), showed that CD56 expression was detected more in M2 and M5 patients. Our data may differ due to small number of patients expressing CD56 molecule.

Complete remission (CR) is an important parameter for evaluating the response of the disease to therapy. In the present study, no significant difference in treatment response was observed between the two groups for either CD200 or CD56, aligning with the findings of ***Aref et al.*** (2020)[4] and ***Sun et al.*** (2021)[20] respectively.

Regarding total deaths, we found that positive CD200 antigen expression is associated with higher mortality risk (OR = 4.38, p=0.037) and this may suggest a negative impact of CD200 expression on survival rate in comparison to lack of CD200 expression and these data are in accordance with ***Zhang et al.***(2014)[28] who concluded that the CD200 antigen expression in AML may associate with a poor prognosis. On the other hand, CD56 has no significant effect on mortality which is similar to studies reported by ***Teke et al.*** (2017)[29].

Furthermore, our study examined the death rate during chemotherapy induction (induction death) to determine if the group expressing CD200 or CD56 was more susceptible to induction death. However, we found no statistically significant difference associated with either marker or induction death. This finding may be due to the limited size of the study population and aligns with the results reported by ***Aref et al.*** (2020)[4].

Several factors that contributed to these discrepancies include methodological differences in antigen detection, the size of the study population, whether patients were drawn from one institution or multiple institutions, as well as factors like age and cytogenetic variations.

We observed that the group of patients with double negative expression of CD200 and CD56 has some significant data in comparison to the rest of patients included in the study; 76.92% of patients with double negative expression were among males (p= 0.045), with M4-M5 (46.15%) and M3 (15.38%) as the commonest FAB subtypes among them (p= 0.006) and this group had a lower incidence of mortality (p= 0.037).

Regarding disease free survival (DFS) and its correlation with any of the two markers, we couldn't have enough and significant data due to small sample size and relatively small number of living patients.

This study has some limitations; at first only 51 patients were included in the study, lack of some data as karyotyping and some molecular profiles. Therefore, further studies are required to confirm the expression of CD200 and CD56 in a larger sample size, including full chromosomal and molecular studies to get more reliable data on correlation between both markers and cytogenetic risk groups. Secondly, the present study couldn't get enough data on the cumulative disease-free survival and the cumulative overall survival, so follow up for longer duration is better recommended for assessment of overall survival (OS) and disease-free survival (DFS).

CONCLUSION

In the current study, a statistically significant difference was found between CD200 and gender (p= 0.45), between CD56 and age (p= 0.002) but no significance was found between any of the two markers and rest of demographic and clinical. As regards laboratory parameters, a significant difference was found only between CD56 expression and CRP (p= 0.031). Moreover, this work could not prove any association between either CD200 or CD56 expression and cytogenetic risk stratification of the studied AML patients. Only what we could prove is that CD200 expression is associated with higher incidence of mortality in our study (OR 4.38, p= 0.037) which suggests a negative impact of CD200 expression on survival rate while CD56 is not associated with significant mortality.

PUBLICATION STATUS

The paper has not been published in its current form or substantially similar form elsewhere including on a web site and also, it has not been accepted for publication elsewhere.

CONFLICTS OF INTEREST

There are no conflicts of interest, including financial and other relationships that can bias the results.

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الأثر التنبؤي لتعبير سي دي ٢٠٠ وسي دي ٥٦ في مرضى سرطان الدم النقوي الحاد في جامعة عين شمس

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المقدمة: يُعدّ سرطان الدم النقوي الحاد (AML)من امراض الدم الخبيثة حيث انه يتميز بتباين في النتائج التنبؤية ، وينتج عن توقف التمايز الطبيعي للخلايا الجذعية المكوّنة للدم، مع تكاثر غير مسيطر عليه لخلايا ذات أصل نقوي، مما يؤدي إلى ارتشاح نخاع العظم والأنسجة الأخرى بالخلايا السرطانية. تتهرب الخلايا السرطانية من المناعة الطبيعية عن طريق تحفيز التثبيط المناعي من خلال ظهورجزيئات سطحية خلوية ذات وظيفة مناعية تنظيمية. تُشكّل الأساليب العلاجية المناعية المبتكرة محورًا رئيسيًا في الأبحاث السريرية الحالية.

الهدف: تقييم مستويات سي دي ٥٦وسي دي٢٠٠ وتحديد الأهمية التنبؤية لتعبيرهما لدى المرضى الذين تم تشخيصهم حديثًا بسرطان الدم النقوي الحاد.

الطرق: أُجريت هذه الدراسة المقطعية في مستشفيات جامعة عين شمس على ٥١ مريضًا بالغًا تم تشخيصهم حديثا بمرض سرطان الدم النقوي الحاد، والذين يترددون على وحدة أورام الدم في مستشفيات جامعة عين شمس، وذلك خلال الفترة من فبراير ٢٠٢٢ وحتى يونيو ٢٠٢٣.

النتائج: تم تسجيل تعبير إيجابي لسي دي ٢٠٠ في ٧٤,٥٪ من المرضى، بينما أظهر ٩,٨٪ من المرضى تعبيرًا إيجابيًا لسي دي ٥٦ وُجد أن النمطين الفرعيين M١ وM٢ هما الأكثر شيوعًا وفقًا لتصنيف FAB. كان التعبير الإيجابي لسي دي ٢٠٠ أعلى بين المريضات الإناث (p= 0.045) ومن ناحية أخرى، كان المرضى الذين أظهروا تعبيرًا إيجابيًا لسي دي ٥٦ أصغر سنًا مقارنة بالمرضى الذين لم يظهروا هذا التعبير (p= 0.002) كما كانت معدلات الوفيات الإجمالية أعلى بين المرضى الذين لديهم تعبير إيجابي لسي دي ٢٠٠ مقارنةً بالمرضى الذين لم يظهروا هذا التعبير. (p= 0.037).

الخلاصة: تشير دراستنا إلى أن تعبير سي دي ٢٠٠ يرتبط بمعدل وفيات أعلى، مما يدل على تأثير سلبي على البقاء على قيد الحياة، بينما لا يظهر تعبير سي دي ٥٦ ارتباطًا كبيرًا بمعدل الوفيات .