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The effect of neutrophil to lymphocyte ratio (NLR), lymphocyte to monocyte ratio (LMR) and mean platelet volume to thrombocyte ratio (MPV/PLT) on survival in myelodysplastyc syndrome

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Abstract

Aim: The aim of the study is to evaluate the relationship between age and leukocyte subtype ratio and their effects on survival in patients diagnosed with myelodysplastic syndrome (MDS).

Materials and Methods: We retrospectively examined total of 101 patients diagnosed with MDS between January 2010 and June 2020. The patients were analysed by dividing into two groups; $<$ 70 years and $\geq$70 years.

Results: The median of overall survival was significantly higher in $<$ 70 years' group (96 vs 40 month, OR 3.6; 95% CI, 1.6-8.7, $p < 0.001$). Whereas neutrophil-to-lymphocyte ratio (NLR) was significantly higher in $\geq$70 years group, lymphocyte-to-monocyte ratio (LMR) was significantly higher in $<$ 70 years group ($p = 0{,}013$ and $p = 0{,}041$, respectively). NLR was positively correlated with age (rho: 0.27, $p = 0.007$) but negatively correlated with clinical risk (rho: -0.24, $p = 0.018$), MPV/PLT ratio was positively correlated with IPSS group (rho: 0.40, $p < 0.001$). In multivariate analysis, its found that age and IPSS group effects overall survival. HR was 1.064 (95% CI; 1.033-1.096, $p < 0.001$) for age and was 3.664 (95% CI; 1.285-10.445, $p < 0.015$) for IPSS group (low versus intermediate-2).

Conclusion: We concluded that NLR and LMR may have a prognostic value for patients who are $\geq$70 years diagnosed MDS.

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Introduction

Myelodysplastic syndrome (MDS) is a clonal disease, which has been associated with genetic anomalies found to occur in hematopoietic stem cells [1]. Pancytopenia is expected since all series are affected; however, anemia is the most common finding. Symptoms are typically non-specific, although fatigue is evident [2]. MDS is a disease of advanced age. The median age is 77, and its incidence reaches to 162/100,000 in people with the age of $\geq$65 [3]. On the other hand, it is well-documented that survival is longer in patients aged under 50 age [4]. Cytopenia and genetic anomalies are among the basic parameters that determine the prognosis in MDS. Various prognostic scoring systems have been developed for this purpose: The International Prognostic Scoring System (IPSS), the Revised IPSS (R-IPSS), and the WHO-Based Prognostic Scoring System (WPSS) are most up-to-date [5]. In recent years, the search for novel parameters to determine the activation severity of inflammatory diseases and to predict the prognosis of malignancies has been remarkable. For this purpose, ratios of leukocyte subtypes have been established and their relationship with various diseases has been investigated. Whereas the Neutrophil/Lymphocyte Ratio (NLR) was determined to be increased in breast cancer, the Lymphocyte/Monocyte Ratio (LMR) was determined to be decreased in gastric cancer and colorectal cancers [6,8]. In addition to NLR and LMR, ratios related to platelet count such as Platelet/Lymphocyte Ratio (PLR) and Mean Platelet Volume (MPV)/Mean Platelet Ratio (MPR) were also calculated and their relationship with the prognosis of various solid organ tumors and some lymphoid and myeloid malignancies has been demonstrated [6].

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In this study, we investigated the effect of age and leukocyte subtype ratios on the prognosis of MDS.

Materials and Methods

Patients who had been diagnosed with MDS between January 2010 and June 2020 in the Division of Hematology, Department of Internal Medicine, Necmettin Erbakan University Meram Faculty of Medicine were included in our study. Patients whose follow-up and treatment data were available were assessed retrospectively. Patients' epidemiological data (age, gender), characteristics associated with MDS (Subtype, IPSS risk and clinical risk groups), treatment modalities, hemogram parameters at the time of diagnosis, and related ratios (Lymphocyte/Neutrophil Ratio; LNR, Lymphocyte/Monocyte Ratio; LMR, MPV/PLT Ratio; MPR), ferritin levels and baseline laboratory values and survival status were recorded. Overall survival (OS) was considered as the period from diagnosis to death or, for surviving patients, the period until the assessment. Patients were compared in two groups, as those with the age of < 70 years and those with the age of ≥ 70 years.

Statistical analysis

The statistical analysis of our study was performed using the SPSS IBM Statistic for Windows, version 22.0. Independent samples t-test or Mann-Whitney U test was used for comparison of continuous numerical data between groups, depending on the distribution normality of the variables. Categorical variables were expressed as percentages (%) and compared via the chi-square test. Spearman's correlation test was used for correlation analysis. Survival analysis was performed by the Kaplan Meier method and the difference between survival curves was analyzed by the Long Rank test. Based on the univariate analysis, potential effective parameters on survival were assessed by Cox regression analysis using the Backward selection method in multivariate analysis. The results were considered statistically significant at $p < 0.05$ (95% confidence).

The study was approved by the Local Ethics Research Committee of Necmettin Erbakan University Meram Faculty of Medicine with protocol number 2020/2907.

Results

One hundred one patients were assessed in our study. The mean age of the patients was 67.4 ± 11.5 (M: 67.8 ± 12.6 F: 67.9 ± 1121), and 49 (48.5%) were female while 52 (51.5%) were male. Disease subtype, R-ISS, and first-line treatment distributions of the patients are presented in Table 1.

While 31 patients (30.8%) did not require treatment, other patients received medical or supportive treatment. The patients who received thalidomide, filgrastim, danasin, methylprednisolone, and cyclosporine in the first-line treatment, apart from demethilizan and erythropoietin, were included in the other group. 34 (48.5%) of the patients receiving medical or supportive treatment aged $<$ 70 years while 36 of them (51.59%) aged $\geq$ 70 years. Of

Table 1. Table 1: Distribution of Patient: MDS-Subtype, IPSS, Clinical Risk and Treatment (N: 101)

	n	%
MDS-Subtype		
SLD	40	39.6
MLD	29	28.7
RARS	3	3
RAEB-1	15	14.8
RAEB-2	9	8.9
Isole del5q	5	4.9
IPSS		
Low	41	40.5
Intermediate-1	48	47.7
Intermediate-2	9	8.9
High	3	2.9
Clinical Risk		
Low	89	88.1
High	12	11.9
Treatment		
Demethylation	25	24.7
EPO	18	17.8
Supportive care	8	7.9
Others	19	18.8
No treatment	31	30.8

Table 2. Table 2: The Comparison of Groups Based on Laboratuary Parameters (N:101)

	<70 years	≥70 years	p
	(n: 50, %49.5)	(n: 51, %50.5)	
Age	58.7±9.2	77±5.8	<0.001[a]
Hb (g/dL)	9.9±2.6	9.9±2.0	0.896
WBC (µL)	3.555 (1000-16000)	3.880 (800-18.000)	0.167
Neutrophyl (µL)	1.700 (100-10.350)	2.300 (50-10.900)	0.060
Lymphocyte (µL)	1.400 (280-3.180)	1.200 (500-4.840)	0.352
Monocyte (µL)	300 (100-2400)	400 (40-2300)	0.101
PLT (103/µL)	98 (11-583)	95 (22-802)	0.870
MPV	10.2±2.0	10.1±1.8	0.819
Ferritin (µg/L)	197.5 (15-2463)	240 (20-2673)	0.500
NLR	1.2 (0.1-16.8)	1.8 (0.08-6)	0.013 [b]
LMR	4.0 (0.7-21.4)	2.8 (0.4-53.7)	0.041[b]
MPR	0.08 (0.02-0.8)	0.1 (0.01-0.51)	0.780

a Independent samples t- test, b Mann-Whitney U Test, NLR: Neutrophyl/Lymphocyte Ratio, LMR: Lymphocyte/Monocyte Ratio, MPR: MPV/PLT Ratio

Table 3. Survival Analysis of Age-related Groups

Groups	Estimated Median Survival	5 Years OS (%)	p
< 70	96 (95% CI; 58.9-133)	73	< 0.001
≥ 70	40 (95% CI; 12.2-67.7)	21	

Table 4. Table 4: Multivariate Analysis of Risk Factors for Overall Survival*

Risk Factor	Hazard Ratio (95% CI)	p
Age	1.064 (1.033-1.096)	< 0.001
IPSS Group (Reference Group: Low risk)		0.049
Intermediate-1 vs Low risk	1.603 (0.833-3.084)	0.158
Intermediate-2 vs Low risk	3.664 (1.285-10.445)	0.015
High risk vs Low risk	6.04 (0.687-59.748)	0.103

*The possible factors identified by univariate analyses were entered into the model. In order to determine independent predictors on survival, Cox regression analysis with backward selection was used and statistical significant step was taken on the table.

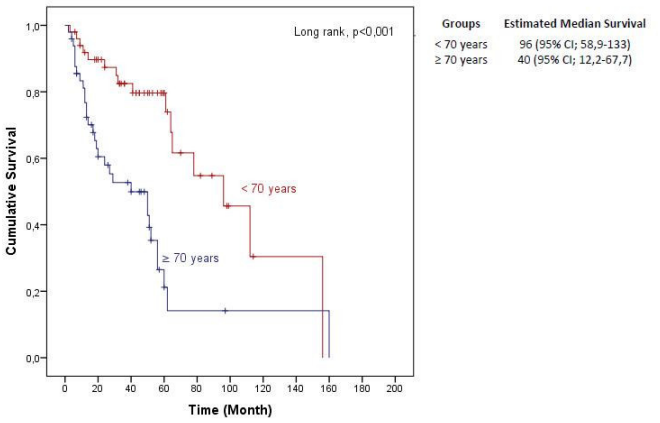

Figure 1. The survival graph of the two groups

the 12 patients in the high-risk group clinically, 7 (58.3%) aged < 70 years, and 5 (41.7%) aged ≥ 70 years. No significant difference was determined between the two age groups regarding clinical risk frequency (Fisher's Exact test p: 0.741)

In the assessment of laboratory testing, which was performed at the time of diagnosis, NLR was determined to be significantly higher in the group of patients aged ≥70 (1.8 vs. 1.2; p: 0.013). A weak positive correlation was found between age and NLR (rho: 0.27, p: 0.007). The median LMR was 2.8 in the group of patients aged ≥70, while it was 4 in patients aged < 70, and the difference between the two groups was found to be significant (p: 0.041). However, the correlation between age and LMR was not significant (rho: 0.21, p: 0.053). The comparison of laboratory parameters by age groups is presented in Table 2.

Other statistically significant correlations were as follows: A negative (rho: -0.24, p: 0.018) correlation was found between NLR and clinical risk, as well as between Hb and ferritin (rho: -0.48, $p < 0.001$), whereas a positive correlation was found between MPR and IPSS group (rho: 0.40, $p < 0.001$).

The median overall survival of all patients was found to be 62.5 months (95% CI: 50.2-72.1). As seen in Table 3 [Table3], the estimated median survival of patients who aged < 70 years was 96 months (95% CI; 58.9-133) and it was 40 months (95% CI; 12.2-67.7) in patients who aged ≥70 and there was a significant difference between the two age groups (OR, 3.6; 95% CI, 1.6-8.7 Long Rank $p < 0.001$). Besides, five-year survival rates are 73% and 21%, respectively. The survival graph of the two groups is presented in the Figure 1.

The significant result step of the multivariate analysis is presented in Table 4.

Based on these results, one unit increase in age increases the risk of death by 1.064 (95% CI; 12.2-67.7 and $p < 0.001$); For IPSS groups, being in group 3 increases the risk of death by 3.664 (95% CI; 1.285-10.445 and p: 0.015) compared to group 1.

Discussion

MDS patients are often diagnosed at an advanced age, and the incidence of the disease increases with age. In the ten-year cohort study, its incidence was reported as 0.5/100,000 in the population aged under 50, while it was 89/100,000 in the population aged over 80 [7]. Data on the epidemiology of MDS in Asian populations are limited. In the study of Chihara et al., which included 7995 patients, the median age was found to be 76 years, and the incidence was revealed to increase significantly, particularly over the age of 70 [8]. Besides, the median age was reported to be 58 (18-90) in China [9]. In our study, the number of patients aged under 50 years was 7 (6.9%). The mean age was 67.4 ± 11.5 years, and almost half of the patients aged over 70.

In the 2016 update of WHO, MDS was assessed in 6 subtypes. The most common subtype in our study is MDS-SLD and it accounts for 39.6% of the patients. On the other hand, in Porta et al.'s data of 5326 diseases, the most commonly diagnosed subtype is MDS-MLD (29.6%), and the rate of patients with MDS-SLD is 17.4% [5].

IPSS and R-IPSS are the most used prognostic scoring systems. In both, cytopenia, bone marrow blast ratio, and genetic features are assessed. Cytopenia and genetic features have been detailed in R-IPSS [5]. Various factors such as serum ferritin and $\beta 2$ microglobulin levels, which are not included in these scoring systems, have also been associated with poor prognosis [10]. In the analysis of Pleggi et al., which included 1855 patients, it was demonstrated that overall survival was shorter in patients with a ferritin value of ≥500 ng/ml [11]. Serum ferritin level in MDS is higher compared to the healthy population, even without transfusion. In addition to this finding, it has been shown with multivariate analysis in the study of Kikuchi et al., which included 47 un-transfused MDS patients, that the risk of death was 9.1 and 1.6 times higher in clinically high-risk patients (intermediate-2 and high risk based on the IPSS) and in patients with a ferritin level of ≥500 ng/ml, respectively ($p < 0.001$ and p: 0.039, respectively) [12]. In the multivariate modeling of our study, the risk of death was found to be 3.6 times higher in IPSS intermediate-2 patients compared to low-risk patients, but the effect of ferritin on the risk of death was not demonstrated statistically. Moreover, based on our model, the risk of death increases as the age increases. When the clinical risk is assessed, it is noticed that 88.1% of the patients

have low clinical risk (low risk and intermediate-1 according to IPSS). This reflects the poor prognostic impact of age without affecting the risk group, as revealed in the literature [10]. In the retrospective analysis of Nösslinger et al., it was suggested that patients who aged ≥66 years had a shorter survival compared to patients who aged <66 years, even if they were at low risk [13] . Consistent with this data, in our study, the median survival of the group consisting of patients aged ≥70 years was significantly shorter, and the 5-year OS was found to be lower in this group as well. When the correlation between age and ferritin is examined, although ferritin does not show a significant difference between the two age groups, it is higher in patients aged ≥70 years. On the other hand, although the mean Hb value was the same between the two groups, a medium strength negative correlation was determined between ferritin and Hb. These findings support the negative effect of ferritin elevation on prognosis, independent of anemia, albeit no significant result was obtained in the established model. However, in our study, the fact that the median ferritin in both groups was below 500 ng/ml and the effects of iron accumulation on survival and the erythrocyte replacement frequency were not assessed, hinders interpreting the results safely.

In recent years, the ratios of leukocyte subtypes have been the subject of research in various inflammatory diseases, notably in malignancies. NLR and LMR are among the most recent of these. One of the building blocks of the microenvironment in malignancies is immune and inflammatory cells. The relationship between absolute lymphocyte, monocyte counts and ratios, and the surveillance and progression of lymphoid hematologic malignancies and solid organ cancers is well-known [7, 8].

In the meta-analysis of Mu et al., which included 2515 patients with diffuse large B-cell lymphoma (DLBCL), it was revealed that NLR elevation was an independent risk factor for low OS and progression-free survival (PFS). Furthermore, advanced age, advanced stage, high-risk group, and high LDH have been associated with higher NLR [14]. Similarly, in our study, NLR was found to be significantly higher in patients aged ≥70 years and it was found to be weak positively correlated with age. However, contrary to this, a negative correlation was determined between NLR and clinical risk. In literature, NLR was associated with several pathological processes related inflammation in elderly population especially [15]. In our study co-morbidities and inflammatory markers exception of ferritin were not evaluated. Therefore, relationship between NLR and age could not be elucidated clearly. In the study of Wang et al., it was concluded that low LMR is an indicator of poor anti-tumor efficacy in patients with DLBCL. The LMR cut-off value was determined as 2.71 [16]. Macrophage and lymphocyte subtypes are not known since our study was retrospective.

Increased NLR in Hodgkin lymphoma (HL) patients has also been considered as a predictor for poor OS and PFS in high-risk and advanced-stage patients. The cut-off values vary between 4.3-6.4 in studies [17]. In another study, NLR was found related to response of treatment [18]. Cut-off analysis was not performed in our study. The LMR in HL was assessed in the meta-analysis of Lee, which included 3319 patients. Low LMR was considered as an unfavorable factor for OS and PFS, as well as for treatment tolerance [19].

Low absolute lymphocyte count and advanced age are used in the prognostic index of lymphoid malignancies and increase the risk score, though it varies depending on its subtypes [20]. In this regard, the prognostic correlation of easily obtainable NLR and LMR in lymphoproliferative diseases makes sense.

There are few related studies investigating leukocyte subgroup ratios in myeloproliferative diseases. Mushtaq et al. assessed 63 patients with relapsed/refractory acute myeloid leukemia, and OS was determined to be significantly lower among patients with an NLR of > 3; 3.4 months vs. 9.2 months [21]. Likewise, in a retrospective analysis of 102 patients with myelofibrosis, OS was found to be significantly shorter in patients with an NLR of ≥10 [22]. In the literature, there are no data examining LNR and LMR in MDS, which is a series of myeloid diseases. Furthermore, the inclusion of 101 patients in our study is satisfactory considering the studies on series of myeloid diseases.

MPR, one of the platelet-related indices, has been investigated in solid organ tumors. It has been shown to be lower in gastric and colorectal cancers due to platelet activation and significantly lower in bone marrow and distant organ metastases [23]. Nagaki et al. also found that MPR was lower in patients with non-squamous cell lung cancer compared to the control healthy population; It has been demonstrated that OS is significantly higher among patients with an MPR of > 0.40 and maybe an independent factor in multivariate analyzes [24]. In our study, MPR was detected to be higher in patients aged ≥70 years, and a positive correlation was determined between MPR and IPSS risk group. Considering the negative impact of advanced age and high-risk disease on survival, high MPR could be considered as an unfavorable prognostic marker in MDS patients, contrary to the literature. However, it might be inaccurate to attribute the meaning to MPR alone, and it should be assessed together with PLT [24]. Because, thrombocytopenia can be seen more prevalently among high-risk patients, as well as these patients may have received thrombocyte replacement during the diagnosis process.

The main points that limit our study can be listed as follows: MDS subtypes, IPSS risk groups, and treatment modalities could not be analyzed since MDS is a heterogeneous disease group, and cut-off values for NLR and LMR could not be revealed.

In conclusion, the fact that the NLR is significantly higher in patients aged ≥70 years for whom the surveillance is shorter, whereas the LMR is lower, and the weak correlation between age and NLR suggests that these parameters may have prognostic value, particularly in elderly patients, although their effects could not be demonstrated in multivariate analysis.

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