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Original Article

The Role of CD38 in Predicting Outcomes for Non-M3 Acute Myeloid Leukemia Patients

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Abstract

Background: Acute Myeloid Leukemia (AML) is a rare but aggressive type of cancer with different survival rates around the world. While factors such as age, cytogenetic, and molecular abnormalities play an important role that impacts the prognosis of AML patients, the correlation between CD38 and other hematologic markers and the survival of AML patients for therapy initiation was investigated in this study.

Methods: In this retrospective cohort study, we relied on flow cytometry to examine CD38 expression on AML blasts and evaluated its correlation with Overall Survival (OS) and one-year survival in newly diagnosed AML patients at the Hematology-Oncology Research Center, Iran, Tabriz.

Results: Seventy-two newly diagnosed non M3-AML patients were followed in this study. The results showed there was a significant relationship between the OS and one year survival CD38 levels. Besides, increasing the CD38 level by 1% increased the hazard of mortality by 1 percent (HR=0.99; 95% CI: 0.98 to 1.01).

Conclusion: The expression of certain membrane molecules like CD38 on leukemic cells can provide valuable information about the prognosis of AML patients and their treatment options.

Keywords: Flow cytometry, Hematology, Humans, Iran, Leukemia, Myeloid, Acute, Prognosis, Retrospective studies, Survival rate

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Introduction

Adults suffering acute leukemia tend to acquire Acute Myeloid Leukemia (AML). It is a type of hematologic malignancy which has heterogenic clinical and molecular features. AML can develop quickly, with fast progression that can be fatal. Even with prolonged chemotherapy and tailored medicines, adult AML patients have extremely low survival rates. For those suffering AML aged over 65, the chance of surviving for five years is less than 5% (1). Unlike the poor prognosis of this disease, its treatment has not changed much in recent decades, and high-dose chemotherapy is still the basis of treatment (2). In many patients receiving standard chemotherapy, Complete Remission (CR) is observed, while many of them relapse due to therapy resistant leukemic cells. CR is defined as <5% blasts in bone marrow, no blasts in peripheral blood, and recovery of blood counts (platelets ≥100,000/μL, neutrophils ≥1,000/μL). CR is a key treatment goal, associated with improved survival, and may include additional criteria like minimal residual disease negativity (3). Clinical findings such as advanced age, history of exposure to radiotherapy or cytotoxic agents, history of previous myelodysplasia or other blood disorders such as myeloproliferative neoplasms, and cytogenetic or molecular findings in tumor cells is helpful in patients with AML to predict the possibility of CR and Disease-Free Survival (DFS) (4). Studies have shown that increasing the expression of some membrane molecules such as CD25, CD40, and CD11a are effective in poor prognosis of AML detection (5, 6). Accurate risk assessment is crucial in tailoring consolidation treatment strategies for AML, whether through chemotherapy, autologous, or allogeneic stem cell transplantation. As a result, the discovery of new predictive markers is essential to improve relapse prediction and new treatment strategies (7).

One promising target in AML therapy is CD38, a type II transmembrane glycoprotein that plays a role in essential cellular functions, such as calcium signaling, cell adhesion, and intracellular signal transduction (8). While CD38 is expressed in various cell types, its overexpression in hematological cancers, including AML, has made it an attractive target for monoclonal antibody therapies. The identification of CD38 as a potential therapeutic target in AML has led to increased interest in understanding its contribution to leukemia cell survival and the therapeutic benefits of targeting this molecule (9).

Recent research has revealed that CD38 inhibition in AML not only affects the survival of leukemic cells but also interrupts the critical interactions between these cells and their surrounding microenvironment within the bone marrow demonstrated that blocking CD38 hinders the movement of leukemic cells and enhances their clearance through phagocytosis, both of which are crucial to slowing disease progression (10). Moreover, CD38 is involved in the transfer of mitochondria from mesenchymal stromal cells (MSCs) to leukemic cells, a process vital for the metabolic support of leukemia cells. Inhibition of CD38 with daratumumab has been shown to prevent this mitochondrial transfer, thereby reducing the metabolic function of AML cells and limiting their ability to survive (11). Furthermore, combining CD38-targeted therapies with other treatments has demonstrated the potential to boost therapeutic effectiveness. One notable example is the combination of daratumumab with venetoclax, a BCL-2 inhibitor that induces apoptosis by blocking BCL-2. While venetoclax alone has revealed success in AML treatment, the addition of daratumumab has produced enhanced therapeutic outcomes in preclinical models. This combination has shown synergistic effects, suggesting it may provide better results for patients with AML (12). These observations provide strong motivation for investigating CD38-targeted treatments in conjunction with existing therapies for AML.

The therapeutic impact of CD38 inhibition extends beyond the direct targeting of leukemic cells. Research has highlighted that CD38 plays a crucial role in the interactions within the bone marrow microenvironment, which supports leukemia cell survival. This includes disrupting the signaling between leukemia cells and the bone marrow niche, which supplies critical survival signals to the leukemic cells. As AML progression and relapse are often influenced by these supportive interactions, targeting CD38 could potentially disrupt these mechanisms, offering hope for improved long-term outcomes (13). Given the growing preclinical evidence supporting

CD38 as a viable therapeutic target, this study aims to investigate the relationship between CD38 expression levels and Overall Survival (OS) in AML patients. A better understanding of how CD38 expression correlates with patient outcomes could help optimize treatment strategies and ultimately improve survival rates in this challenging malignancy.

Materials and Methods

This retrospective cohort study analyzed newly diagnosed non-M3 AML patients treated between 2017 and 2021, assessing CD38 expression *via* flow cytometry and its correlation with survival outcomes. The sample size was determined with the reasoning that all the newly diagnosed patients with non-ALM3 were included, in accordance with the study conducted by Raisi *et al* (14). The study protocol was approved by the ethics committee of Tabriz University of Medical Sciences (IR.TBZMED.REC.1400.442). AML is an aggressive myeloid neoplasm characterized by the presence of ≥20% myeloblasts in the blood or bone marrow (15). Patients' disease had been confirmed by flow-cytometry of bone marrow samples. Patients diagnosed with Acute Lymphoblastic Leukemia (ALL) and acute promyelocytic leukemia (APL) were not considered in this study.

The standard consolidation regimen for AML, particularly in younger and fit patients, includes high-dose cytarabine (HiDAC). However, in our cohort, the consolidation therapy was determined based on institutional protocols and patient-specific factors, including age, comorbidities, and overall performance status. A significant proportion of the patients were older adults or had underlying conditions that precluded the use of HiDAC due to its associated toxicities, such as neurotoxicity and prolonged myelosuppression. Instead, a modified consolidation approach was utilized, prioritizing tolerability and individualized treatment decisions. Additionally, resource availability and national treatment guidelines influenced our treatment approach. This started with induction therapy using a 3+7 regimen (daunorubicin at 45 *mg/m²* and cytosine arabinoside at 100 *mg/m²*), followed by two cycles of a 5+2 regimen after remission (daunorubicin at 45 *mg/m²* for 2 days, and cytosine arabinoside at 100 *mg/m²* for an additional 5 days). This regimen achieves complete remission in approximately 50-66% of patients, depending on age and risk factors. Toxicity is generally manageable, with hematologic toxicity being the most common side effect. Long-term survival rates vary, with younger patients achieving better outcomes compared to older populations (16-18).

While the regimen remains effective, newer studies suggest that higher doses of daunorubicin (*e.g.*, 60-90 *mg/m²*) may improve remission rates in some populations without significantly increasing toxicity (19). However, the 45 *mg/m²* dose is still widely used, particularly in older or frail patients, to balance efficacy and safety.(20) For patients who did not achieve CR morphologically after the first round of induction chemotherapy, treatment was escalated with cytosine arabinoside at 500 *mg/m²* administered *via* slow intravenous push twice daily for 7 days, along with Novantrone at 12 *mg/m²* daily for 3 days.

While allogeneic Bone Marrow Transplantation (BMT) remains the preferred curative option for eligible AML patients, several factors influenced why it was not performed in our study population. First, a significant proportion of our patients were either older adults or had comorbidities that made them ineligible for BMT due to the high risk of treatment-related mortality and complications. Second, donor availability was a major limiting factor, as a matched sibling or unrelated donor was not accessible for many patients. Additionally, financial and logistical constraints, as well as institutional protocols, played a role in treatment decisions.

Bone marrow samples stored in anticoagulant Ethylenediaminetetraacetic Acid (EDTA) tubes were prepared as a suspension. Operating with a cytochemistry technique with a H1 autoanalyzer (Technicon, USA) cell counts were performed. Leukocyte numbers adjusted to between 5,000 and 10,000 cells/μL. After that samples were stained directly with antibodies (monoclonal) conjugated with fluorescent markers. Flowcytometry was performed using BD FACS caliber device and cell guest software and dedicated panel was used directly against specific antigens, especially CD38, CD64, CD33, CD117, and HLA DR. A 20% threshold was set to determine cases positive for CDs.

After achieving CR, the patients were monitored monthly during the first year and then annually. The

primary outcomes of interest were OS and one-year survival. OS was outlined as the duration from the AML diagnosis to either leukemia caused death or the last follow-up date (December 2021).

The normality of the baseline patient characteristics was evaluated utilizing a skewness test, and the based on the outcomes, the data were presented as counts and percentages or as mean (±SD). To categorize quantitative values, median values were computed and used as thresholds to distinguish between high and low expression levels. The following points were applied for other parameters: hemoglobin, <8 and ≥8 *g/dL*; WBC, <4,000 and ≥4,000 /mm^3; Neutrophil <100 and ≥100/mm^3; and platelets, <50,000 and ≥50,000/mm^3. For the survival analyses, we utilized the Kaplan–Meier method along with log-rank tests to evaluate the prognostic effects of CD38, CD64, CD117, CD33, and HLA DR expressions on AML patients, independently. Additionally, Cox proportional hazards regression analysis was carried out to determine the 95% Confidence Intervals (CIs), standard errors, and Hazard Ratios (HRs) for the prognostic factors. The worth of the prognostic indexes on OS and one-year survival was assessed using the Kaplan–Meier method and log-rank tests. Using STATA 11.0. a p-value of ≤ 0.05 was deemed statistically significant.

Results

In this retrospective cohort 72 newly diagnosed non M3-AML patients were followed in this study. Of them 45.8% (n=33) were male and 54.2% (n=39) were female. The Kolmogorov-Smirnov test indicated that the age distribution did not follow a normal distribution ($p < 0.001$). The age of 33.3 % (n=24) were older than 60 years with the mean of 50.29 ± 18.38 years. AML subtypes were diagnosed as M1 (n=16, 22.2%), M2 (n=21, 29.2%), M4 (n=21, 29.2%) and M5 (n=14, 19.4%). OS was 37.5% with the mean of 336.41 days (95% CI; 249.87 -422.95) and median 219 days (95% CI; 249.87 -422.95). Among the 72 patients, 39 patients (54%) experienced disease relapse. At the last follow-up (December 2021), all relapsed patients had succumbed to disease progression or treatment complications. The primary causes of death in our cohort were disease progression, infection-related complications (such as sepsis due to prolonged neutropenia), and treatment-related toxicities, including multi-organ failure. Supportive care measures were provided to manage complications, including broad-spectrum antibiotics for infections, transfusion support for cytopenias, and intensive care for patients with organ failure. Patients who were eligible for salvage chemotherapy received additional treatment upon relapse. However, response rates remained limited. Demographic characteristics of included patients summarized in table 1.

Furthermore, CD38 expression mean was 84.21% (± 16.35) which is more than 20% cutoff. Therefore, Log rank test of equality of survival distributions for the different levels of CD38 showed that there was a significant relationship between OS and CD38 levels (p log rank<0.000).

Table 1. Demographic characteristics of included patients

Variable	Category	Number (%) Mean±SD (Median)
Age(years)		36±20.19(36)
Gender	Male	308(62.2)
	Female	186(37.6)
Acute Myeloid Leukemia (AML)	0	2(2.8)
	1	7(9.7)
	2	14(19.4)
	4	14(19.4)
	5	5(6.9)
	None M3	30(41.7)
CD markers	CD38	84.208±16.3526
	CD64	28.39±28.504
	CD33	67.89±86.452
	CD117	47.9±31.926
	HLA DR	39.35±29.922
Hematologic factors	WBC	3554.07±4452.38
	Hb	6.197±3
	Plt	5587.86±4731.60
	Neut	22.3873±25.55
Outcome	Death	45(62.5)
	Survival duration	224.18±222.648

One year survival rate was 18% (95% CI; 0.08 to 0.31) and there was significant relationship between CD38 levels and one year survival rates (p log rank<0.000). However Stratified log-rank test for equality of survivor functions adjusted for CD38 level, revealed that one-year survival rates were significantly associated with age (p log rank<0.000), and gender (p log rank<0.000) of AML patients, means that female and ≥60 years old patients had significantly lower one-year survival rates. Cox-regression analysis at univariate level showed that increasing of CD38 level by 1% increased the hazard of mortality by 1 percent (HR=0.99; 95% CI: 0.98 to 1.01). Hazard of mortality was 1.17 times higher in ≥60 years *vs.* <60 years AML patients (HR=1.17; 95% CI: 0.63-2.16, p=0.62), but this difference was not statistically significant. This conclusion also applied to some extent to investigate the effect of sex on mortality (HR=1.17; 95% CI: 0.64-2.12, p=0.61). Patient characteristics were summarized in table 1.

In addition to CD38, the effect of other markers including CD64, CD33, CD117, and HLA DR on mortality was investigated by using the 20% cutoff which demonstrated non-significant relations. Among blood markers patients with WBC count of 4000 to 11000 had 2.11-times higher mortality hazard than patients with WBC count less than 4000. The hemoglobin level under 8 *mg/dl* had about 2 times higher mortality hazard and this was statically significant.

Cox-regression analysis at multivariate level (after adjustment for all confounder variables) showed that AML (M2) subtypes had significantly lower hazard of mortality than other types (HR=0.34; 95% CI: 0.12-0.93, p=0.035). However, AMLs with WBC count of 4000-11000 and >11000 had respectively 4.5- and 2-times higher mortality hazard than patients with WBC count < 4000 (HR=4.50; 95% CI: 1.24-16.36, p=0.023) and (HR=2.05; 95% CI: 0.32-13.28, p=0.451) (Table 2).

Discussion

AML, the most widespread form of acute leukemia in

Table 2. Univariable and multivariable analysis

Variables		Frequency	Univariable(unadjusted)				Multivariable(adjusted)			
			HR	95%CI		p-value	HR	95%CI		p-value
				Lower	Upper			Lower	Upper	
Age (year)	<60	48(66.7)	Ref.							
	≥60	24(33.3)	1.17	0.63	2.16	0.62	0.9	0.4	2.01	0.79
Gender	Male	33(45.8)	Ref.							
	Female	39(54.2)	1.17	0.64	2.12	0.61	1.39	0.7	2.77	0.34
CD38*	≥20	72(100)	*CD38 expression mean was 84.21% (±16.35) which is more than 20% cutoff Therefore, log-rank test (Kaplan-Meier analysis) and a Cox regression model using CD38 as a continuous variable was performed							
	<20	0								
CD64	≥20	35(48.6)	Ref.							
	<20	37(51.4)	1.62	0.88	2.99	0.12	1.87	0.17	1.3	0.13
CD33	≥20	64(88.9)	Ref.							
	<20	8(11.1)	1.01	0.42	2.4	0.98	0.9	0.4	2.01	0.36
CD117	<20	18(25)	Ref.							
	≥20	54(75)	1.3	0.63	2.64	0.47	1	0.37	2.6	0.98
HLA DR	<20	22(30.6)	Ref.							
	≥20	50(69.4)	1.26	0.66	2.41	0.48	1.05	0.44	2.5	0.91

Contd. table 2.

WBC	<4000	17(23.6)	Ref.							
	4000-11000	16(22.2)	2.11	0.9	4.95	0.86	4.5	1.23	16.36	0.23
	>11000	39(54.2)	2.11	0.95	4.7	0.66	2.05	0.31	13.28	0.45
Hb	≥8	30(41.7)	Ref.							
	<8	42(58.3)	2.08	1.11	3.91	0.022	2.25	1.08	4.7	0.03
Plt	>50000	31(43.1)	Ref.							
	≤50000	41(56.9)	1.95	1.04	3.64	0.036	1.73	0.77	3.88	0.17
Neut	<100	11(15.3)	Ref.							
	100-500	8(11.1)	0.97	0.3	3.07	0.96	0.52	0.11	2.38	0.4
	500-1500	12(16.7)	0.83	0.27	2.52	0.75	0.4	0.1	1.55	0.18
	>1500	41(56.9)	1.6	0.64	3.97	0.3	0.68	0.11	4.23	0.68

grown up population, has poor survival rates despite extensive chemotherapy and targeted therapies. (1) The Leukemic Stem Cell (LSC) population plays a crucial role in chemotherapy resistance and disease relapse. Although previous studies have explored the association of individual LSC markers with prognosis, relatively few have investigated the combined effect of multiple markers. A study analyzing CD25, CD96, and CD123 in AML patients revealed that co-expression of multiple LSC markers significantly correlated with shorter three-year OS compared to single or no LSC marker expression (18.2 *vs*. 65.0%, p<0.001). Multivariate analysis further confirmed this association (HR: 3.80, p=0.001), emphasizing the need for evaluating multiple LSC markers to predict clinical outcomes in AML.(21)

One of the key molecules involved in AML pathophysiology is CD38, a 45 *kDa* single-chain transmembrane glycoprotein that acts as an external catalyst, adhesion molecule, and regulator of cellular proliferation and apoptosis.(22) There are some studies which assessed the small subpopulations of malignant cells with different immunophenotypes like CD34+CD38− or CD34+CD38−CD123+. Increasing evidence suggests that these subpopulations are more resistant to treatment than the majority of leukemia cells and act a key role in the resurgence of the disease following relapse.(23) Whereas, there is a few studies that shows the prognostic effect of CD38 on survival and relatively little has been discovered about the role of CD38 in adult AML patients. Our study illustrated a significant relationship between OS and CD38 levels (P log rank<0.000). Univariate analysis showed that increasing of CD38 level by 1% increased the hazard of mortality by 1 percent (HR=0.99; 95% CI: 0.98 to 1.01). A study by Keyhani *et al* with 304 AML patients showed, those with higher CD38 expression had significantly longer durations of complete remission and survival compared to lower levels (p:0.036 and p:0.048, respectively).(24)

In AML, CD33 is a commonly expressed antigen, found in approximately 85–90% of cases. Normally, CD33 expression is limited to early multi-lineage hematopoietic progenitors, myelomonocytic precursors, and more mature myeloid cells, but it is absent in normal pluripotent hematopoietic stem cells. This makes CD33 clinically significant as a potential target for antibody-based therapies in AML (25). According to the study by Liu *et al*, patients with high CD33 expression had worse OS, with median survival times of 39.0 months compared to 16.7 months (χ^2 = 13.06, p<0.001). According to the Cox survival regression analysis, CD33 functions as a separate prognostic factor (HR=0.233, p=0.008). Furthermore, univariate analysis revealed that

elevated CD33 levels are associated with a poorer prognosis. Whereas, it was found the effect of CD33 on mortality demonstrated non-significant relations, as well (HR=1.009, p=0.984) (26).

The FMS-like tyrosine kinase 3 (FLT3), also known as CD135, is a critical class III Receptor Tyrosine Kinase (RTK) involved in hematopoietic development and cellular proliferation. Its expression is prevalent in B-lineage ALL and AML, highlighting its importance in these malignancies. When FLT3 is activated, it triggers a cascade of downstream signaling pathways through the phosphorylation of secondary mediators. These mediators play vital roles in regulating cell differentiation, proliferation, and survival, making FLT3 a key player in the pathophysiology of hematologic cancers (27). According to Raeisi *et al*'s study, a low CD135 was substantially correlated with a poor Event Free Survival (EFS) (HR 0.34, 95% CI 0.13–0.88, p=0.02). Cox-regression analysis revealed a strong association between a low CD135 and a poor OS (HR 0.36, 95% CI 0.14–0.93, p=0.03). There were no statistically significant correlations observed between the average WBC, CD117 expression level, or CD135+117 co-expression and the EFS or the OS (14).

Beyond these myeloid markers, co-expression of lymphoid markers has also been explored in AML prognosis. A retrospective study of 50 AML patients at the Hematology Unit of Nasser Institute Hospital found that CD7 was the most frequently expressed lymphoid marker, while CD19 expression correlated with the highest relapse rate. In contrast, CD4 expression was associated with higher complete remission rates compared to CD7, CD5, CD2, and CD19. These findings suggest that lymphoid marker co-expression may influence AML prognosis and treatment response (28). Furthermore, emerging evidence has highlighted the role of endoglin (CD105) in AML. CD105, a 180 *kDa* glycoprotein involved in tumor angiogenesis, has been identified as a proliferation-associated antigen in both leukemic and endothelial cells. Higher CD105 expression levels have been observed in AML and chronic myeloproliferative disorders compared to healthy individuals. A study conducted at Tanta University Hospitals examined CD105 expression in newly diagnosed AML patients and found a significant correlation between CD105 levels and hemoglobin concentration, WBC count, and blast count. Kaplan-Meier survival analysis revealed that patients with negative CD105 expression had significantly higher overall and disease-free survival than those with positive CD105 expression. These findings suggest that CD105 may serve as a potential prognostic marker and should be routinely assessed in AML patients (29).

As a result, CD38 is being investigated as a potential target for new therapies for AML. Some drugs that target CD38 like daratumumab are already approved for use in other types of cancer, such as multiple myeloma, and are being tested in clinical trials for AML. While one of the study limitations is the failure to classify patients cytogenetically due to lack of access, more studies are needed regarding the effect of CD38 role in AML prognosis. Moreover, the inclusion of primary refractory patients may have influenced OS outcomes, as these patients typically have worse prognoses. CD38 expression was assessed in all the patients, including those who were primary refractory. However, due to the sample size limitations, a separate subgroup analysis was not performed for refractory cases. Future studies with larger cohorts could further investigate the prognostic role of CD38 specifically in refractory AML patients.

Conclusion

The findings of the current study suggest that patients with higher CD38 expression may require tailored therapeutic strategies, given its potential prognostic significance. This highlights the importance of CD38 as a potential biomarker for treatment intensity. Additionally, these results pave the way for exploring novel therapeutic approaches targeting CD38 in the management of acute leukemia, potentially improving patient outcomes. Future experimental studies will attempt to uncover the mechanisms that explain why lower levels of CD38 expression are associated with a more favorable prognosis.

Informed consent

Informed consent was obtained from all the patients for participation in an observational research study. The participation in this study was entirely voluntary. The included participants were free to withdraw from

the study at any time without any penalty or loss of benefits.

Consent for publication

Consent for publication was obtained from all the individuals included in the study.

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Conflict of Interest

There was no conflict of interest in this manuscript.

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