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The effects of mean platelet volume and red cell distribution width on prognosis in patients with myelodysplastic syndrome

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ABSTRACT

Objective: In this study, the relationship between changes in mean platelet volume (MPV) and erythrocyte distribution width (RDW) with hematological response and survival in patients with myelodysplastic syndrome was investigated.

Patients and Methods: Between 1 January 2011 and 31 December 2018, patient characteristics and hemogram results were evaluated during the treatment process among 158 patients diagnosed with myelodysplastic syndrome.

Results: The mean age of the patients who were included in the study was 71.53±12.6 years. The MPV percentage change in the 2-year follow-up of the patients with and without hematological response was significant, at 0.022±0.11 (2.2%) in those who responded and at 0.069±0.15 (6.9%) in those who did not (p=0.049). Throughout the same period, the degree of RDW changes in the patients who died was 13.23±22.97, the degree in those who survived was 2.86±21.42, and the difference between the two groups was statistically significant (p=0.006).

Conclusion: In patients diagnosed with myelodysplastic syndrome, MPV and RDW values can be considered inexpensive and simple laboratory markers that can be used in follow-ups and promising tests to predict both treatment response and survival in the early period and change treatment modalities.

Keywords: Myelodysplastic syndrome; Mean platelet volume; Red cell distribution width; Treatment response

1. INTRODUCTION

Myelodysplastic syndrome (MDS) is a heterogeneous group of myeloid diseases characterized by cytopenia(s) in the peripheral blood and dysplastic changes in the bone marrow. This disease has genetic instability and carries the risk of transforming into acute myeloid leukemia (AML). For the diagnosis of MDS, one or more of the diagnostic parameters of dysplasia by more than 10 percent in at least one hematopoietic series, an increase in the blast rate, and/or cytogenetic anomaly compatible with MDS should accompany one cytopenia [1].

The mean platelet volume (MPV) is a marker that is used to measure platelet size and provides an idea about platelet reactivity. Large platelets are metabolically and enzymatically more active and may predispose the patient to prothrombotic events. In this context, high MPV values were associated with hypertension, hypercholesterolemia, obesity, and cardiovascular diseases [2]. Additionally, MPV is often high in diseases like ITP, disseminated intravascular coagulation, congenital thrombocytopenia with giant platelets, and MDS [3]. The red blood cell distribution width (RDW) is a unit that measures the heterogeneity of the size distribution of erythrocytes. The heterogeneity of red blood cells is described by a peripheral smear test as a result of qualitative observation in medical history. If this heterogeneity is above the degree that is accepted as normal, it is defined as anisocytosis. In previous studies, the diameters of erythrocytes have been measured, and the coefficients of variation between the results have been calculated. Histograms have been obtained from these measurements with a bell-shaped distribution using the mean particle volume and coefficients of variation (similar to RDW). Later, it was understood that these data changed numerically in some diseases like pernicious anemia or bleeding. Unfortunately, it is not easy to see the sizes of red blood cells and anisocytosis on a peripheral smear. However, thanks to particle sizing technologies, the heterogeneity of erythrocytes can be measured quantitatively, quickly, and precisely [4]. When these measurements were examined in various patients, it was

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observed that they were high in chronic heart failure, peripheral artery disease, and kidney transplant patients, and they were associated with mortality in diseases like acute coronary infarction, acute pulmonary embolism, acute heart failure, pneumonia, and acute kidney injury [5]. As evidenced by many different studies, an increase in the RDW value (typically over 14.6%) is recognized as a significant marker for morbidity and mortality in the general population [6,7].

In some studies, an increase in MPV values was found between the control group and the group with MDS, but no relationship was established with mortality [8]. According to the recent studies investigated the relationship between MPV to platelet ratio and survival in MDS patients, and this index was found to be higher in patients over 70 years of age, and a positive correlation was observed with the IPSS scores [9]. Similarly, in a study conducted with RDW, the association of RDW with chromosomal anomalies in patients with MDS was examined and a significant result was tried to be obtained in MDS due to ineffective erythropoiesis. However, a relationship between RDW and chromosomal abnormalities in MDS could not be established [10].

In this study, we aimed to investigate the relationship between MPV and RDW values in MDS patients with hematological response and survival.

2. PATIENTS and METHODS

This study was conducted with the participation of 158 patients diagnosed with MDS who presented to Zonguldak Bulent Ecevit University (ZBEU) Hematology Department Outpatient Clinic between 1 January 2011 and 31 December 2018. Written informed consent was obtained from all participants. Ethical approval for the study was obtained from Zonguldak Bulent Ecevit University Non-Interventional Clinical Research Ethics Committee (08/01/2019 – 33479383). The files of the patients who were included in the study were retrospectively scanned from the hospital database in accordance with the permissions of the relevant university ethics committee and the institution. The variables to be evaluated within the scope of the study were recorded for analysis at the time of presentation, and at the 6th month, the 12th month, the 18th month, and the 24th month in follow-ups. Complete blood count tests were performed using a Beckman Coulter LH 780 brand device on approximately 3 milliliters of venous blood samples each taken into an EDTA tube in the biochemistry laboratory of our hospital.

The diagnosis of MDS is based on one or more cytopenias, ≥10 percent morphological dysplastic change in at least one series of nucleated cells, the presence of <20 percent blasts in bone marrow and peripheral blood, and/or characteristic cytogenetic or molecular findings.

Patients were scored according to the percentage of blasts in the bone marrow, karyotype, hemoglobin, platelets and absolute neutrophil counts according to the IPSS-R classification and categorized as very low, low, medium risk level-1, medium risk level-2 and high risk [11].

In the complete blood counts obtained during the follow-ups of the patients, an absolute neutrophil count equal to or greater than 1000/mm^3, a hemoglobin count equal to or greater than 11 g/dL, a platelet count equal to or greater than 100,000/mm^3, and the absence of blasts in the peripheral blood were accepted as hematological response for MDS.

Statistical Analysis

The statistical analyses of the study were conducted using the SPSS 19.0 package program. The continuous variables in the study are presented with mean, standard deviation, median, minimum, and maximum values as descriptive statistics. The categorical variables are presented with frequencies and percentages. The normality of the distributions of the continuous variables was examined using the Shapiro-Wilk test. The Mann-Whitney U test was used in the comparisons of two groups of variables that were not normally distributed. The Friedman test was used for the intragroup comparisons of the dependent variables. Pearson's, Yates, and Fisher's exact chi-squared tests were used for the intergroup comparisons of the categorical variables. In all statistical analyses in the study, results with a p-value below 0.05 were considered statistically significant.

3. RESULTS

One-hundred and fifty-eight patients with the diagnosis of MDS were included in the study. Eighty-nine (56.3%) of the cases were female, and 69 (43.7%) were male. The mean age of the patients was 71.53 ± 12.6 years, and the majority of the group was female. In the follow-ups, 83 (47.5%) patients had a hematological response, and 75 (52.5%) patients did not have such a response. It was observed that 87 (55.1%) patients survived, and 71 (44.9%) patients died. In their follow-up periods, 24 patients used Azacytidine, whereas 13 patients used decitabine, 16 patients used drugs other than hypomethylating agents, 80 patients used EPO, and 58 patients received G-CSF support (Table I). In the classification according to the IPSS scores of the patients, 12 (22.2%) patients were classified as low-risk, 31 (57.4%) were classified as medium-risk level 1, 7 (13%) were classified as medium-risk level 2, and 4 (7.5%) were classified as high-risk.

In the comparison of the hematological response statuses of the patients based on their IPSS scores, hematological response was observed in 9 (75%) of the low-risk patient group, and no response was observed in the remaining 3 (25%) patients. Hematological response was observed in 12 (38.7%) patients in the medium-risk level 1 group, and no response was observed in the remaining 19 (61.3%) patients. Response was observed in 3 (42.9%) patients in the medium-risk level 2 group, and no response was observed in the remaining 4 (57.1%) patients. In the high-risk patient group, none of the 4 (100%) patients showed hematological response. A statistically significant (p=0.021) difference was found among the risk groups in terms of their hematological response statuses.

In the comparison of the MPV values of the patients according to their hematological response statuses through time, no significant change was found in the patients who responded (p=0.077), and a highly significant change (p<0.001) was found in the patients who did not respond. In the comparison of the RDW values of the patients according to their hematological response statuses through time, no significant change was found in the patients who responded (p=0.905) or the patients who did not respond (p=0.146) (Table II).

In the comparison of the MPV values of the patients according to their survival statuses through time, a significant change was found in the patients who died (p=0.008), while a significant change was found in the patients who survived (p=0.025). According to the results of the comparison of the RDW values of the patients, there was no significant change in the values of the patients who survived (p=0.798), whereas a significant change was found in the deceased patients (p<0.001) (Table II).

The mean percentage change in the MPV values of the patients who showed hematological response between the 0th and 24th months was 0.022±0.11, while this value was 0.069±0.15 in the non-responders, and the difference between these groups was statistically significant (p=0.049). The mean percentage change in the MPV values of the deceased patients between the 0th and 24th months was 0.072±0.16, while the mean percentage change in the patients who survived was 0.023±0.11, and no significant difference was found between the two groups (p=0.098). The mean percentage change in the RDW values of the patients with hematological response between the 0th and 24th months was 0.066±0.21, the mean percentage change in those who did not respond was 0.078±0.23, and the difference between the two groups was not statistically significant (p=0.375). The mean percentage change in the RDW values of the patients who died between their measurements at the 0th and 24th months was 13.23±22.97, the mean percentage change in the patients who survived was 2.86±21.42, and a highly significant difference was found between the two groups (p=0.006) (Table III).

Table I. *Descriptive characteristics of patients diagnosed with myelodysplastic syndrome*

Characteristics (n=158)	Number (n)	Percentage (%)
Gender		
Male	69	43.7
Female	89	56.3
Age (year)	Mean±SD: 71.53±12.6	
Hematological Response		
Responders	83	52.5
Non-responders	75	47.5
Survival		
Alive	87	55.1
Deceased	71	44.9
Treatment		
Azacitidine	24	15.2
Decitabine	13	8.2
Other medications	16	10.1
Erythropoietin	80	50.6
G-CSF	58	36.7

G-CSF: Granulocyte stimulating factor, SD: Standard deviation

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Table II. *Comparison of MPV and RDW values with hematological response and survival*

		MPV			RDW		
Hematological Response (month)	**n**	**Mean±SD**	**Median (min – max)**	**p**	**Mean±SD**	**Median (min – max)**	**p**
Responder							
0th Month	83	8.43±1.15	8.40(6.4-10.6)		16.81±2.94	16.10(12.6-27.8)	
6th Month	83	8.48±1.02	8.40(5.9-12.5)	0.077	17.49±3.82	16.20(12.4-29.9)	0.905
12th Month	82	8.51±1.02	8.45(6.6-10.6)		17.05±3.20	16.25(12.9-27.4)	
18th Month	80	8.67±1.13	8.60(6.5-12.6)		17.09±3.28	16.40(12.8-28.1)	
24th Month	73	8.59±1.05	8.50(5.8-10.9)		17.77±3.77	16.90(12.8-31.6)	
Non-Responder							
0th Month	75	8.89±1.42	8.90(6.4-13.6)		18.62±4.15	17.70(12.9-34.1)	
6th Month	73	8.96±1.44	8.70(6.4-13.3)		19.4±5.16	17.80(13.6-35.1)	
12th Month	67	9.01±1.44	8.90(5.4-13.7)	**<0.001**	19.47±4.56	18.20(13.6-32.2)	0.146
18th Month	64	9.15±1.55	8.70(5.6-13.0)		19.82±4.78	18.25(13.6-31.1)	
24th Month	61	9.43±1.40	9.10(6.5-13.1)		19.70±4.23	18.90(13.1-31.3)	
Survival (month)							
Alive							
0th Month	87	8.76±1.29	8.80(6.4-13.6)		17.41±3.76	16.40(12.6-34.1)	
6th Month	85	8.67±1.28	8.50(6.5-13.3)		18.73±5.06	17.50(12.4-35.1)	
12th Month	83	8.77±1.14	8.90(6.4-11.7)	**0.025**	17.97±4.26	16.50(12.9-32.2)	0.798
18th Month	82	8.94±1.19	8.80(6.7-13.0)		17.81±4.47	16.30(12.8-31.1)	
24th Month	78	8.95±1.07	8.90(7.0-12.3)		17.73±3.84	16.70(12.8-31.6)	
Deceased							
0th Month	71	8.51±1.26	8.50(6.4-13.6)		17.99±3.55	17.70(13.1-31.9)	
6th Month	71	8.75±1.36	8.50(5.9-13.3)		17.98±3.94	16.90(13.3-30.3)	
12th Month	66	8.68±1.39	8.70(5.4-13.7)	**0.008**	18.35±3.77	17.70(13.6-30.1)	**<0.001**
18th Month	62	8.81±1.55	8.60(5.6-13.0)		18.96±3.81	18.35(13.6-30.8)	
24th Month	56	8.99±1.55	8.85(5.8-13.1)		19.92±4.12	18.55(14.2-31.3)	

SD: Standard deviation, MPV: Mean platelet volume, RDW: Red cell distribution width. Friedman test was applied to compare the mean value of parameters between all groups.

Table III. *Comparison of percentage changes in MPVs and RDWs of patients with hematological response and survival*

	n	MPV			RDW		
Hematological Response		**Mean±SD**	**Median (min – max)**	**p**	**Mean±SD**	**Median (min – max)**	**p**
Responder	73	0.022±0.11	0.021(-0.22 – 0.28)	**0.049**	0.066±0.21	0.028(-0.30 – 0.95)	0.375
Non-Responder	61	0.069±0.15	0.39(-0.039 – 0.85)		0.078±0.23	0.09(-0.53 – 0.76)	
Survival							
Alive	78	0.023±0.11	0.01 (-0.33 – 0.31)	0.098	2.86±21.42	0.45(-53.37 – 94.89)	**0.006**
Deceased	56	0.072±0.16	0.05 (-0.22 – 0.85)		13.23±22.97	10.58(-43.73 – 75.66)	

SD: Standard deviation. Mann-Whitney test was applied to compare the mean value of parameters between all groups.

4. DISCUSSION

Although, classification systems like those of WHO and FAB are used for diagnosis in MDS, these systems do not provide clues prognostically. Classification systems like IPSS and IPSS-R are used for current prognostic data. According to the statistics in these classification systems, there is a higher risk of mortality and morbidity in some IPSS (medium-risk level 2, high-risk) and IPSS-R (medium-risk, high-risk, very high-risk) patient groups than in some other IPSS (low-risk, medium-risk level 1) and IPSS-R (very low-risk, low-risk, medium-risk) patient groups, considering the duration of transformation to AML and the average life expectancy. The incidence and prevalence of MDS were higher in male patients compared to female patients in previous studies [9,12]. In our study, the number of female patients (56.3%) was higher than the number of male patients (43.7%). This result may have occurred due to the fact

that some diagnosed patients who presented to the outpatient clinic once and continued their follow-ups in other centers were excluded from the study. In this study, the frequency of MDS was determined to increase with age, the incidence of MDS increased up to 40-50 cases per 100,000 people in the population over 70 years of age, and the mean age of the patients included in our study, which was 71.53±12.6 [median 74.5 (minimum: 29, maximum: 94)], was found to be consistent with ages reported in previous studies [12].

In the study by Wijermans et al., the mean hematological response rate was found 49%, and the rate of cases with hematological response in our study was 52.5%, which was similar [13].

According to the evaluations of the patients according to their IPSS scores, hematological response was observed in 9 (75%) patients in the low-risk group, but no response was observed in 3 (25%) patients in the same group. In the high-risk patient group, none of the 4 (100%) patients showed hematological response. A significant difference was observed among the hematological response rates of the groups that were assigned based on their IPSS values (p=0.021), and response rates decreased significantly as risk levels increased. Similarly, Greenberg et al., reported that markers such as hemoglobin and neutrophil counts are important in prognosis, and as the risk classification increases, the response decreases, and the mean survival time is shorter [14].

Masutani et al., evaluated the usability of MPV and mean platelet component values (platelet count x MPV) for screening purposes in cases with MDS. MPV and mean platelet component (MPC) values at the time of first diagnosis in MDS, aplastic anemia, ITP, and myeloproliferative neoplasms were compared to reference values. In the samples collected from 1304 healthy individuals, the mean MPV was 8.1±1.5 fL, while the mean MPV value was 8.9±2.9 fL in patients with aplastic anemia, 9.7±4.4 fL in ITP patients, and 9.0±2.7 fL in patients with myeloproliferative neoplasms, whereas it was relatively high at 12.0±5.0 fL in MDS patients (p<0.001) [8]. In our study, the MPV values of the patients who showed hematological response did not significantly change through the measurement times (p=0.077). The MPV values of the patients without hematological response, on the other hand, showed changes with a high degree of significance (p<0.001). In the analyses of the mean MPV values of the treatment-independent patients who died and those who survived, statistically significant changes were observed through time in both the deceased group (p=0.008) and the group that survived (p=0.025). This was thought to be due to the advanced age of the patients and their causes of death other than MDS. In the comparison of the MPV percentage changes of the patients from the initial measurements to the twenty-fourth month measurements, a statistically significant difference was found (p<0.05) between the patients with hematological response (2.2%) and those with no hematological response (6.9%). This gives us a clue for monitoring patients who show an increase in MPV values more closely during their follow-ups and perhaps preparing them for early stem cell transplantation. The percentage increase through time in the MPV values of the patients regardless of treatment was 2.3% in those who survived and 7.2% in those who died, while the difference between the two groups was not statistically significant [8].

Baba et al., associated RDW with clinical outcomes in MDS patients, and no significant correlation was found between RDW and prognosis in patients with increased blast counts, while a significant relationship was found between increased RDW (≥15.0%) and poor prognosis (p=0.0086) in MDS patients with refractory anemia [10]. In our study, the RDW values of the patients did not change significantly over time in the group with hematological response (p=0.905) or the group without hematological response (p=0.14). While the RDW values of the patients who survived regardless of the treatment did not show a statistically significant change through the measurement times (p=0.798), the values of those who died increased to a statistically highly significant extent (p<0.001). Thereupon, the percentage changes in RDW values were compared based on hematological response status and survival status, and no significant relationship was identified between RDW changes and hematological response statuses (p=0.375), while these values significantly differed based on survival status (p=0.006) [10]. Furthermore, in a similar study, it was reported that RDW has a potential as a prognostic marker in MDS patients [15]. For these reasons, while the RDW value could not be associated with response to treatment in this study, it was found to be significantly associated with mortality.

Limitations

There were two major factors limiting the analyses in this study. First, some patients did not comply with the two-year follow-up period. Second, there was relatively little cytogenetic information available compared to the entire patient population (cytogenetic analysis could be performed for only 54 of the 158 patients, which corresponded to a rate of 34.1%).

Conclusion

We investigated the effects of MPV and RDW values on prognosis in myelodysplastic syndrome cases. MPV value changes were found to be significantly associated with hematological response status (p=0.049). While no relationship could be established between survival status and MPV changes, a highly significant relationship was found between RDW changes and survival status (p=0.006). In this study, it was aimed to reveal prognostic markers that can be used practically in the hematology clinic to change prognosis and treatment modalities in MDS and facilitate follow-ups. Without highly invasive procedures like bone marrow examination, MPV is a simple, inexpensive hemogram parameter that can be used daily in the follow-up of MDS patients, and it is a promising predictor of prognosis. When there is an increase in MPV values that is determined by only looking at routine blood tests in the follow-up of patients, this increase can be considered an indicator of poor diagnosis.

Compliance with Ethical Standards

Ethical Approval: This study was approved by the Zonguldak Bulent Ecevit University Non-Interventional Clinical Research Ethics Committee (08/01/2019 – 33479383).

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