Zagazig Journal of Pharmaceutical Sciences

Journal homepage: https://zjps.journals.ekb.eg/

Print ISSN: 1110-5089 Online ISSN: 2356-9786

The Prognostic Value of Aberrant Expression of Cluster Differentiation Markers in Patients with Acute Leukemia

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ARTICLE INFO

Article History:
Received: 3 June 2023
Accepted: 24 July 2023
Published: 30 July 2023

Key words:
Acute Leukemia; Aberrant expression; CD markers; Prognosis

ABSTRACT

In patients with acute leukemia, aberrant expression of Cluster Differentiation (CD) markers may have an influence on clinical response, remission rate, and overall survival (OS). The current study aimed to evaluate the effect of aberrant expression of cluster differentiation markers on the prognosis of acute leukemia patients. The present cohort research included patients who were newly diagnosed with Acute Leukemia between January 2019 and December 2022 were included in the current cohort study. The current study comprised 163 individuals diagnosed with acute leukemia, including 98 patients with Acute Myeloid Leukemia (AML) (60.1%) and 65 patients with Acute Lymphoid Leukemia (ALL) (39.9%). The ratio of males to females was (1.1:1). According to the current study, 40.8% and 29.2% of AML and ALL patients showed aberrant expression, respectively. The current research also found that aberrant expression of CD2 in AML and CD13 in ALL was the most common. The current study's findings suggested that aberrant expressions CD2, CD5, and CD7 have been correlated with poor prognosis. However, no statistically significant differences were detected between the aberrant expressions of CD10, CD13, CD19, CD20, CD22, and CD33 markers and prognosis.

1. Introduction

Historically, acute leukemias were categorized using the French-American-British (FAB) classification system. In 2008, the World Health Organization (WHO) revised the classification to include not just cell morphological examination, but also new methods such as flow cytometry (FCM), cytochemistry, immunohistochemistry, and cytogenetics. This expanded technique allows for a more detailed and accurate categorization of acute leukemias [1,2].

Acute myeloid leukemia and acute lymphoid leukemia are the two primary forms of AL. These blast cells have distinct clinical, morphological, immunological, and molecular characteristics, as well as discrete patterns of surface antigen expression recognized by specifically CD antigens [3].
Immunophenotyping, in conjunction with other clinical and biological characteristics, can aid in the prediction of therapy response and patient survival in acute leukemia [4]. When morphology interpretation is difficult, immunotyping can be very effective in

DOI: 10.21608/zjps.2023.210836.1048
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identifying certain leukemia subtypes that cannot be identified just by morphological criteria. While immunotyping of peripheral blood and bone marrow is insufficient to define the precise treatment approach, it does serve as a useful prognostic indicator [5]. Accurate detection, identification, and characterization of leukemic cells are critical for acute leukemia diagnosis and therapy. While certain subtypes may be recognized by morphology or immunohistochemistry, immunophenotyping is still required for reliable identification of specific subtypes [6].

Lineage infidelity (expression of lymphoid markers in myeloid blast cells, such as CD7, CD19, CD79a, CD10, CD2, CD5, CD3), asynchronous antigen expression (presence of both early and late markers in a single cell, such as CD34, and CD15 in AML), and antigen overexpression (abnormally high expression of certain antigens per cell) are all examples of abnormal antigen expression in acute leukemia. Abnormal light scatter characteristics and the absence of lineage-specific antigens (such as the absence of CD13 and CD33 on myeloid blasts) are examples of aberrancy. Cross-lineage expression of myeloid antigens in ALL, B-lineage antigens in T-ALL, or T-lineage antigens in B-ALL7 is an example of aberrant antigen expression in ALL [7].

A situation in which myeloblasts display lymphoid-associated or other myeloid lineage markers or lymphoblasts express lymphoid-associated markers is known as an aberrant phenotype. This condition has been documented in both ALL and AML, with reported incidence rates of up to 88% [8,9] .

Aberrant antigen expression can have a poor impact on the clinical response, remission rate, and overall survival of patients with acute leukemia, indicating its significance as a prognostic factor [10-12].

Hyperleukocytosis, previously known as a white blood cells (WBC) count of more than 100x109/L, has been related to a poor prognosis due to early death and an increased probability of relapse [13]. On the other hand, compared to patients without hyperleukocytosis, a patient with hyperleukocytosis was correlated with higher rates of disseminated intravascular coagulation, and tumor lysis syndrome [14].

The purpose of this study is to assess the prevalence of aberrant phenotypes and their relationship to known prognostic markers such as gender, age, WBC count, and blast percentage in Syrian patients with Acute Leukemia.

2. Materials and Methods

2.1 Study design

The present cohort research included patients who were newly diagnosed with Acute Leukemia using the WHO and FAB classifications and were treated with standard leukemia chemotherapy (7+3) protocol for all AML subtypes except acute promyelocytic leukemia (APL), which is treated with ATRA [15], and BFM chemotherapy protocol for ALL patients [16] between January 2019 and December 2022. All participants in this research had their bone marrow aspirated and collected in heparin or EDTA coagulation tubes for immunophenotyping.

2.2 Prognostic criteria

Patients with acute leukemia who did not die or relapse were classified as a good prognosis, otherwise patients were classified as a poor prognosis.

2.3 Ethical consideration

Aleppo University's Ethical Committees approved our research (Registration number /34/; date 7/1/2019). Declare that the study was done in accordance with the ethical international standards outlined in the 2010 Declaration of Helsinki and its advanced versions dating back to 1975. Before enrolling in our trial, patients were asked to provide written informed permission.

2.4 Patient follow-up

The present study comprised 163 patients with acute Leukemia from Aleppo University Hospital and Ibn Al Rushd Hospital's hematology departments. The overall survival (OS) time and other patient data were obtained from the patient admission and follow-up offices.

2.5 Immunophenotyping

Flow cytometry was used to analyze immunophenotype blast cell samples. Four distinct fluorochrome-conjugated monoclonal antibodies were used to stain and analyze single-cell suspensions (about 106 cells/mL). The CD2-PerCp, CD3-FITC, CD4-PE, CD5-APC, CD7-FITC, CD8-PreCP were used for T Cell lineage, the CD10-PE, CD19-PerCP, CD20-FITC, CD22-PerCp, CD23-APC, CD38-FITC were used for B Cell lineage, the CD11b-FITC, CD13-PE, CD14-PerCp, CD33-FITC, CD163-FITC were used for myeloid Cell lineage, and CD34-APC,

CD117-APC were used for blast cell (Becton Dickinson Biosciences). Gently combined and incubated at room temperature in the dark for 30 minutes. Following that, the RBCs were lyzed using a lysis solution (100 mL distilled water, 0.84 ammonium chloride, 0.12 gr potassium bicarbonate, and 0.002 tetrasodium EDTA). After 10 minutes of incubation at room temperature in the dark, the mixture was centrifuged at 1200 rpm for 5 minutes. Before being analyzed using the BD FACSCanto (two lasers, six parameters) analyzer, the cells were treated with 0.5 mL of 2% paraformaldehyde solution, and data were processed with BD FACSDivaTM software Figure (1).

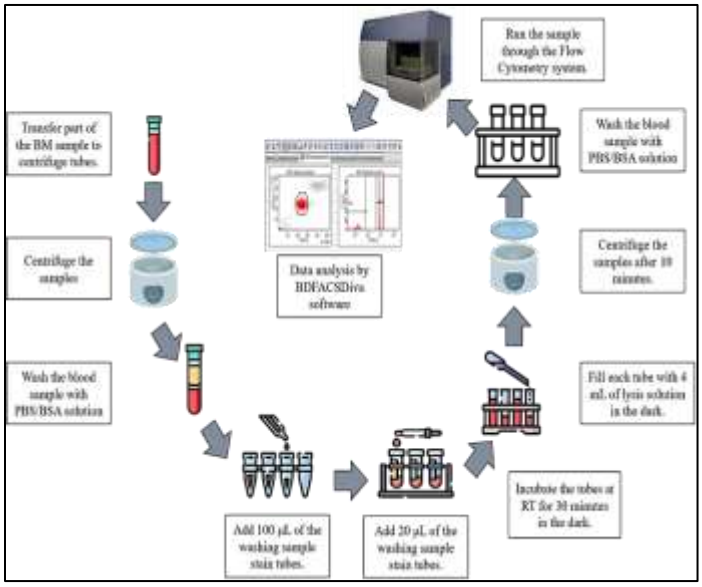

Figure 1: *Sample preparation workflow for detecting aberrant expiration of CD markers by flow cytometric immunophenotyping. BM: Bone Marrow, PBS/BSA: Phosphate Buffer Solution with/ 1% Bovine Buffer Solution, RT: Room Temperature.*

2.6 Statistical analysis

The One Way ANOVA and the Mann-Whitney U test were used to compare continuous and categorical variables between groups, respectively. The Kaplan-Meier method was used to estimate survival curves, and to compare survival curves between groups. The groups were divided based on gender, age (<18 years versus >18 years), WBC count (<100 X109/L versus >100 X109/L), and Blast% (<50% versus >50%). The IBM SPSS software (version 24) was used for statistical analysis. A significance level for analyses was a P value ≤0.05.

3. Results

3.1 Clinical features

The current study included 163 individuals who had acute leukemia, including 98 cases of AML (60.1%) and 65 cases of ALL (39.9%). There were 79 children and 84 adults among the patients, with a male-to-female ratio of (1:1.1).

The average age of AML patients was 24 ± 39 years (range, 1-85 years), divided into 46 cases of males and 52 cases of females, with a ratio of (1:0.88), and 69.4% of AML patients were adults. However, hyperleukocytosis and blasts of more than 50% have been detected in about (34.6%) and (71.4%) of AML patients, respectively. Approximately (57.1%) of AML patients had a good indication to respond to treatment.

The average age of ALL patients was 14 ± 16 years (range, 1-69 years), divided into 40 cases of males and 25 cases of females, with a ratio of (1.1:1), and 75.4% of ALL patients were child. However, hyperleukocytosis and blasts of more than 50% have been detected in about (36.9%) and (44.6%) of ALL patients, respectively. Approximately (72.3%) of ALL patients had a good indication to respond to treatment Table (1).

Table 1: *The correlation between age, gender, WBC, blast%, and prognosis groups in patients with acute leukemia.*

Variable		Acute Leukemia		P Value
		AML	ALL	
Gender Group	Male	46	40	0.068
	Female	52	25	
Age Group	Child	30	49	<0.000
	Adult	68	16	
WBC Group	<100X10^9	61	41	<0.000
	≥100X10^9	37	24	
Blast%	<50%	28	36	0.001
	≥50%	70	29	
Prognosis	Good	56	47	0.035
	Poor	42	18	
Total		98	65	-
(%)		(60.1%)	(39.9%)	-

ALL: Acute Leukemia, AML: Acute Myeloid Leukemia, WBC: White Blood Cell

3.2 Immunophenotyping Analysi

According to the current study, roughly 40.8% of AML patients showed aberrant lymphocyte antigen.

expression. The current study also found that aberrant expression of CD2, CD10, and CD19 antigens was the most common, with rates of 11.2%, 10.2%, and 9.1%, respectively Table (2).

While the current study found that approximately 29.2% of patients with ALL had aberrant expression of myeloid antigens Figure (2), the current study also found that aberrant expressed of CD13 and CD33 antigens was the most common, at 21.5% and 7.7%, respectively Table (3).

3.3 Survival Analysis

From January 2019 to December 2022, 163 individuals with acute leukemia were followed up; the median follow-up length was 21.07 ±14.32 months (range, 2 days to 47.1 months). At the end of the follow-up period, (58/98) patients with AML (59.2%) and (47/65) patients with ALL (72.3%) were still alive.

The findings of the Kaplan-Meier statistical analysis indicated statistically significant differences in overall survival time and blast percentage, WBC, and aberrant expression of CD2, CD5, CD7. However, the patients with WBC count less than 100 X109/L, and BMB percentage less than 50% and without aberrant expression of cluster of differentiation marker had a longer overall survival time than those with WBC count higher than 100 X109/L (32.20 versus 15.85, P value <0.000), bone marrow blast cells higher than 50 % (32.52 versus 16.99, P value <0.000), aberrant expression of CD2 (22.09 versus 14.10, P value=0.020), aberrant expression of CD5 (22.09 versus 11.4, P value=0.025), aberrant expression of CD7 (22.09 versus 3.18, P value<0.000) Figure (3). However, the current investigation found no statistically significant differences between patient age and gender and aberrant expression of CD13, CD19, and CD33 (P-values were 0.234, 0.499, 0.425, 0.243, and 0.158, respectively), Table (4).

Table 2: *Frequencies of Lymphoid CD markers in patients with AML. AML: Acute Myeloid Leukemia, WBC: White Blood Cell, CD: Cluster differentiation.*

Variable		Frequencies of Aberrant Lymphoid Markers in AML						
		CD2	CD5	CD7	CD10	CD19	CD20	CD22
Gender	Male	7	5	2	1	4	1	1
Group	Female	4	5	4	1	5	0	0
Age	Child	4	4	2	1	2	1	1
Group	Adult	7	6	4	1	7	0	0
WBC	$<100X10^9$	3	3	0	0	3	0	0
Group	$\geq100X10^9$	8	7	6	2	6	1	1
Blast%	<50%	0	2	0	0	2	0	0
	≥50%	11	8	6	2	7	1	1
Prognosis	Good	3	4	0	0	4	0	0
	Poor	8	6	6	2	5	1	1
Total (%)		(11/98) 11.2%	(10/98) 10.2%	(6/98) 6.1%	(2/98) 2.0%	(9/98) 9.1%	(1/98) 1.0%	(1/98) 1.0%

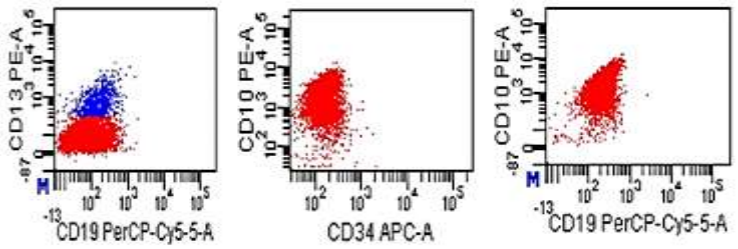

Figure 2: *Histogram of flow cytometry in a case of ALL expressing CD13 myeloid marker. CD: Cluster Differentiation, PerCP: Peridinin-Chlorophyll-Protein, APC: Allophycocyanin,* PE: phycoerythrin.

Table 3: *Frequencies of Myeloid CD markers in patients with ALL. LL: Acute Lymphoblastic Leukemia, WBC: White Blood Cell, CD: Cluster differentiation*

Variable		Frequencies of Aberrant Myeloid Markers in ALL	
		CD13	**CD33**
Gander Group	Male	12	3
	Female	2	2
Age Group	Child	14	4
	Adult	0	1
WBC Group	$<100X10^9$	9	3
	$\geq100X10^9$	5	2
Blast%	<50%	9	2
	≥50%	5	3
Prognosis	Good	11	5
	Poor	3	0
Total (%)		**(14/65) (21.5%)**	**(5/65) (7.7%)**

Table 4: *The correlation between overall survival times and aberrant expression of CD markers, BM blast%, and WBCs in patients with acute leukemia patients.*

Variables	**(%)**	**Overall Survival time (months) Mean** ± SD	**P value**
Gender			0.234
Male	(46.9%)	24.94±13.72	
Female	(53.1%)	21.62±15.45	
Age, Year			0.499
<18	(30.6%)	25.04±14.33	
>18	(69.4%)	21.80±14.79	
Patients with AML			<0.000
Without Aberrant LyAg	(59.4%)	22.69±14.67	
With Aberrant LyAg			
CD2	(11.2%)	14.10±12.36	
CD5	(10.2%)	11.44±10.48	
CD7	(6.1%)	3.18±2.63	
CD10	(2.0%)	7.80±3.77	
CD19	(9.1%)	18.41±12.88	
CD20	(1.0%)	-	
CD22	(1.0%)	-	
Patients with ALL			<0.000
Without Aberrant MyAg	(70.8%)	29.97±14.13	
With Aberrant MyAg			
CD13	(21.5%)	16.90±7.62	
CD33	(7.7%)	16.99±13.79	
Bone marrow blast (%)			<0.000
50% >	(39.3%)	32.52±11.45	
50% ≤	(60.7%)	20.36±1.46	
WBC (X 10^9/L)			<0.000
100 >	(77.4%)	32.20±10.34	
100 ≤	(22.6%)	15.85±13.55	

4. Discussion

Acute leukemia are malignant clonal illnesses of the blood-forming organs characterized by the presence of one or more hematopoietic cell lines. The extensive replacement of bone marrow with aberrant immature and undifferentiated hematopoietic cells in these disorders results in a reduction in the total number of erythrocytes and platelets in the peripheral blood [17].

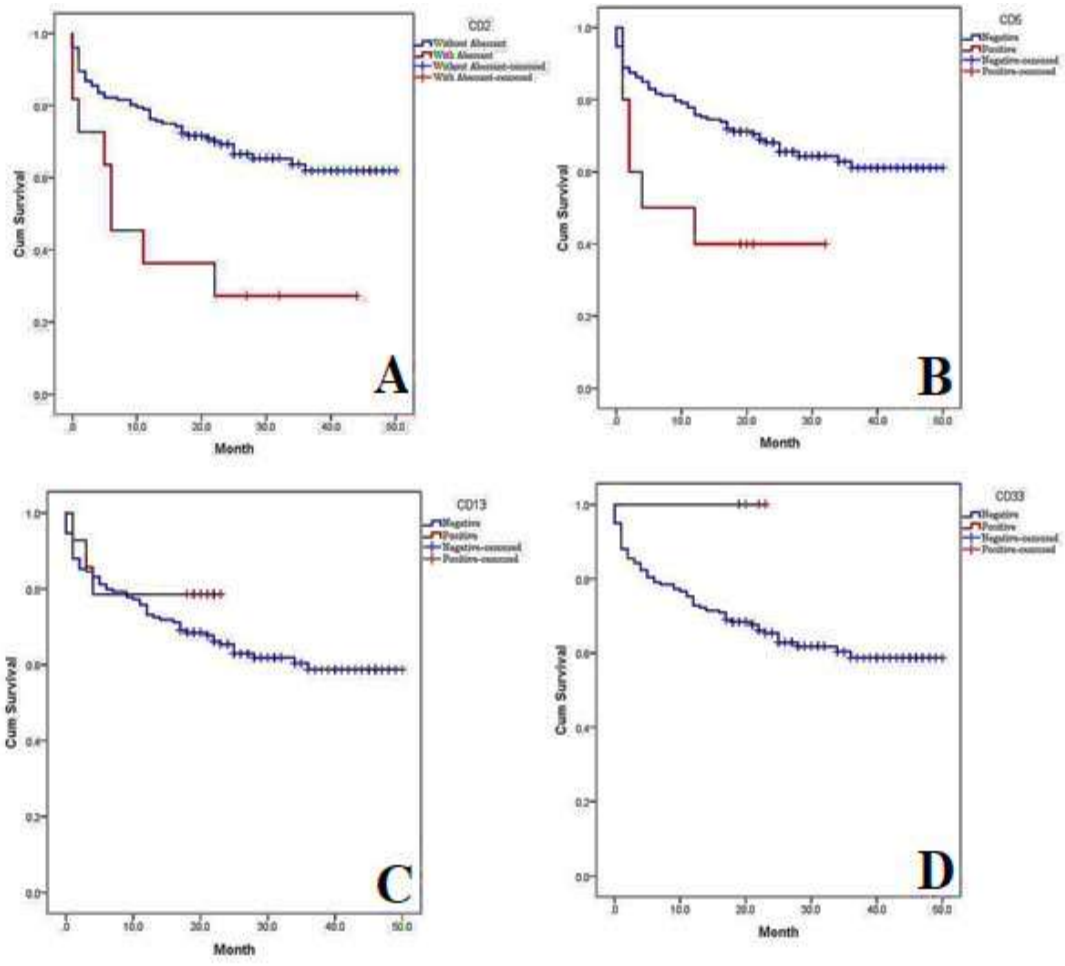

Figure 3: *Relation between overall survival times and CD2 in patient with AML (A), CD5 in patient with AML (B), CD13 in patient with ALL (C), and CD33 in patient with ALL (D). CD: Cluster Differentiation, ALL: Acute Lymphoblastic Leukemia, AML: Acute Myeloid Leukemia.*

ALL is the most common type of leukemia in children. Our current study results indicate that around 75.4% of ALL patients were children, which is comparable to [18,19], which reported an incidence rate of approximately 70.0% and 80.6% among ALL children patients, respectively. AML, on the other hand, is the most common type of leukemia in adults. Our current study results indicate that around 69.4% of AML patients were adults, which is comparable to [20-23], which indicated an incidence rate of approximately 76.0%, 84.6%, 89.8%, and 87.3 among adult patients with AML, respectively. A variation in the biology of hematopoiesis between children and adults may explain the increased frequency of acute lymphoblastic leukemia in children. Children naturally have a higher percentage of lymphocytes, while adults have a higher percentage of myeloid cells, which may contribute to the development of different types of leukemia.

Males and females can both be affected by acute leukemia. The current study found that men were the most affected by acute leukemia, which was similar to previous results21-23. The specific mechanism behind this disparity is unknown, but it does show that hormone variations may play a role in disease-altering biological and social consequences [24].

In patients with acute leukemia, hyperleukocytosis is defined as a white blood cell count higher than 100,000/mL, and it is usually associated with higher morbidity and mortality, which can be up to 40% if undiagnosed [25,26]. However, the present study showed that 35.6% of patients with acute leukemia had hyperleukocytosis, which has been associated with a poor prognosis which is comparable to [27-

29]. This might be related to the emergence of symptoms such as leukostasis, tumor lysis syndrome, and disseminated intravascular coagulopathy (DIC) [30].

Myeloid CD markers in ALL and lymphoid CD markers in AML might affect prognosis. In our study, 98 individuals were diagnosed with AML, and CD2 was the most frequently aberrant expressed antigen in 11 (11.2%) of the cases, followed by CD5 in ten (10.2%), CD19 in nine (9.1%), CD7 in six (6.1%) cases, CD10 in two (2.0%) cases, CD20 in one (1.0%) case, and CD22 in one (1.0%) case. Our current study's findings agreed with the findings of another study [31], which found aberrant expression of the CD2 antigen most prevalent in AML patients, but contradicted the findings of other studies [32,33], which found aberrant expression of the CD7 antigen most prevalent in AML patients. This might be due to the wide variety of genetic disorders that can accompany individuals.

The current study's findings suggested that aberrant expression of CD2, CD5, and CD7 antigens was related with a poor prognosis, which was consistent with previous findings [33,34]. This might have related to FLT3, CEBPA, RAS and RUNX1 mutations [35-37]. However, no statistically significant differences were detected between the aberrant expressions of CD10, CD19, CD20, and CD22 markers and prognosis.

On the other hand, in our study, 65 individuals were diagnosed with ALL, and CD13 was the most frequently aberrant expressed antigen in 14 (21.5%) of the cases, followed by CD33 in ten (7.7%). Our current study's findings agreed with the findings of another study [38,39], which found aberrant expression of the CD13 antigen most prevalent in ALL patients. However, no statistically significant differences were detected between the aberrant expressions of CD13 and CD33 markers and prognosis.

Conclusion

We find that aberrant CD marker expression is present in many cases of acute leukemia. The present study also discovered that individuals with AML had the most aberrant expression of CD2, CD10, and CD19 antigens, whereas ALL patients had the most aberrant expression of CD13 and CD33 antigens. Furthermore, the current study found that aberrant expression of CD2, CD5, and CD7 antigens was associated with poor prognosis in AML patients. However, there were no statistically significant differences between aberrant expression of CD13 and CD33 markers and prognosis in ALL patients.

Conflict of interest

The author declares no conflicts of interest

Author contribution

The author was responsible for conception and design of the study, acquisition of data, analysis and interpretation of data, in addition to drafting and revising the manuscript and approving it for submission.

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Please cite this article as: **Memeh, A.H. et al. (2023) The prognostic value of aberrant expression of cluster differentiation markers in patients with acute leukemia, Zagazig Journal of Pharmaceutical Sciences, 32(2): pp. 1-9.** Available at: https://zjps.journals.ekb.eg/article_321397.html.