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Lymphocyte-to-Monocyte Ratio as a Novel Tumor Microenvironment Marker of Adverse Prognosis in Adults with Acute Myeloid Leukemia

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Abstract **Background:** The Lymphocyte-to-Monocyte Ratio (LMR) is an inexpensive complete blood count-derived marker that may reflect the balance between host immune status and the leukemia-associated microenvironment. This prospective cohort study evaluated baseline LMR as an exploratory prognostic biomarker in adults with de novo non-M3 Acute Myeloid Leukemia (AML). **Methods:** We prospectively enrolled 100 treatment-naive adults with de novo non-M3 AML at the Clinical Hematology Unit, Zagazig University Hospitals. Receiver operating characteristic analysis identified an LMR cutoff of 3 for survival outcomes (Area Under the Curve [AUC], 0.613; 95% Confidence Interval [CI], 0.511-0.709; sensitivity, 73.33%; specificity, 55%; p = 0.047). Overall Survival (OS) and Disease-Free Survival (DFS) were estimated using Kaplan-Meier analysis. Cox proportional hazards models were used to assess prognostic factors. **Results:** Over a median follow-up of 7.7 months (range: 0.5-33.2 months), patients with LMR ≤3 demonstrated significantly inferior outcomes compared with those having LMR >3: lower Complete Remission (CR) rates (51.6% vs. 73.7%; p = 0.029), worse 3 year OS (0 vs. 44.9%; p = 0.03) and poorer 3 year DFS (0 vs. 45%; p = 0.021). Mortality and relapse rates were significantly elevated in the low LMR group (71.0 vs. 42.1%, p = 0.004; 62.5 vs. 12.6%, p = 0.009, respectively). Multivariate Cox regression identified low LMR as an independent adverse prognostic factor for DFS (HR 4.51; 95% CI: 1.57-12.97; p = 0.005). **Conclusions:** Low baseline LMR was associated with adverse DFS in this exploratory cohort. LMR should be considered a candidate supplementary biomarker rather than a replacement for established molecular and cytogenetic risk stratification. Multicenter validation is required before routine clinical use.

Key Words Acute Myeloid Leukemia, Lymphocyte-To-Monocyte Ratio, Prognosis, Disease-Free Survival, Tumor Microenvironment

INTRODUCTION

The immune system is crucial to the development of tumors. The Lymphocyte-to-Monocyte Ratio (LMR), a biomarker of the host immune system that is determined by dividing the Absolute Lymphocyte Count (ALC) by the Absolute Monocyte Count (AMC), has been proposed to have a predictive role in some cancers [1,2].

In patients with hematologic malignancies, particularly Hodgkin Lymphoma (HL) and Diffuse Large B-Cell Lymphoma (DLBCL), a low LMR was first observed to be a poor prognostic factor [3,4]. This association may be explained by tumor-infiltrating immune cells, which are crucial for suppressing or promoting tumor growth [5].

It is believed that Tumor-Infiltrating Lymphocytes (TILs) are responsible for the cellular and humoral antitumor immune responses that aid tumor control. Additionally, tumor-derived chemotactic proteins aggressively recruit Tumor-Associated Macrophages (TMAs), which are generated from circulating monocytes. TMAs hasten the development of tumors by provoking cytokines and growth factors that promote angiogenesis and immunological responses [6].

Remarkably, monocytosis is also reported to be a poor prognostic marker in hematological and solid tumors [7-9]. A peripheral blood AMC may be an alternative biomarker for TAMs. Hence, a low LMR may suggest a weak antitumor immunity allowing tumor growth in this favorable microenvironment [5].

Accordingly, both lymphocytes and monocytes may be potential candidates for playing a role in the pathogenesis and prognosis of acute leukemia. Accordingly, both lymphocytes and monocytes may contribute to the pathogenesis and prognosis of acute leukemia. Preliminary findings from this cohort were previously presented as a conference-supplement poster abstract. The present full-length report provides a detailed evaluation of the prognostic significance of baseline LMR in adults with de novo non-M3 AML.

We hypothesized that a low baseline LMR would be associated with poorer treatment response and survival. We therefore prospectively evaluated the relationship between baseline LMR and complete remission, overall survival and disease-free survival in an exploratory single-center cohort.

METHODS

This study is a prospective cohort study conducted in the Clinical Hematology Unit, Internal Medicine Department, Zagazig University Hospitals, for a total duration of 3 years.

The study included 100 previously untreated patients aged ≥18 years with de novo non-M3 AML and good performance status. Patients with acute promyelocytic leukemia (APL; FAB M3) were excluded because APL is biologically and clinically distinct from other AML subtypes. It is characterized by the PML::RARA fusion, has a specific treatment approach based onf all-trans retinoic acid and arsenic trioxide and is associated with a different early-mortality profile, particularly because of coagulopathy. Including APL patients could therefore introduce substantial clinical heterogeneity and confound the assessment of the prognostic value of baseline LMR.

Furthermore, we excluded Patients with Preceding hematological disorders, Previous exposure to chemotherapy or therapy-related AML, Co-existing chronic major organ failure and pregnant females.

Before enrollment, each participant was given a written explanation of the study's objectives and written consent was taken. All study protocols were approved by the Zagazig Institutional Review Board (ZU- IRB #2899-7-6-2016).

According to FAB [10] and the WHO 2016 criteria [11], our patients' diagnoses and AML subtype classifications were made based on the immunophenotyping and cytogenetics of their leukemic blast cells in addition to their morphology.

Baseline white blood cell count, Absolute Lymphocyte Count (ALC) and Absolute Monocyte Count (AMC) were obtained using an automated hematology analyzer and were reviewed alongside Leishman-stained peripheral blood smears for differential leukocyte counting. The Lymphocyte-to-Monocyte Ratio (LMR) was calculated by dividing the ALC by the AMC. Laboratory measurements were performed according to the routine quality-control procedures of the hospital laboratory, including analyzer calibration and internal quality-control checks. When an automated differential count was flagged or considered inconsistent with the peripheral blood smear findings, the differential count was reassessed manually before the final value was recorded [12].

The detection of CD34 in bone marrow biopsy (BMB) was achieved through the use of a monoclonal mouse anti-human CD34 antibody (Thermo Fisher Scientific Invitrogen: Catalogue # MA1-19119) via immunohistochemical methods. Immunostaining was performed on dewaxed formalin-fixed paraffin sections in citrate buffer using an automated immunostainer (Techmate 500 plus, DAKO) with a DAB-peroxidase-based detection system (pH 6.0) after a 20-minute microwave processing. The specimen was stained with K5001 from DAKO. The proportion of CD34+ cells exhibiting immunoreactivity through membranous staining was determined by dividing the count of stained CD34+ cells by the overall count of invading cells, including both stained and non-stained cells. The internal positive controls utilized in the study were reactive peripheral blood cells sourced from human subjects. Negative control was established by incubating sections without primary antibodies.

An anthracycline and cytarabine-based induction chemotherapy regimen known as the 3+7 regimen, consisting of continuous infusion Ara-C (100mg/m2) daily for 7 consecutive days supplemented with 3 days of doxorubicin (30 mg/m^2), was administered to all patients. Consolidation therapy (post-induction therapy) was administered to patients who obtained Complete Remission (CR). This therapy included three to four courses of high-dose cytosine arabinoside (1.5-2 g/m^2 every 12 h on days 1, 3 and 5; a total of 12 g/m^2) [13].

All patients were managed according to the same institutional chemotherapy protocols and supportive care was provided according to the same institutional standards. Detailed quantitative data on treatment adherence, dose modifications, transfusion requirements, antimicrobial use and other supportive-care interventions were not prospectively collected. Therefore, residual confounding related to differences in treatment delivery or supportive care cannot be completely excluded.

After one or two chemotherapy courses, we evaluated the clinical outcome and effectiveness of induction therapy. Standard definitions of CR include less than 5% Bone Marrow (BM) blasts with cellular maturation and restoration of peripheral blood counts in the absence of extramedullary leukemia [14]. However, the worse outcome was represented by Primary Induction Failure (PIF) defined as the inability to achieve CR after two chemotherapy cycles, Early Death (ED) within 30 days of starting chemotherapy [15] and when

extramedullary leukemia appeared or when BM aspirates contained more than 5% blasts, hematological relapse was taken into consideration.

In terms of survival, Disease-Free Survival (DFS) was calculated from the time of Complete Remission (CR) to the time of recurrence or death and Overall Survival (OS) was calculated from the time of initial diagnosis to the time of death or the last follow-up.

Clinical examinations and laboratory investigations, such as CBCs with blood smears, were performed when the consolidation was finished every 1-3 months for 2 years, then every 3-6 months moving forward until the end of the study. According to the NCCN guidelines [16], BM aspiration and biopsy should only be performed if the peripheral smear is abnormal or cytopenias appear in order to rule out relapse. At the time of the transplant, patients who had undergone allogeneic HCT were censored.

Statistical Analysis

To allow the selection of the LMR cut-off point for the survival result of AML patients, a Receiver Operating Characteristic (ROC) curve was designed.

Using the Shapiro-Wilk test, the data distribution was checked for normality. The Fisher's exact or Chi-square tests were used to compare categorical covariates. Dunn's Post hoc test for multiple comparisons used the Kruskal-Wallis test to determine the difference between quantitative variables in more than two groups. The non-parametric variables were correlated using Spearman's correlation test. The Kaplan-Meier method was used to determine the OS and DFS and the log-rank test was used to compare the survival curves.

For univariate analysis, the Cox proportional hazards model was employed. The multivariate Cox proportional hazards model also included variables that were statistically significant in the univariate analysis. Multivariate logistic regression was used for the response outcome.

All tests were two-sided and a p-value of less than 0.05 was regarded as statistically significant for all two-sided tests. We used Statistical Package for Social Sciences to perform all statistical analyses (SPSS 24th Inc. Chicago, IL, USA).

RESULTS

One hundred previously untreated adult patients with de novo non-M3 AML were included in this study. Most of them (90 of the 100 patients) were <60 years of age and there were 60 (60%) males and 40 (40%) females with a ratio of [1.5:1]. The median age was 44 years (range, 18-75 years); other specific baseline characteristics of the patients are shown in Table 1.

Table 1: Patient characteristics and Clinical outcomes [median (range) or n (%)] based on the initial LMR (ALC/AMC)

Variable		Initial LMR ≤3 (N = 62)	Initial LMR >3 (N = 38)	All patients (N = 100)	p-value
Age (years)	≤60	52 [83.9%]	38 [100%]	90 [90.0%]	0.009
	>60	10 [16.1%]	0 [0.0%]	10 [10.0%]	
Sex	Female	28 [45.2%]	12 [31.6%]	40 [40.0%]	0.178
	Male	34 [54.8%]	26 [68.4%]	60 [60.0%]	
FAB	M0	0 [0.0%]	4 [10.5%]	4 [4.0%]	<0.001
	M1	4 [6.5%]	4 [10.5%]	8 [8.0%]	
	M2	12 [19.4%]	20 [52.6%]	32 [32.0%]	
	M4	34 [54.8%]	6 [15.8%]	40 [40.0%]	
	M5	12 [19.4%]	4 [10.5%]	16 [16.0%]	
Cytogenetics Risk	Failure	20 [32.3%]	4 [10.5%]	24 [24.0%]	0.02
	Favorable	4 [6.5%]	4 [10.5%]	8 [8.0%]	
	Intermediate	36 [58.1%]	24 [63.2%]	60 [60.0%]	
	Unfavorable	2 [3.2%]	6 [15.8%]	8 [8.0%]	
BM Blasts%	<50%	12 [19.4%]	6 [15.8%]	18 [18.0%]	0.652
	≥50%	50 [80.6%]	32 [84.2%]	82 [82.0%]	
PB Blast %		55.5 [13-98]	60 [0-93]	56 [0-98]	0.986
WBC×10⁹/L		20 [3.5-152.5]	4.7 [1.3-120]	17 [1.3-152.5]	<0.001
ANC×10⁹/L		7.1 [0.2-52]	0.9 [0.1-41]	4.1 [0.1-52]	<0.001
AMC×10⁹/L		6.5 [0.5-35.1]	0.3 [0.1-15]	2.8 [0.1-35.1]	<0.001
ALC×10⁹/L		4 [0.6-50]	2.9 [0.8-64]	3.8 [0.6-64]	0.504
Hb g/L		8 [4-11]	7 [5.6-10]	7 [4-11]	0.605
PLT×10⁹/L		34 [5-576]	33 [10-171]	33.5 [5-576]	0.334
Outcome		Initial LMR ≤3 (N = 62)	Initial LMR >3 (N = 38)		p-value
Response	CR	32 [51.6%]	28 [73.7%]	60 [60.0%]	0.029
	NR	30 [48.4%]	10 [26.3%]	40 [40.0%]	
Death		44 [71.0%]	16 [42.1%]	60 [60.0%]	0.004
PIF		30 [48.4%]	12 [31.6%]	42 [42.0%]	0.098
ED		8 [12.9%]	6 [15.8%]	14 [14.0%]	0.686
Underwent HCT		10 [16.1%]	12 [31.6%]	22 [22.0%]	0.07
Responders		Initial LMR ≤3 (N = 32)	Initial LMR >3 (N = 28)		p-value
Relapse		20 [62.5%]	8 [12.6%]	28 [46.7%]	0.009

AMC: Absolute monocyte count, ALC: Absolute lymphocyte count, FAB: French-American-British, BM: Bone marrow, PB: Peripheral blood, WBC: White blood cell count, ANC: Absolute neutrophil count, Hb: Hemoglobin, PLT: Platelets, LMR: Lymphocyte-monocyte ratio, CR: Complete remission, NR: No remission, PIF: Primary induction failure, ED: Early death, HCT: Hematopoietic stem cell transplantation [median (range) or n (%)]

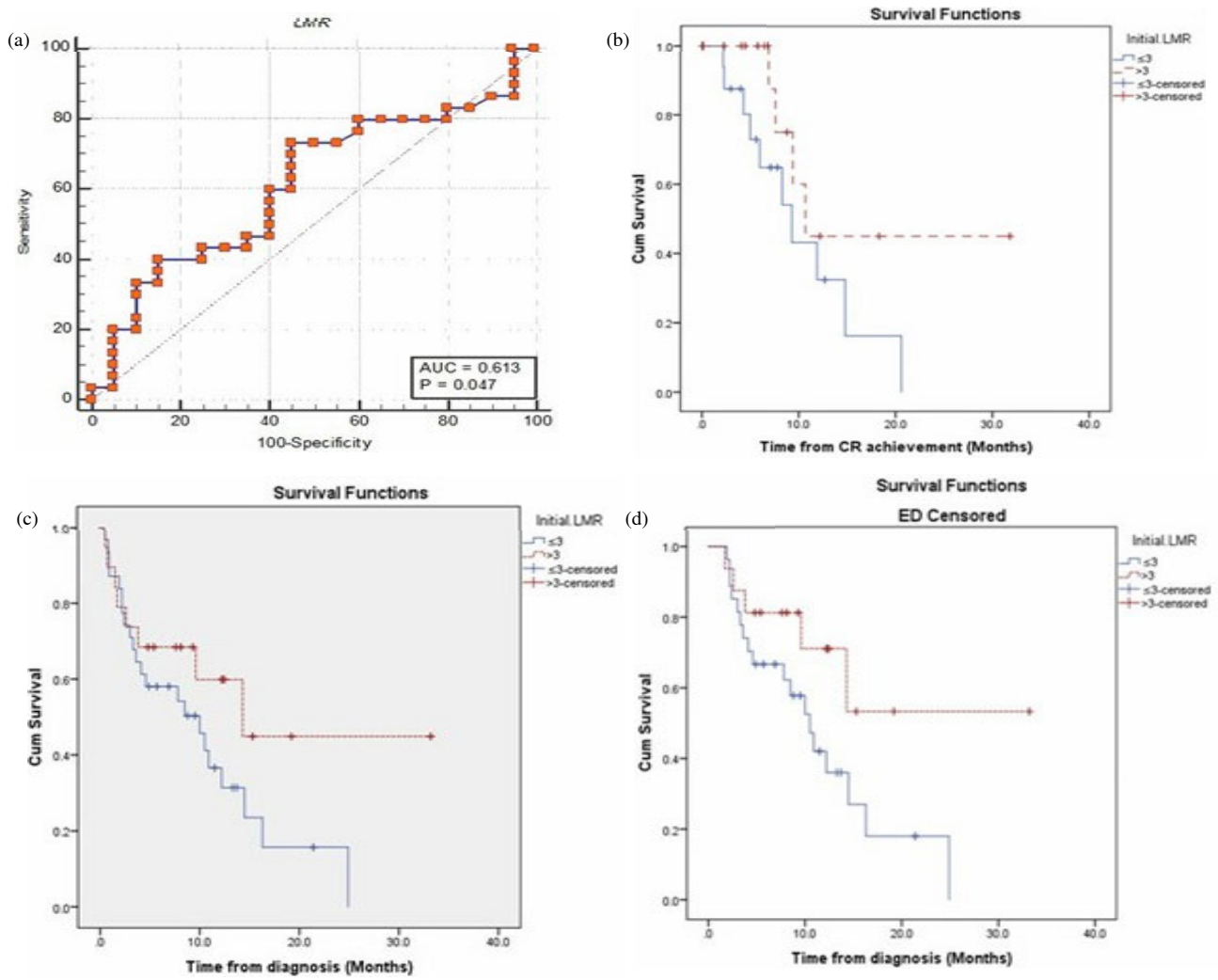

Figure 1(a-d): (a) Receiver Operating Characteristic Curve (ROC) for LMR at Diagnosis for Survival Analysis, (b) Kaplan-Meier Survival Curves Illustrating 3 year Disease-Free Survival Rate Differences in Patients as Regards the Initial LMR, (c) Kaplan-Meier Survival Curves Illustrating 3 year Overall Survival Rate Differences in Patients as Regards the Initial LMR in the Whole Cohort and (d) After Ruling Out Early Deaths

With a sensitivity of 73.33% (95% CI, 60.3-83.9%) and a specificity of 55% (95% CI, 38.5-70.7%), an initial LMR cut-off of >3 had an AUC of 0.613 (95% CI, 0.511 to 0.709); Figure 1.

According to their initial LMR, patients were divided into low- and high-LMR groups: 62 patients (62%) had an initial LMR≤3 and 38 patients (38%) had an initial LMR>3.

As shown in Table 1, there was a significantly higher frequency of age group <60 years, M2 subtype and intermediate risk cytogenetics in patients with high initial LMR, p = 0.009, <0.001 and 0.02, respectively.

Furthermore, WBC count, ANC and AMC were significantly higher in patients with an initial LMR≤3 than in those with an initial LMR>3 (all p<0.001).

Remission Induction and Disease Outcome

After at least two induction chemotherapy cycles, sixty (60%) patients achieved CR, whereas forty-two (42%) patients did not achieve CR (PIF) and 28/60 cases relapsed (as calculated from the CR cases).

Based on the initial LMR (ALC/AMC), Clinical outcomes [n (%)] are demonstrated in Table 1 and show that a significantly higher CR rate was achieved in patients with LMR>3; (73.7%) compared to only (51.6%) in patients with LMR≤3, p = 0.029. Additionally, the death and relapse rates were significantly higher in patients with LMR≤3 (71.0%) and (62.5%) compared to those with LMR>3, which had rates of (42.1%) and 8 (12.6%), respectively, p = 0.004, 0.009.

According to the univariate logistic regression analysis results for the Response to therapy, the Response was dependently associated with both favorable cytogenetics and high pretreatment LMR, with an HR of 6.00 [2.061-17.467], p = 0.001 and 0.38 [0.158-0.916, p = 0.031, respectively.

Table 2: Univariate and Multivariable Logistic Regression Analyses for Response to Therapy

	Response (Achievement of CR)			
	Univariate		Multivariate	
Parameter	Sig.	HR [95% CI]	Sig.	HR [95% CI]
Age (>60 year vs. ≤60 year)	0.184	2.47 [0.650-9.388]	-	-
Sex (M vs. F)	0.405	0.70 [0.308-1.609]		
PIF (yes vs. No)	0.996	0.003 [0.001-0.008]		
FAB				
FAB (M1 vs. M0)	>0.999	1.00 [0.091-11.028]	-	-
FAB (M2 vs. M0)	0.461	0.45 [0.056-3.703]		
FAB (M4 vs. M0)	>0.999	1.00 [0.128-7.812]		
FAB (M5 vs. M0)	0.341	0.33 [0.035-3.205]		
Cytogenetics Risk				
Cytogenetics (Fav vs. Inter)	0.001	6.00 [2.061-17.467]	0.002	5.5 [1.846-16.140]
Cytogenetics (Unfav vs. Inter)	0.638	0.67 [0.123-3.605]		
Cytogenetics (Fail vs. Inter)	0.999	0.004 [0.001-0.007]		
Initial LMR (>3 vs. ≤3)	0.031	0.38 [0.158-0.916]	0.035	0.62 [0.235-1.628]
Initial AMC				
Initial AMC (low vs. normal)	0.860	0.88 [0.199-3.850]	-	-
Initial AMC (high vs. normal)	0.617	1.29 [0.476-3.493]		
Initial ALC				
Initial ALC (low vs. normal)	0.369	0.59 [0.186-1.867]	-	-
Initial ALC (high vs. normal)	0.946	1.03 [0.424-2.506]		
Intensive induction (yes vs. No)	0.128	1.91 [0.830-4.389]		
M4l5 (yes vs. No)	0.511	0.76 [0.339-1.714]		
BM Blasts (<50% vs. ≥50%)	0.671	0.80 [0.286-2.241]		
PB Blasts (%)	0.781	0.98 [0.94-1.0]		
WBC	0.224	1.01 [0.99-1.02]		

AMC: Absolute monocyte count, ALC: Absolute lymphocyte count, FAB: French-American-British, BM: Bone marrow, PB: Peripheral blood, WBC: White blood cell count, LMR: Lymphocyte-monocyte ratio

However, on multivariable analysis, favorable cytogenetics was found to be independently related to therapeutic Response with an HR of 5.5 [1.846-16.140], p = 0.002, Table 2.

Survival Analysis

In the first 30 days of induction therapy, 14/100 patients (14%) died early (ED) and by the completion of follow-up, a total mortality rate was 60/100 (60%), as shown in Table 1 after a median follow-up time of 7.7 months (range, 0.5-33.2 months).

The mean Overall Survival (OS) was 12.71.4 months (95% CI: 10.0-15 months) and the median was 10.51.1 (95% CI: 8.4-12.6 months) for a 3 year overall survival rate of 12.5%.

The median was 10.71.1 months (95% CI; 8.5-12.9) and the mean was 13.71.7 months (95% CI; 10.5-17.0), with a 3 year disease-free survival rate of 14.5%.

28/60 patients who had attained CR had relapsed and 22.0% [22/100] patients had been referred to HCT after the follow-up period, as shown in Table 1.

The 3 year OS Rate to the Initial LMR

In Table 3, Kaplan-Meier analysis showed the Initial LMR≤3 had a significantly worse 3 year OS (0.00%) compared with (44.9%) in those with Initial LMR>3 (p = 0.03) (Figure 1).

The 3 year DFS Rate to the Initial LMR

In Table 3, Kaplan-Meier analysis showed the initial LMR≤3 had a significantly worse 3 year DFS (0.0%) compared with (45%) in those with Initial LMR>3 (p = 0.21) (Figure 1).

Because of the direct association between the AMC and TLC observed in our study, it makes sense to assume that complications associated with Proliferative leukemia with (hyperleukocytosis; TLC 30×109/L) in patients with a higher AMC would lead to a difference in OS. Thus, on ruling-out early deaths that occurred within the induction course, we discovered that those with an initial LMR≤3 had a significantly worse 3 year OS (18%) compared to those with an initial LMR>3, (p = 0.007) (Table 3, Figure 1).

The Univariate and Multivariate Analysis (Cox Regression) for OS and DFS

In univariate Cox regression analysis, Primary Induction Failure (PIF) and initial LMR were significantly associated with Overall Survival (OS). However, after adjustment in the multivariate model, only PIF remained an independent predictor of shorter OS (HR 7.50; 95% CI, 3.87-14.50; p<0.001). Initial LMR was no longer significantly associated with OS after multivariate adjustment (HR 1.15; 95% CI, 0.56-2.38; p = 0.706).

For Disease-Free Survival (DFS), unfavorable cytogenetic risk and initial LMR remained independent prognostic factors in the multivariate model. Patients with an initial LMR>3 had a lower hazard of relapse or death than those with an initial LMR≤3 (HR 0.22; 95% CI, 0.08-0.64; p = 0.005).

However, the cytogenetic (unfavorable risk) group, as well as initial LMR, were shown to be independent prognostic factors for the DFS (HR; 11.9 [3.3-43.9], p<0.001 and 0.22 [0.08-0.64], p = 0.005), respectively (Table 4).

Table 3: The Survival Rate in Relation to Initial LMR

	Survival Rate (%)			Survival Time (Months)			
Parameter	3 year OS %	P_1	P_2	Mean	95% CI for the mean	Median	95% CI for the median
Initial LMR							
≤3	0.0%	0.03*	-	10	7.7-12.3	10	4.1-10.9
>3	44.9%		-	18.4	13.1-23.8	14.3	9.6-14.3
Overall Survival							
	12.50%	-	-	12.7	10.0-15.3	10.5	7.8-14.3
	Survival Rate (%)			Survival Time (Months)			
Parameter	3 year DFS %	P_1	P_2	Mean	95% CI for the mean	Median	95% CI for the median
Initial LMR							
≤3	0.00%	0.021*	-	10.4	7.8-12.9	9.3	6.0-14.8
>3	45.00%		-	19.1	13.1-25.1	10.7	9.4-10.7
Overall disease-free Survival							
	14.50%			13.7	10.5-17.0	10.7	8.3-14.8

	Survival rate (%) (After ruling-out early deaths)		
	3 year OS Rate (%)	P_1	P_2
Initial LMR			
≤3	18.00%	0.007*	-
>3	53.00%		-
Overall Survival	23.90%		

P_1: When comparing all patients together, P_2: When comparing patients to patients within the normal range, OS: Overall Survival

Table 4: Univariate and multivariate Cox-regression analyses for overall & Disease-free survival.

	Overall Survival				Disease-free Survival			
	Univariate		Multivariate		Univariate		Multivariate	
Variable	HR [95% CI]	Sig.	HR [95% CI]	Sig.	HR [95% CI]	Sig.	HR [95% CI]	Sig.
Age (>60 year vs. ≤60 year)								
	1.12 [0.53-2.37]	0.769	-	-	0.94 [0.22-4.01]	0.93	-	-
Sex (M vs. F)								
	0.99 [0.76-1.29]	0.963	-	-	1.28 [0.59-2.78]	0.537	-	-
M4I5 (yes vs. No)								
	0.99 [0.59-1.66]	0.98	-	-	1.45 [0.68-3.09]	0.339	-	-
PIF (yes vs. No)								
	8.46 [4.67-15.32]	<0.001	7.5 [3.87-14.50]	<0.001	0.31 [0.07-1.38]	0.123	-	-
BM Blasts (%)								
	1.02 [0.52-2.03]	0.946	-	-	0.52 [0.20-1.32]	0.169	-	-
Cytogenetics Risk								
Cytogenetics (Failure vs. Intermediate)								
	3.38 [1.94-5.90]	<0.001	1.77 [0.95-3.29]	0.071	2.15 [0.70-6.63]	0.184	1.2 [0.4-4.1]	0.673
Cytogenetics (Favorable vs. Intermediate)								
	0.68 [0.23-2.00]	0.485	0.95 [0.30-2.99]	0.925	0.33 [0.08-1.48]	0.15	0.4 [0.09-1.7]	0.215
Cytogenetics (unfavorable vs. Intermediate)								
	1.03 [0.36-2.96]	0.954	0.61 [0.19-1.98]	0.408	5.17 [1.73-15.40]	0.003	11.9 [3.3-43.9]	<0.001
Initial AMC (low vs. normal)								
	0.53 [0.18-1.60]	0.263	-	-	0.003 [0.001-.007]	0.974	-	-
Initial AMC (high vs. normal)								
	0.82 [0.46-1.48]	0.514	-	-	1.52 [0.61-3.78]	0.369	-	-
Initial ALC (low vs. normal)								
	0.59 [0.28-1.25]	0.169	-	-	0.37 [0.11-1.19]	0.095	-	-
Initial ALC (high vs. normal)								
	0.70 [0.40-1.22]	0.207	-	-	0.70 [0.30-1.65]	0.412	-	-
Initial LMR (>3 vs. ≤3)								
	0.54 [0.31-0.96]	0.036	1.15 [0.56-2.38]	0.706	0.41 [0.18-0.92]	0.031	0.22 [0.08-0.64]	0.005

AMC: Absolute monocyte count, ALC: Absolute lymphocyte count, HR: Hazard ratio, 95%CI: 95% confidence interval, Sig.: Significance

DISCUSSION

AML is considered one of the most common fatal hematologic malignancies [17]. Despite recent advancements in treatment, there hasn't been any improvement in the AML prognosis. Therefore, evaluating potential biomarkers is crucial for early diagnosis, tracking the development of the disease and adjusting the severity of the treatment [18].

ALC, a significant biomarker of tumor-infiltrating lymphocytes representing host immune status in hematologic and solid malignancies, has received much research [19].

AMC is a surrogate biomarker of tumor-associated macrophages and a subgroup of myeloid-lineage cells within the tumor microenvironment. It can produce a range of cytokines to support angiogenesis, tumorigenesis and distant metastasis, including transforming growth factor-, tumor necrosis factor-, interleukin-1 (IL-1) and IL-6 [20] and was found to have a prognostic impact when studied in AML [21] and AML with monocytic differentiation [22].

Combining the above characteristics to represent a better tumor prognosis is theoretically feasible because host immunity and the tumor microenvironment

enhance carcinogenesis [23]. Moreover, it reflects the underlying chronic inflammation in several disorders [24]

To the best of our knowledge, this study provides one of the earliest detailed evaluations of baseline LMR as a prognostic marker in adults with de novo non-M3 AML. Interestingly, this was done prospectively to reduce selection bias.

Our findings indicate that a higher initial LMR was associated with improved treatment response and lower relapse and mortality rates. Although LMR was significantly associated with both OS and DFS in univariate analysis, it retained independent prognostic significance only for DFS after multivariate adjustment. Its association with OS was no longer significant in the multivariate model. Therefore, baseline LMR should be interpreted primarily as a supplementary marker of relapse-related prognosis rather than as an independent predictor of overall mortality.

These findings support the potential value of baseline LMR as an accessible indicator of systemic inflammation and relapse-related prognosis in AML.

The adverse prognostic impact of Low LMR in AML can be explained by the oncogenetic changes accompanying the inflammatory microenvironment and promote carcinogenesis when inflammatory cells and mediators are present, for example, nuclear factor-B [25], signal transducer and activator of transcription-3 [26] and hypoxia-inducible factor 1 [27] that represent transcription factors activated by oncogenetic changes in tumor cells. These factors all encourage the production of inflammatory mediators like cytokines and chemokines [28]. These responses draw in inflammatory cells, including those of the myelomonocytic lineage. Patients with oncogenetic mutations may consequently exhibit a low LMR.

Despite no published matched results available for AML, low LMR levels have been related to poor prognosis and reduced survival in other solid tumors such as breast cancer [29] and pancreatic adenocarcinoma [30].

Moreover, various studies found that low LMR was independently associated with a poor prognosis, shorter OS and PFS in several hematological malignancies, including HL [31,32], DLBCL [33], follicular lymphoma [34], extranodal NK/T cell lymphoma [35], anaplastic large B-cell lymphoma [36] and multiple myeloma [37].

The reported LMR cut-off values from the aforementioned hematological malignancies ranged from 2 to 6, which aligns with our LMR cut-off value; of 3 based on the ROC.

On the contrary, a higher LMR cut-off value, 26, was reported in CLL patients [12]; that is associated with low OS and PFS (although not statistically significant) in patients with high LMR and this could be explained by the fact that CLL is a lymphocytosis-based malignancy.

Although the ROC analysis identified an LMR cutoff value of 3, the discriminative performance was modest, with an AUC of 0.613. Therefore, baseline LMR should not be interpreted as a standalone prognostic tool or as a replacement for established cytogenetic and molecular risk-stratification systems. Rather, it may serve as an inexpensive supplementary biomarker that could help refine risk assessment, particularly in resource-limited settings where advanced molecular testing is not readily available. The proposed cutoff value should be interpreted cautiously because it was derived from a single-center cohort and was not subjected to internal or external validation. Further multicenter studies with larger cohorts are required to validate the cutoff value and assess its incremental prognostic value when combined with established AML risk models.

Furthermore, obtaining LMR from routine CBC at diagnosis is straightforward, broadly accessible and usable in medical practice, particularly in places lacking resources.

However, we have some limitations; for instance, because our results were based exclusively on the CBC and blood smear tests used in routine medical practice, we could not identify phenotypic and functional changes within the lymphocyte subsets originating from monocytes that might affect survival.

Besides, when used separately, lymphocyte and monocyte levels are nonspecific parameters, as they may be affected in situations like inflammation, infections and medications commonly encountered in leukemic patients. In addition, a lack of standardization of the LMR reference values. Although routine laboratory quality-control procedures were applied, formal interobserver agreement for manual differential counting was not assessed.

Detailed quantitative data on treatment adherence, dose modifications and supportive-care interventions were not prospectively analyzed and their potential confounding effects cannot be fully excluded.

Finally, this was a single-center study with a relatively small sample size, which may limit the generalizability of the findings. Molecular abnormalities required for contemporary AML risk stratification, such as FLT3, NPM1 and CEBPA mutations, were not assessed. The exclusion of patients with APL improved cohort homogeneity because APL has distinct biology, treatment and early-mortality patterns; however, the present findings should not be extrapolated to patients with APL.

Future multicenter studies should validate the cutoff prospectively, incorporate molecular risk variables and measurable residual disease, evaluate competing prognostic models and assess whether LMR improves discrimination beyond established risk stratification.

Preliminary findings from this cohort were previously presented as a conference-supplement poster abstract. The present article provides an expanded full-length report, including detailed methodology, tabulated results, multivariable analyses, figures, interpretation and limitations.

CONCLUSIONS

Low baseline LMR was independently associated with poorer DFS in adults with de novo non-M3 AML. Because LMR is inexpensive and readily available, it may have potential as a supplementary prognostic biomarker. However, multicenter validation and assessment of its incremental value alongside contemporary molecular and cytogenetic risk models are required before routine clinical implementation.

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