Reading between the lines – complete blood count parameters as prognostic factors in patients with newly diagnosed acute myeloid leukemia

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Abstract

Numerous research proved the prognostic significance of Neutrophil to Lymphocyte Ratio (NLR), Lymphocyte to Monocyte Ratio (LMR), Platelet to Lymphocyte Ratio (PLR) and Red Blood Cell Distribution Width (RDW) in few hematological malignancies. This retrospective cohort study conducted on a group of 204 patients aimed to analyze the role of NLR, LMR, PLR and RDW as markers of prognosis in newly diagnosed acute myeloid leukemia (AML). Initial NLR, RDW-CV were on average higher and LMR, PLR lower within dead patients compared to patients alive at 36 month of observation, MD = 0.29 CI95 [0.01;0.48], p = 0.035; MD = 1.50 CI95 [0.80;2.70], p = 0.001; MD = -0.71 CI95 [-1.69;-0.25], p = 0.001; MD = -16.92 CI95 [-25.25;-3.03], p = 0.004, respectively. Additionally, NLR, RDW-CV and RDW-SD were higher, and LMR lower on average within patients not responding to therapy compared with patients with any response, MD = 0.34 CI95 [0.08;0.49], p = 0.005; MD = 2.00 CI95 [1.10;2.60], p < 0.00; MD = 3.75 CI95 [0.10;6.70], p = 0.043; MD = -0.34 CI95 [-0.91;-0.05], p = 0.015, respectively. Higher NLR, RDW-CV, RDW-SD and lower LMR, PLR are poor prognostic factors, that may help risk-stratify patients with AML.

Introduction

Acute myeloid leukemia (AML) is a group of neoplastic disorders, characterized by the clonal expansion of myeloid blasts in the peripheral blood, bone marrow and other tissues [1]. It is the most common type of acute leukemias in adults [2]. Despite the presence of numerous recognized prognostic factors, the survival and clinical outcome is often variable even within patients with the same cytogenetic risk status. New prognostic strategies are being looked for, in order to stratify the risk more precisely and thus, use the treatment of appropriate intensity.

Numerous research proved the correlation between inflammation markers and the clinical course of the various diseases, including malignant neoplasms [3–5]. The markers that have been quite widely evaluated recently, are the proportions of different populations of white blood cells and of platelets, such as: the Neutrophil to Lymphocyte Ratio (NLR), the Lymphocyte to Monocyte Ratio (LMR) and the Platelet to Lymphocyte Ratio (PLR). NLR is calculated by dividing the total neutrophil count by the total lymphocyte count, LMR: by dividing the total lymphocyte count by the total monocyte count, and PLR: by dividing the total platelet count by the total lymphocyte count [6–7].

The red blood cell distribution width (RDW) is an indicator of anysocytosis i.e. the variation of erythrocytes volume. It is derived from the red blood cell distribution curves generated by automatic counters. RDW can be measured as red cell distribution width - coefficient of variation (RDW-CV) and the red cell distribution width - standard deviation (RDW-SD) [8]. RDW-CV is calculated by dividing the standard deviation of the mean cell size by the MCV of the red blood cells and converting the score to a percentage. RDW-SD is a measurement of the width of the red cell distribution curve in femtoliters (fL) [9]. Normal values of RDW-CV and RDW-SD rage from 11,6–14,6% and 39–46 fL, respectively [8]. RDW has been classically used to classify anemia. However starting from 2007, when Felker et al. [10] proved that RDW is a poor prognostic factor in the heart failure, new applications of this indicator have been being discovered. It was reported useful in prognostic stratification of cardiovascular diseases [10–12], autoimmunological diseases [13], pulmonary diseases [11] and infectious diseases [14]. RDW is also a prognostic factor in a variety of solid tumors [15], including prostate cancer [16], hepatocellular carcinoma [17], esophageal cancer [18], lung cancer [19], as well as in hematological malignancies [20]: chronic lymphocytic leukemia [21], multiple myeloma [22], Hodgkin's lymphoma [23], diffuse large B cell lymphoma (DLBCL) [24], extranodal NK/T lymphoma [25], chronic myeloid leukemia (CML) [26].

Despite the reports of the prognostic significance of NLR, LMR, PLR, RDW-CV and RDW-SD in various medical conditions, there is still limited data regarding the clinical value of these parameters in AML. Our study aimed to analyze the possible role of NLR, LMR, PLR, RDW-SD and RDW-CV as markers of prognosis in patients with newly diagnosed AML. We also investigated whether a correlation exists between those markers and some of the recognized prognostic factors.

Materials and methods

Patients characteristics

The characteristics of 204 patients with newly diagnosed AML is given in Table 1. All patients included in the study met the criteria of diagnosis of AML according to the revised fourth edition of WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues [27] and were diagnosed from 2006 to 2022 in the Departament of Hematooncology and Bone Marrow Transplantation of Medical University of Lublin. The research has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) and was approved by the Committee on Bioethics of Medical University of Lublin (KE-0254/60/2021).

Table 1
Baseline characteristics of the group (N = 204)

Variable	n (%) / M ± SD / Me (Q1;Q3)
Sex	
Female	101 (49.5)
Male	103 (50.5)
Age of diagnosis (years)	54.51 ± 17.43
Age of diagnosis group	
≤ 65 years	144 (70.6)
> 65 years	60 (29.4)
FAB * subtype	
Other than acute promyelocytic leukemia	171 (92.9)
Acute promyelocytic leukemia	13 (7.1)
AML type	
De novo AML	136 (68.7)
Secondary AML	62 (31.3)
ECOG score	
≥ 2	60 (34.7)
< 2	113 (65.3)
Blasts in bone marrow (%)	61.00 (39.35;82.00)
Karyotype	
Unfavourable abnormalities	52 (30.2)
Favourable abnormalities	8 (4.7)
Normal karyotype/intermediate risk abnormalities	112 (65.1)
FLT3 mutation	
ITD.	17 (13.1)
D-835	5 (3.8)
ITD + D-835	1 (0.8)
NPM1 mutation	18 (14.6)
CEBPA mutation	14 (15.7)
Cytogenetic risk group	
Unfavourable	53 (36.3)
Intermediate	70 (47.9)
Favourable	23 (15.8)
Therapeutic approach	
Intensive induction chemotherapy	127 (62.3)
Non-intensive induction chemotherapy	63 (30.9)
Best supportive treatment	14 (6.9)
Response to induction therapy	
NR (no response)	78 (40.6)
PR (partial response)	13 (6.8)
ORR overall response rate**	101 (52.6)
Progression	99 (55.3)
Death	72 (40.2)

M – mean, SD – standard deviation, Me – median, Q1, Q3 – first and third quartile. Data presented as n (%) for categorical parameters and mean ± standard deviation or median (interquartile range), depending on distribution normality, for numerical parameters.

* FAB classification - The French-American-British AML classification

**ORR = CR (complete remission) + CRi (Complete Remission with Incomplete Blood Count Recovery).

Data collection and statistical analysis

Lymphocytes, monocytes, neutrophils, platelets, RDW-CD, RDW-CV were measured at the time of the diagnosis. NLR, LMR and PLR were calculated by dividing adequate cell counts. Baseline characteristics of patients' complete blood count is presented in Table 2. Data of cytogenetics was obtained retrospectively from patients' medical records. Cytogenetics was classified according to 2022 European LeukemiaNet genetic risk classification [28]. Response criteria were defined according to 2022 edition of the European LeukemiaNet (ELN) recommendations for diagnosis and management of AML [28]. Overall survival (OS) was calculated from the date of diagnosis to death regardless of its cause. Progression free survival (PFS) was calculated from the date of reported CR/CRi/PR to documented peripheral or bone marrow relapse with blast percentage of $\geq$ 5%.

Statistical calculations were run in R software, version R4.1.2. Numerical variables were presented as mean and standard deviation or median and interquartile range, depending on normality of distribution. Categorical variables were presented with absolute and relative frequency. Normality was checked with Shapiro-Wilk test and additionally verified with skewness and kurtosis. Variance homogeneity was verified with Levene test. Comparisons between groups were performed with independent t-Student, independent t-Welch, Mann-Whitney or Kruskal-Wallis tests, as appropriate. Post-hoc evaluation was executed with Dunn test with Bonferroni correction. Correlation analyses were performed with Spearman method. All regression analyses were conducted in 2 steps: univariate and multivariate. Logistic regression models fit was verified with Negelkerke R2 and Hosmer-Lemeshow test. Cox models fit was verified with Wald test. For collinearity verification VIF indicators were calculated. Survival analysis was run with Kaplan-Meier method. Log rank test was used to determine of survival was dependant on levels of analyzed parameters.

All statistical tests assumed significance when $\alpha < 0.05$.

Table 2
Baseline characteristics of patients's complete blood count (N = 204)

Variable	M ± SD / Me (Q1;Q3)
HB (g/dl)	8.95 ± 1.74
WBC (K/uL)	10.62 (2.48;60.44)
PLT (K/uL)	45.50 (24.00;97.00)
LYMPH (K/uL)	2.64 (1.06;8.11)
MONO (K/uL)	2.82 (0.44;25.01)
NEU (K/uL)	1.63 (0.52;5.80)
NLR	0.58 (0.28;1.33)
LMR	0.99 (0.37;3.52)
PLR	14.72 (5.00;47.67)
RDW-SD (fl)	56.50 (50.40;62.20)
RDW-CV (%)	16.35 (14.60;18.60)

M – mean, SD – standard deviation, Me – median, Q1, Q3 – first and third quartile. Data presented as mean ± standard deviation or median (interquartile range), depending on distribution normality.

HB- hemoglobin, WBC- white blood cells, PLT -platelets, LYMPH -lymphocytes, MONO -monocytes, NEU -neutrophils, NLR – neutrophil to lymphocyte ratio, LMR- lymphocyte to monocyte ratio, PLR -platelet to lymphocyte ratio, RDW-SD - red cell distribution width - standard deviation, RDW-CV -red cell distribution width - coefficient of variation

Results

Associations between NLR, LMR, RDW-CV, RDW-SD, PLR and selected variables

Significant positive correlations between older age (both in years and between age groups: $\leq$ 65 years and > 65 years) and RDW-CV and RDW-SD were found. Also, there was a significant negative correlation between hemoglobin and RDW-SD ($p = 0.020$), meaning that each additional g/dl was associated with lower RDW-SD. The strength of those relations was limited. Significant correlations between proportion of blasts in bone marrow at the time of the diagnosis and LMR and PLR were found ($p < 0.001$ each). Both associations were negative with moderate effect (rho = -0.47 and rho = -0.37, respectively),

meaning that each additional percentage point of blasts in bone marrow was associated with lower level of LMR and PLR with moderate strength of the effect. Correlation between the analyzed predictors and selected numeric variables are shown in Table 3.

Table 3
Correlation between the analyzed predictors and selected numeric variables

Variable	Correlation with age (years)		Correlation with HB (g/dl)		Correlation with blasts in MB (%)	
	rho	P	rho	p	rho	p
NLR	0.09	0.221	-0.01	0.882	-0.09	0.257
LMR	0.02	0.751	0.10	0.158	-0.47	**< 0.001**
RDW-CV (%)	0.22	**0.002**	-0.12	0.104	-0.06	0.460
RDW-SD (fl)	0.18	**0.027**	-0.19	**0.020**	-0.01	0.896
PLR	0.04	0.575	0.11	0.124	-0.37	**< 0.001**

rho – Spearman correlation coefficient.

In patients with the ECOG score ≥ 2, NLR was significantly higher and LMR was significantly lower compared to patients with the ECOG score < 2, MD = 0.27 CI95 [0.01;0.39], p = 0.043 and MD = -0.45 CI95 [-0.19;-0.92], p = 0.001, respectively. The frequency of *FLT3* mutations differed significantly, depending on the level of LMR, RDW-CV, RDW-SD and PLR (p = 0.009, p = 0.021, p = 0.032 and p = 0.042, respectively). Post-hoc evaluation aimed at identifying pairs of subgroups with significant association, revealed that LMR was significantly lower within patients with *FLT3-ITD* mutation compared to patients with no *FLT3* mutation (median 0.41 vs 1.12) and RDW-CV was significantly higher within patients with *FLT3-ITD* mutation compared with patients with *FLT3 D-835* mutation (median 17.90% vs 14.40%). Post-hoc tests didn't identify pairs of subgroups significantly differentiating RDW-SD and PLR. Significantly higher RDW-CV was observed within patients with *CEBPA* mutation compared with patients with no mutation, MD = 2.10 CI95 [0.10;4.20], p = 0.041. NLR, RDW-SD and RDW- CV were on average higher, as well as LMR and PLR were lower in the unfavorable cytogenetic risk group, compared with the favorable risk group, but none of these correlations were significant. Described correlations are presented in Table 4.

Table 4
Associations between NLR, LMR, RDW-CV, RDW-SD, PLR and selected variables

Variable	NLR		LMR		RDW-CV (%)		RDW-SD (fl)		PLR	
	Me (Q1;Q3)	P	Me (Q1;Q3)	p	Me (Q1;Q3)	p	Me (Q1;Q3)	p	Me (Q1;Q3)	p
Age of diagnosis (groups)										
≤ 65 years	0.54 (0.26;1.52)	0.727	1.03 (0.36;2.98)	0.529	16.00 (14.40;18.50)	**0.011**	54.95 (48.80;60.40)	**0.030**	12.04 (4.95;47.67)	0.754
> 65 years	0.59 (0.34;1.17)		0.98 (0.40;3.94)		17.20 (15.83;18.60)		58.50 (51.82;63.50)		15.41 (5.57;49.95)	
AML type										
De novo AML	0.48 (0.24;1.15)	0.068	0.85 (0.31;2.32)	**0.006**	16.00 (14.35;17.75)	**0.034**	55.70 (49.50;60.75)	0.167	10.87 (4.01;35.85)	**0.004**
Secondary AML	0.68 (0.37;1.82)		1.69 (0.61;4.78)		16.70 (15.38;18.88)		57.65 (51.58;64.52)		24.44 (9.68;87.08)	
ECOG score										
≥ 2	0.73 (0.39;1.83)	**0.043**	0.69 (0.21;1.31)	**0.001**	17.40 (15.73;18.70)	0.133	58.00 (51.20;61.70)	0.280	9.89 (4.11;24.77)	0.051
< 2	0.46 (0.25;1.09)		1.14 (0.48;4.33)		16.30 (14.80;18.60)		55.70 (49.80;62.20)		16.30 (5.00;50.44)	
Karyotype										
Unfavourable risk abnormalities	0.61 (0.38;1.15)	0.086[1]	1.21 (0.60;3.60)	0.533[1]	16.20 (14.38;18.70)	0.634[1]	57.35 (48.85;63.27)	0.346[1]	25.14 (8.18;50.76)	0.141[1]
Favourable risk abnormalities	0.97 (0.55;1.49)		1.06 (0.69;2.31)		16.20 (15.95;17.55)		54.10 (51.90;56.20)		16.89 (7.89;23.73)	
Normal/intermediate risk abnormalities	0.46 (0.22;1.21)		0.92 (0.34;3.92)		16.40 (14.55;17.90)		56.65 (51.15;61.15)		11.12 (4.40;46.54)	
FLT3 mutation*										
ITD	0.81 (0.35;1.78)	0.237[1]	0.41 (0.21;0.85)[a]	**0.009**[1]	17.90 (16.80;18.70)[b]	**0.021**[1]	59.45 (58.58;65.42)	**0.032**[1]	10.69 (1.75;23.51)	**0.042**[1]
D-835	0.20 (0.15;0.41)		0.92 (0.21;0.99)		14.40 (13.90;15.40)[b]		44.75 (41.95;51.90)		4.67 (1.07;10.55)	
Negative	0.51 (0.30;1.10)		1.12 (0.41;3.75)[a]		16.20 (14.50;18.60)		56.25 (50.32;60.73)		19.13 (5.02;56.56)	
NPM1 mutation										
Positive	0.44 (0.37;1.97)	0.561	0.43 (0.23;3.10)	0.165	16.00 (14.60;17.00)	0.551	52.70 (49.60;57.10)	0.067	8.13 (5.47;24.26)	0.486
Negative	0.52 (0.27;1.03)		1.04 (0.38;2.35)		16.20 (14.40;18.60)		57.65 (51.00;63.98)		16.40 (3.90;47.55)	
CEBPA mutation										
Positive	0.47 (0.30;0.86)	0.352	3.05 (0.39;5.40)	0.125	17.90 (15.22;20.10)	**0.041**	57.05 (49.95;69.20)	0.456	30.77 (8.88;94.05)	0.156
Negative	0.57 (0.31;1.40)		0.86 (0.35;2.17)		15.80 (14.10;17.40)		55.35 (50.32;59.75)		13.54 (4.33;47.78)	
Cytogenetic risk group										
Unfavourable	0.61 (0.38;1.40)	0.649[1]	0.97 (0.41;2.27)	0.741[1]	16.60 (14.30;18.70)	0.190[1]	58.20 (48.85;63.27)	0.053[1]	16.44 (4.92;46.91)	0.316[1]
Intermediate	0.63 (0.24;1.46)		0.95 (0.39;2.42)		16.75 (15.05;18.67)		58.55 (54.40;63.77)		11.20 (3.94;41.34)	
Favourable	0.40 (0.29;0.95)		1.14 (0.39;7.65)		15.35 (14.45;17.15)		50.10 (46.82;56.50)		22.96 (6.33;107.91)	

Me – median, Q1, Q3 – first and third quartile. Comparisons performed with Mann-Whitney U test or Kruskal-Wallis test[1]. a, b – pairs with significant difference indicated by post-hoc Dunn test with Bonferroni adjustment.

* One patient having both *ITD* and *D-835* mutations was excluded from the comparisons.

Prognostic significance of NLR, LMR, PLR and RDW in patients with AML

After one-year observation, NLR, LMR and PLR differentiated dead and alive patients in significant way. NLR was higher on average within dead patients compared to alive patients, MD = 0.22 CI_{95} [0.00;0.40], p = 0.049. LMR and PLR were lower within dead patients compared to alive patients, MD = -0.58 CI_{95} [-1.22;-0.24], p < 0.001 and MD = -10.23 CI_{95} [-12.40;-0.87], p = 0.018, respectively. Analogous correlations with regard to NLR, LMR and PLR were also identified after 3-year observation, MD = 0.29 CI_{95} [0.01;0.48], p = 0.035; MD = -0.71 CI_{95} [-1.69;-0.25], p = 0.001 and MD = -16.92 CI_{95} [-25.25;-3.03], p = 0.004, respectively. Additionally, after 3-year observation, RDW-CV was on average higher within dead patients compared to alive patients, MD = 1.50 CI_{95} [0.80;2.70], p = 0.001.

After one- and three-year observation, based on univariate logistic regression models, the odds of death were influenced by LMR. After one year, LMR higher by one resulted in 24% lower odds of death, OR = 0.76 CI95 [0.62–0.88], p = 0.002 and after three years - in 4% lower odds of death, OR = 0.96 CI95 [0.91–0.99], p = 0.041. After three years, RDW-CV higher by one resulted in 29% higher odds of death in univariate model, OR = 1.29 CI95 [1.10–1.54], p = 0.003. However, none of the analyzed factors turned out to impact death odds significantly in the multivariate regressions.

Based on Cox proportional hazard univariate models, the risk of death within the first year after diagnosis, when survival time was taken into account, was significantly influenced by NLR and LMR. NLR higher by one would result in 6% increased risk, HR = 1.06 CI95 [1.01–1.10], p = 0.016 and LMR higher by one in 19% lower risk, HR = 0.81 CI95 [0.70–0.93], p = 0.004. Also, within three years after diagnosis, based on Cox proportional hazard univariate models, the risk of death, when survival time was taken into account, was significantly influenced by NLR and LMR, but also by RDW-CV. NLR higher by one would result in 5% increased risk, HR = 1.05 CI95 [1.00–1.09], p = 0.034. LMR higher by one would result in 6% lower risk, HR = 0.94 CI95 [0.89–0.98], p = 0.010. RDW-CV higher by one would result in 6% higher risk, HR = 1.06 CI95 [1.01–1.10], p = 0.014. In the multivariate model none of the analyzed factors turned out to impact death risk significantly. Kaplan-Meier analysis showed a significant dependence of OS on NLR, LMR, RDW-CV, PLR (Fig. 1).

The risk of progression within the first year after diagnosis, as well as within three years, when survival time was taken into account, was significantly influenced by NLR, both in the univariate and in multivariate models. Within the first year after diagnosis, NLR higher by one would result in 10% increased risk of progression in the univariate analysis, HR = 1.10 CI95 [1.05–1.14], p < 0.001 and in 16% increased risk of progression in multivariate analysis, HR = 1.16 CI95 [1.04–1.28], p = 0.006. The risk of progression was also significantly influenced by RDW-CV, when survival time was taken into account. Within the first year after diagnosis, RDW-CV higher by one percentage point would result in 11% higher risk of progression in univariate analysis, HR = 1.11 CI95 [1.04–1.18], p = 0.002 and in 10% higher risk in multivariate model, HR = 1.10 CI95 [1.02–1.20], p = 0.014. Within 3 years after diagnosis, higher RDW-CV resulted in higher risk of progression in univariate, but not in multivariate analysis, HR = 1.10 CI95 [1.04–1.17], p = 0.002. Kaplan-Meier analysis showed a significant dependence of PFS on RDW-CV, RDW-CD (Fig. 2).

NLR, LMR, RDW-CV and RDW-SD differentiated groups with no response and response to therapy significantly. NLR, RDW-CV and RDW-SD were higher on average within patients not responding to therapy compared to patients with any response, MD = 0.34 CI95 [0.08;0.49], p = 0.005, MD = 2.00 CI95 [1.10;2.60], p < 0.001 and MD = 3.75 CI95 [0.10;6.70], p = 0.043, respectively. LMR was lower within patients with no response compared to patients with partial or overall response (complete remission and complete remission with incomplete blood count recovery), MD = -0.34 CI95 [-0.91;-0.05], p = 0.015.

Based on univariate logistic regression models, the odds of no response grew by 21% with RDW-CV higher by one percentage point, OR = 1.21 CI95 [1.09–2.36], p < 0.001. LMR higher by one unit resulted in 5% lower odds of no response, OR = 0.95 CI95 [0.89–0.99], p = 0.045. NLR, RDW-SD and PLR had no significant impact on the chance of no response. In the multivariate regression none of the analyzed factors turned out to impact the odds significantly.

Discussion

High NLR and low LMR predicted poorer outcome in AML in our study. This is consistent with numerous studies that proved the prognostic role of NLR and LMR in several oncological diseases, including hematological malignancies [7], such as diffuse large B cell lymphoma [29–30], Hodgkin's lymphoma [31] and multiple myeloma [32–34]. Zhang et al. [35] demonstrated that AML patients with over 50% myeloblasts in bone marrow and high NLR at the time of diagnosis, presented shorter OS and disease free survival. Zhang et al. observed no statistical difference in NLR between patients who achieved CR and those who did not achieve CR. On the contrary, in our study NLR was higher on average within patients not responding to the therapy compared with the patients with any response. In Zhang et al. study there was no correlation between the initial NLR and cytogenetic risk stratification group, similarly as in our study. Mushtaq et al [36] explored the association of NLR and OS in 63 patients with relapsed/refractory acute myeloid leukemia (R/R AML). Also in R/R AML, higher NLR predicted poorer OS. According to our knowledge LMR wasn't evaluated in AML in any study published in English. In this study, low PLR was an adverse prognostic factor in AML. However, the prognostic role of PLR seems more complicated, as it varies in different hematological conditions and, sometimes, even within the patients with the same medical condition, but treated with different regimens [37]. Our study is the first to investigate the role of PLR in relatively homogenous AML patients' group. However, in Woelfinger et al. study [38], patients with high pre-HSCT PLR, showed a significant better OS, less relapses, lower non-relapse-mortality and a lower in-hospital mortality. 49.5% of patients included in the study were treated with AML. It is widely accepted that NLR, LMR and PLR have prognostic significance in many medical conditions because they reflect the interaction between the tumor microenvironment and patient's immunological response [7, 39–40].

According to our knowledge, only one published study evaluated the prognostic role of RDW-CV in patients with newly diagnosed AML. In Vucinic et al study [41], RDW-CV higher than 20.7% predicted higher non-relapse mortality, shorter OS and a trend for shorter event free survival. In our study, RDW-CV also identified patients with worse outcomes. In Vucinic et al. study, RDW wasn't associated with cytogenetic risk, similarly as in this AML cohort. The mechanisms underlying the relationship between RDW and worst outcomes in malignant neoplasms remain to a great extent speculative. First of all, high RDW defines a proinflammatory state that can worsen the course of neoplastic diseases. Numerous studies have proved that inflammation plays a crucial role in tumor initiation, growth and progression [42–43]. RDW level correlate with the levels of other inflammatory markers: IL-6, tumor necrosis factor-alpha, hepcidin [15], CRP [44], plasma viscosity, erythrocyte sedimentation rate (ESR), fibrinogen, leukocyte and neutrophil count [45]. Also, RDW seems to reflect the general health condition of the patient, including age, nutritional status [46] and cardiovascular diseases [12]. In this study, we confirmed previously observed association between age and RDW. Both RDW-CV and RDW-SD were higher in older patients, what is consistent with data in healthy individuals [47]. However, we failed to find the significant correlation between RDW and ECOG Performance Status. Patel et al. [44] proved that high RDW is a strong predictor of poorer OS and higher mortality for multiple causes in middle-age and older adults. Our study is the first to evaluate the prognostic role of RDW-SD in AML.

In our study, LMR was significantly lower within patients with *FLT3-ITD* mutations compared to patients with no *FLT3* mutation. It was proved, that patients with *FLT3-ITD* mutations tend to have an increased risk of relapse and shorter OS [48]. In the past, *FLT3-ITD* allelic ratio was an adverse factor according to the European LeukemiaNet cytogenetic risk classification, however from 2022 it is no longer included due to issues with standardizing the measurement of *FLT3-ITD* allelic ratio and the modifying impact of therapy based on midostaurine on *FLT3-ITD* without *NPM1* mutation [28].

Several limitations of this study must be considered thoroughly. First of all,

the data were collected retrospectively from a single center. Moreover, we recruited patients from 2006 to 2022, what is a relatively long time, in which some treatment modalities have changed. The diagnostic criteria and the risk categories also evolved, however we minimized these limitations by using the criteria of revised fourth edition of WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues [27] in every individual enrolled in the study, independently of the year of the diagnosis.

Conclusions

Our study suggests that NLR, LRM, PLR, RDW-CV and RDW-SD could be simple, easily-available and cost-effective prognostic tests, that may be clinically useful to help risk-stratify patients with AML, in order to better adjust the treatment intensity. We identified higher NLR, RDW-SD and RDW-CV as well as lower LMR and PLR as poor prognostic factors. The results of our study should prompt further evaluation of the association between NLR, LRM, PLR, RDW-CV, RDW-SD and the outcomes in AML, preferably in larger, prospective and randomized studies. Also, further studies are needed to address the specific molecular mechanisms linking those markers with adverse prognosis in AML.

Declarations

Ethics statement

The research has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). The study was approved by the Committee on Bioethics of Medical University of Lublin (ref: KE-0254/60/2021). The need for informed consent was waived by the Committee on Bioethics of Medical University of Lublin (Al. Racławickie 1, 20-059 Lublin, room 08, Poland, +48 (0)814485115, komisja.bioetyczna@umlub.pl).

Data availability

Publication-related data are available from the corresponding author on reasonable request.

Author contributions

All authors made substantial contributions to the article. PS designed the research, searched for the patients included in the study, created the database, analyzed the data and wrote the paper. JMK searched for the patients included in the study and created parts of the database. DK analyzed the data and reviewed the paper. MH analyzed the data and reviewed the paper. MP designed the research, analyzed the data and reviewed the paper. All authors read and approved the final manuscript.

Conflict of interest statement

The authors declare that there is no conflict of interest regarding the publication of this article.

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Figures

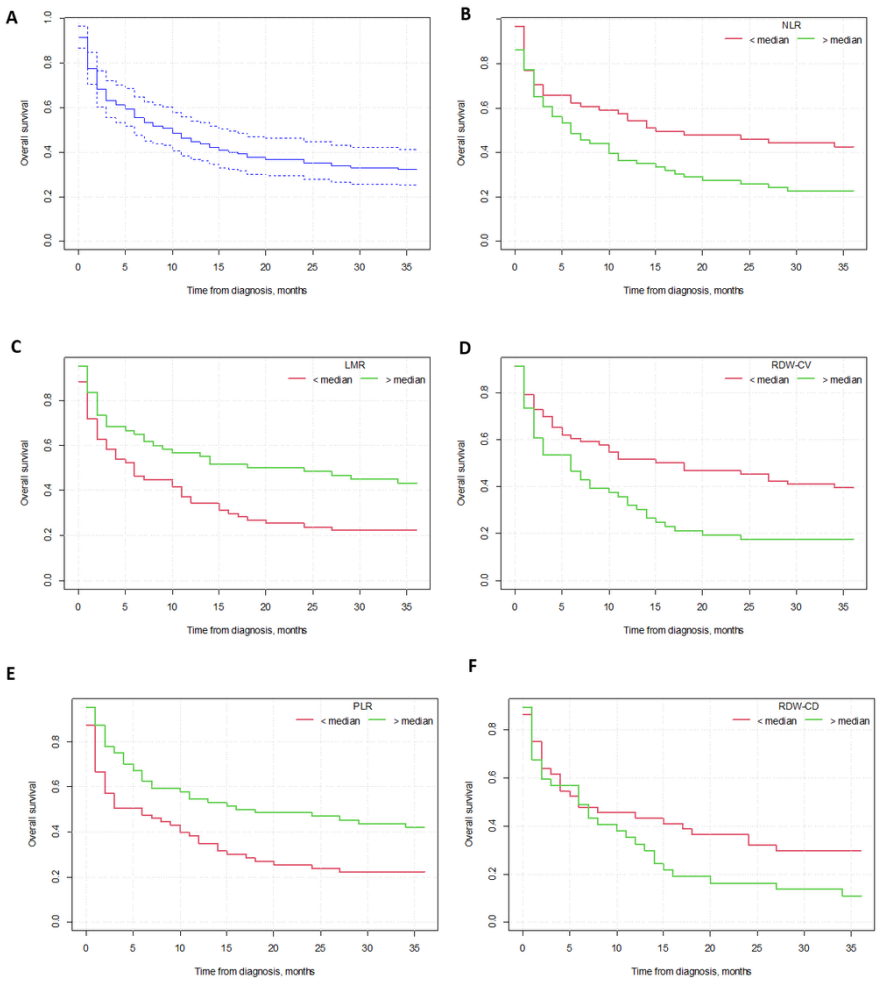

Figure 1

Overall survival (OS) of patients with acute myeloid leukemia grouped according to pretreatment NLR, LMR, RDW-CV, RDW-CD, PLR. A. OS curve on 3 years data (dotted lines represent confidence interval for survival curve);

OS curve on 3 years data in split to: B. NLR, Log rank test outcome: p = 0.020. C. LMR, Log rank test outcome: p = 0.009. D. RDW-CV, Log rank test outcome: p = 0.009. E. RDW-CD, Log rank test outcome: p = 0.102. F. PLR, Log rank test outcome: p = 0.006.There is significant dependence of survival on NLR, LMR, RDW-CV, PLR.

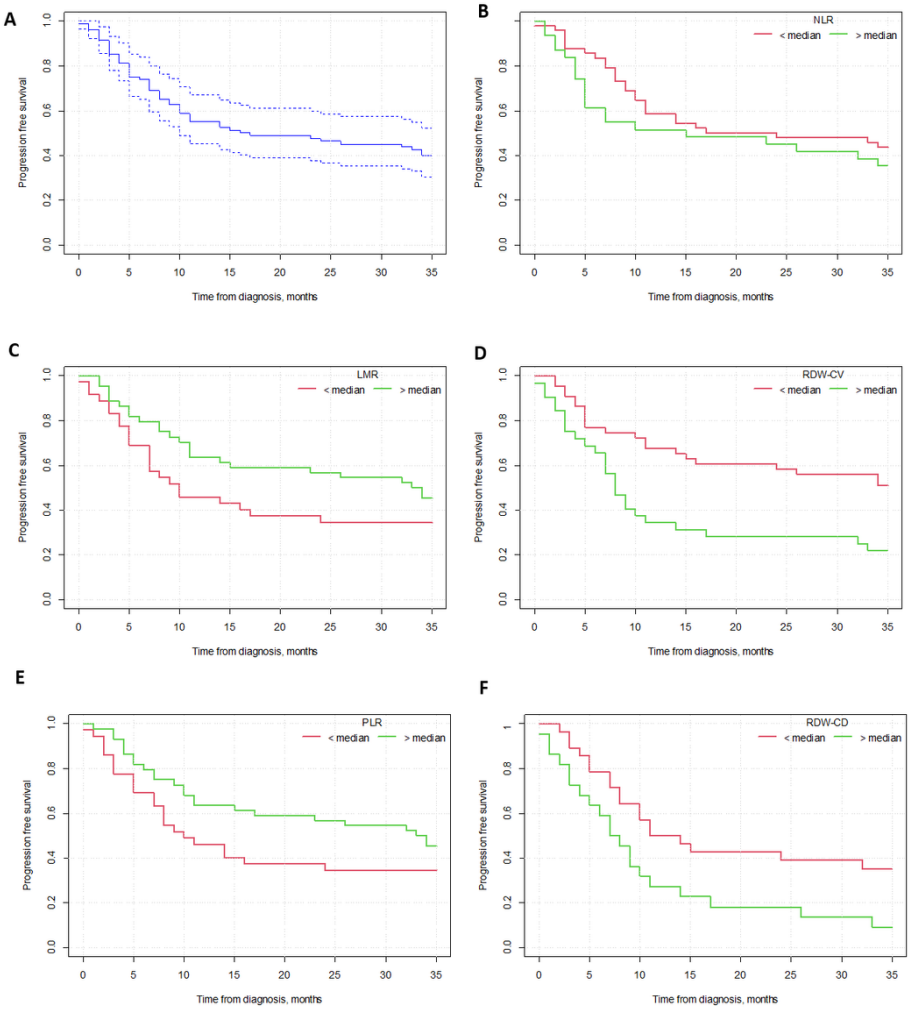

Figure 2

Progression free survival (PFS) of patients with acute myeloid leukemia grouped according to pretreatment NLR, LMR, RDW-CV, RDW-CD, PLR. A. PFS curve on 3 years data (dotted lines represent confidence interval for survival curve);

PFS curve on 3 years data in split to: B. NLR, Log rank test outcome: p = 0.306. C. LMR, Log rank test outcome: p = 0.142. D. RDW-CV, Log rank test outcome: p = 0.003. E. RDW-CD, Log rank test outcome: p = 0.019. F. PLR, Log rank test outcome: p = 0.161. There is significant dependence of survival on RDW-CV, RDW-CD.