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CLINICAL STUDY

Does the platelet-to-lymphocyte ratio have a prognostic effect in patients with myelodysplastic syndrome?

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ABSTRACT

INTRODUCTION: Myelodysplastic syndromes (MDS) include various hematologic abnormalities characterized by chronic cytopenia due to disruption in cellular differentiation. This study aims to evaluate the prognostic value of PLR in patients with MDS.

MATERIAL AND METHODS: Clinical-laboratory findings and the results of bone marrow biopsies of MDS patients before treatment were recorded. p value of <0.05 was considered statistically significant. SPSS version 20.0 was used for statistical analysis.

RESULTS: The study included 62 patients with median follow-up time of 62.8±4.5 months and median age of 68.5 years. In 13 patients, acute leukemia was transformed. In these subjects, a PLR cut-off level of 46 was established for mortality (p=0.015). We found a significant relationship between PLR and multilineage series with the presence of dysplasia (p=0.017). The survival analysis showed a decreased survival in cases with dysplasia in two and/or more series, transformation into acute leukemia, and thrombocytopenia.

CONCLUSION: Our study demonstrated that there was a relationship between PLR and MDS with multilineage dysplasia (mld-MDS). PLR is investigated as an inflammatory finding in various hematologic malignancies. Further studies investigating the value of PLR in MDS are needed to determine whether PLR may be a marker of bone marrow dysplasia grading *(Tab. 2, Fig. 4, Ref. 32)*. Text in PDF *www.elis.sk.*

KEY WORDS: myelodysplastic syndromes,hematologic abnormalities, chronic cytopenia, cellular differentiation, marrow biopsy, acute leukemia, thrombocytopenia.

Introduction

Myelodysplastic syndromes (MDS) are hematological clonal neoplasms in which ineffective hematopoiesis occurs in one or more blood cell lineages due to dysmorphogenesis (1). MDS patients are at increased risk of transformation to acute myeloid leukemia. Defective hematopoiesis may lead to anemia, bleeding, and increased risk of infection. MDS presents as anemia in 85 %, neutropenia in 50 %, and thrombocytopenia and low lymphocyte count in 25–50 % of cases at the time of diagnosis (2).

Scoring systems are usually used to determine the MDS prognosis. There are three different prognostic scoring systems for MDS determined by findings that include bone marrow blast percentage, karyotype, cytogenetics, degree of cytopenia, need for red blood cell transfusion, age, and performance status (3). In addition to the revised International Prognostic Scoring System (IPSS-R), WHO Prognostic Scoring System (WPSS), and MD Anderson Cancer Center (MDACC) MDS model, many clinical and laboratory findings such as elevated ferritin levels, gene expression profiling, increased DNA methylation, increased serum beta-2 microglobulin, and absolute lymphocyte count have been demonstrated to be effective in determining prognosis in MDS patients (4–7). Data from various publications have shown the prognostic impact of low absolute lymphocyte count and thrombocytopenia in MDS (8, 9).

The role of inflammation in cancer biology has been reported with increasing evidence over the years. A complex relationship between host and tumor has been shown through certain mediators and inflammatory cells surrounding the cancer cell and its microenvironment. Biochemical findings such as C-reactive protein, albumin, white blood cell count, and neutrophil count are frequently considered indicators of systemic inflammation (10). It is known that platelets also play a role in the systemic inflammatory response (11).

The effect of inflammation and immunological microenvironment on the pathogenesis of MDS was observed in recently published data (12). In studies involving low-risk MDS patients, T lymphocyte-mediated inhibition of hematopoiesis was observed. Subsequently, the escape from immune surveillance in the later phase of the disease has been shown to be effective in the transformation to acute leukemia. Both thrombocytopenia and decrease in absolute lymphocyte count have been suggested as poor prognostic markers in MDS (8, 9). Although there are studies on the

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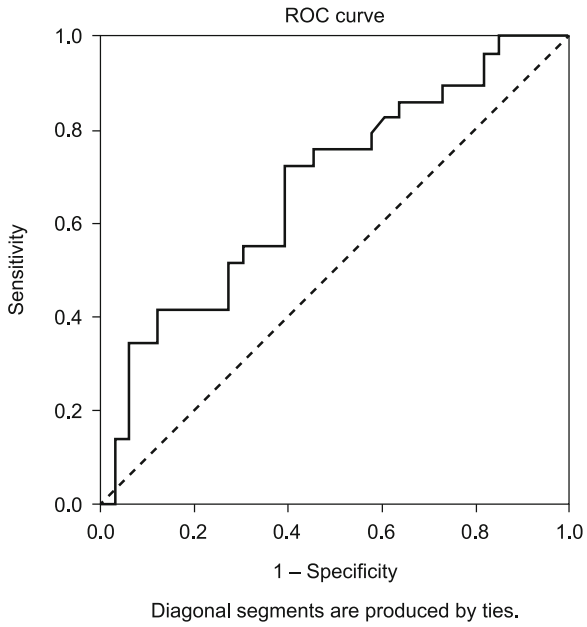

Fig. 1. Roc curve for PLR cut-off value and mortality.

prognostic value of PLR as an indicator of inflammation in both hematologic and solid malignancies (13-16), we did not encounter any study examining PLR in MDS. In this study, we aimed to investigate whether or not PLR is associated with clinical and laboratory findings, prognosis, and leukemic transformation in MDS.

Material and methods

Patients

The clinical data of 62 cases of MDS diagnosed at the Yildirim Beyazit University Hospital, Department of Hematology between 2009 to 2018 were retrospectively examined. Laboratory values measured at initial MDS diagnosis were examined. Bone marrow biopsies performed during diagnosis were reviewed. The subtypes of MDS were defined by using the World Health Organization (WHO) classification system (17).

Clinical data

The demographic data and clinicopathologic features of patients were collected from medical records, including MDS subtype, lactate dehydrogenase (LDH), blood tests, and pathology reports. Leukocyte, lymphocyte, platelet, and neutrophil counts were recorded from standard hemogram results before the initiation of any treatment (pretreatment). PLR was calculated as the absolute platelet count divided by the absolute lymphocyte count. ROC curves were used to determine the best threshold values for sensitivity and specificity.

Statistical analysis

SPSS (Statistical Package for Social Sciences) version 15.0 for Windows was used for statistical analysis. Student's t-test and Chi-square tests were used in addition to descriptive statistics when applicable. Kaplan–Meier's curves were used for overall survival analysis and receiver operating characteristic (ROC) curves were formulated to estimate the cut-off level of PLR for mortality. The Cox proportional hazards model was used for the independent variables affecting overall survival (categorical values consisting of two simple ordinal numbers). $p < 0.05$ was considered statistically significant.

Results

A total of 62 patients diagnosed with MDS were included in this study. The median age of MDS cases was 68.5 (min 35, max 89) years. Male/female ratio was 41/21 (63.1 %/36.9 %). There were 37 (59.7 %) patients over 65 years of age. Median follow up time was 62.8 ± 4.5 months. There were 26 (41.9 %) cases with multilineage dysplasia (mld-MDS), 17 (27.4 %) cases with single lineage dysplasia, 16 (25.8 %) with excess blasts, and 3 (4.8 %) cases with ring sideroblasts.

At the time of initial diagnosis, mean hemoglobin value was 8.4 ± 1.94 gr/dL, median platelet count was 135.5 $x10^9$/L (min: 5$x10^9$/L max: 425$x10^9$/L), median leukocyte count was 3.3 $x10^9$/L (min: 0.6 $x10^9$/L max: 9.9 $x10^9$/L), and median lymphocyte count was 1.13 $x10^9$/L (min:0.15 $x10^9$/L max:5.16 $x10^9$/L). Bone marrow blast percentage was below 5 % in 46 (74.2 %) cases, 5–10 % in 12 (19.4 %), and between 11 and 20 % in 4 (6.5 %) cases. Of the 12 (19.4 %) MDS cases with ring sideroblasts, the percentage of ring sideroblasts in bone marrow was above 15 % in 6 (9.7 %) patients and below 15 % in 6 (9.7 %) patients. MDS cases with single and two and/or more series dysplasia in bone marrow were 27 (43.5 %) and 35 (56.5 %), respectively. There were 40 (61.5 %) cases of bone marrow pathology consisting of grade 1–3 fibrosis, and 25 (38.4 %) cases without fibrosis. Thirteen (20 %) patients underwent transformation into acute myeloid leukemia, and 33 (53.2 %) patients died.

Tab. 1. Comparison of clinical and laboratory findings according to PLR cut-off value of 46 in MDS cases.

Platelet/lymphocyte ratio	PLR >46 (n=39 (62.9%))	PLR ≤46 (n=23(37.1%))	p
Blast percentage <5 %	29 (63%)	17 (37%)	0.598
Neutrophil <1500 /μL	10 (50 %)	10 (20 %)	0.121
Hemoglobin <10 g/dL	38 (63.3%)	22 (36.7 %)	0.608
Hemoglobin <8 g/dL	28 (68.3%)	13 (31.7 %)	0.171
Bone marrow fibrosis	27 (62.8%)	16 (37.2%)	0.609
Cases with MDS with multilineage dysplasia (mld-MDS)	17 (48.6%)	18 (51.4%)	0.008
Ring sideroblasts in bone marrow	8 (66.7%)	4 (33.3%)	0.520
Gender M/F	27(43.5%)/12(19.4%)	15(24.2%)/8(12.9%)	0.478
Age ≥65 years	20 (54.1%)	17 (45.9%)	0.067
Transformation into AML	6 (50 %)	6 (50 %)	0.240
LDH >220 g/dL	23 (60.5 %)	15 (39.5 %)	0.416
Mortality	17 (51.5%)	16 (48.5%)	

Tab. 2. Overall survival analysis of the cases according to clinical and laboratory findings.

	Overall survival (mean±standard deviation)	95% Confidence Interval	p (Logrank)
Age			
<65 years old	63.9±4.9 months	54.33–73.59	0.621
≥65 years old	45.8±6.1 months	33.76–57.86	
Gender			
Male	61.2±4.5months	44.66–82.76	0.219
Female	63.7±9.7 months	51.35–71.06	
PLR			
≤46	59.9±15.2 months	30.05–89.75	0.596
>46	63.4±4.8 months	53.8–72.9	
Multilineage dysplasia			
Positive	49.8±6.8 months	36.5–63.2	**0.001**
Negative	75.3±4.5 months	66.3–84.3	
AML transformation			
Positive	27.1±5.9 months	15.5–38.7	**0.003**
Negative	67.5±4.5 months	58.7–76.4	
Platelet count			
≤50 x10^9/L	20.14±5.37 months	9.6–30.6	**0.021**
>50 x10^9/L	65.5±4.5 months	56.6–74.4	
Leukocyte count			
≤4 x10^9/L	56.41±7.31 months	42.07–70.75	0.546
>4 x10^9/L	66.34±5.57 months	55.41–77.27	
Ring sideroblasts in bone marrow			
Positive	60.3±7.0 months	46.5–74.1	0.758
Negative	65.7±5.7 months	54.4–77.0	
Fibrosis in bone marrow			
Positive	61.2±6.1 months	49.2–73.2	0.710
Negative	64.8±7.0 months	50.9–78.7	
Hemoglobin			
≤8 g/dL	62.8±4.8 months	53.3–72.2	0.605
>8 g/dL	70.5±10.5 months	49.9–91.08	
LDH			
≤220 g/dL	54.6± 7.9 months	39.0–70.16	0.293
>220 g/dL	68.7± 5.4 months	58.0–79.4	
Percentage of blasts in bone marrow			
≤5%	64.2±5.1 months	54.0–74.3	0.210
>5%	53.4±9.6 months	34.4–72.3	

Receiver operating characteristic curves (ROC) were used to obtain cut-off levels of lymphocyte count, platelet count, and PLR for mortality. Cut-off level of 361/μL lymphocyte count was established for mortality (p=0.005). The area under ROC curve for lymphocyte count was 0.236 with a cut-off level of 361/μL, while sensitivity and specificity were 69 % and 88 %, respectively. The cut-off level of platelet count could not be determined for mortality (p > 0.05). A cut-off value of 46 was established for PLR for mortality (p=0.015). The calculated cut-off levels had the highest sensitivity compared to the other cut-off levels. The area under ROC curve for PLR was 0.680 with a cut-off value of 46 with sensitivity and specificity of 89.7 % and 75.8 %, respectively (Fig. 1). A cut-off value of ≤ 46 for PLR was significantly associated with dysplasia in bone marrow (p=0.008) and mld-MDS (p=0.005). Among the 26 patients diagnosed as MDS with multilineage serial dysplasia, 15 (65.2 %) patients had a PLR cut-off value of ≤ 46 (p=0.005). Among the 36 patients diagnosed with other MDS subtypes, 8 (34.2 %) patients had a PLR cut-off level of ≤ 46 (p=0.005). The PLR cut-off values and clinical and laboratory findings are presented in Table 1.

The mean survival time of MDS cases in our study was 62.8 ± 4.5 months. The impact of dysplasia in two and/or more series, transformation into acute leukemia, ring sideroblasts in bone marrow, fibrosis in the bone marrow, anemia, thrombocytopenia, increased LDH value, and PLR > 46 on survival were evaluated. The comparisons of overall survival according to clinical and laboratory findings are presented in Table 2. The decreased survival was found to be significantly associated with the presence of dysplasia in two and/or more series (p=0.001) (Fig. 2), transformation into acute leukemia (p=0.003) (Fig. 3), and thrombocytopenia (<50 x10^9/L; p=0.021) (Fig. 4). There was no significant correlation between the survival and presence of ring sideroblasts in bone marrow (p=0.863), fibrosis in bone marrow (p=0.710), anemia (p=0.605), elevated LDH levels (p=0.293), and PLR of > 46 (p=0.596). The analysis of overall survival according to clinical and laboratory findings is presented in Table 2.

The mortality rate of MDS with multilineage dysplasia was increased five times (95% CI 0.4–3.35; p=0.003). The presence of thrombocytopenia (<50x10^9 / L) increased the mortality eight times ([95% CI 0.42–0.88], p=0.035). Acute leukemia transformation was found to be associated with mortality which was increased seven times (95% CI [0.04–0.65], p=0.01).

Discussion

According to the results of our study, the cases with decreased platelet-to-lymphocyte ratio were associated with MDS subtype with dysplasia in multilineage series in univariate analyzes. However, there was no significant relationship with overall survival. Also, according to multivariate analysis, the overall survival was decreased in patients with thrombocytopenia, transformation to acute myeloid leukemia, and multiple series dysplasia.

The mechanism, by which the immune system can influence prognosis in MDS has not been fully elucidated. Interestingly, chronic immunostimulation involved in the pathogenesis of MDS through proinflammatory cytokines, and inflammatory environment in the bone marrow microenvironment have been shown to cause dysplasia in MDS (18, 19).

In addition, it has been shown that changes in the functions of T-regulatory lymphocyte cells may be a parameter that predicts disease progression and bone marrow failure in the early stage

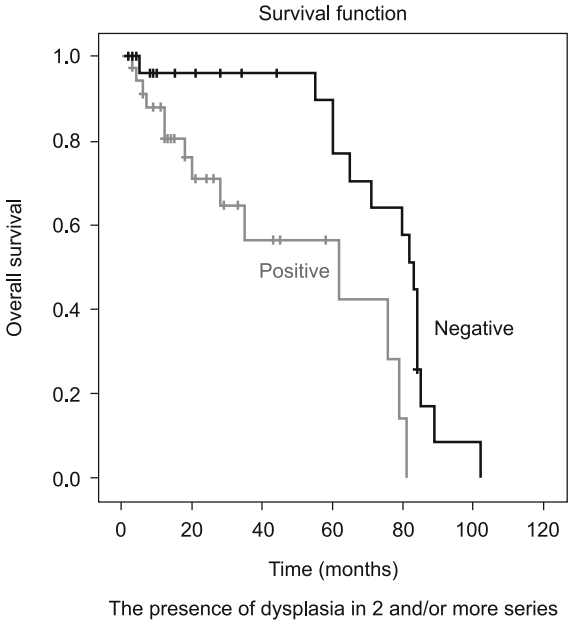

Fig. 2. Kaplan–Meier curves for survival for presence of dysplasia in two and/or more series in MDS cases.

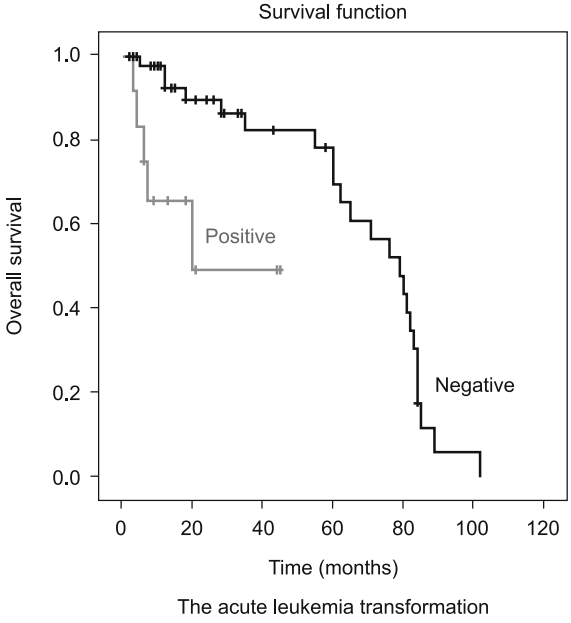

Fig. 3. Kaplan–Meier curves for survival for presence of transformation into acute leukemia in MDS cases.

of MDS (20). Some studies suggest that a defect in T-regulatory lymphocytes in the low-risk MDS patient group supports dysplastic clone selection (21). Furthermore, it has been suggested that increased T-regulatory lymphocyte count promotes leukemic transformation (22). The inflammatory response is associated with cancer pathophysiology in which inflammation markers such as lymphocyte count, platelet count, c-reactive protein, and hypoalbuminemia have been investigated in many cancers as well as

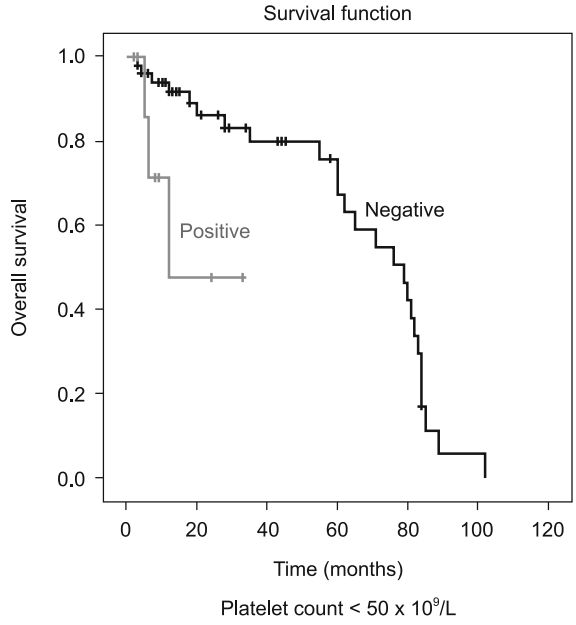

Fig. 4. Kaplan–Meier curves for survival for presence of thrombocytopenia in MDS cases.

in MDS (23). Both low platelet count and leukopenia have been associated with poor prognosis in MDS patients due to impaired pathophysiology (9). In both bone marrow and peripheral blood, the half-life of blood cell lines of all three series was shortened and the function was impaired (2). We could not find any data about the effect of platelet-to-lymphocyte ratio as an inflammatory marker of prognosis in MDS cases. According to our data, we found a significant relationship between mld-MDS subtype and low PLR values. Multilineage dysplasia and blast percentage are important prognostic factors in the classification of WHO when evaluating bone marrow morphology in MDS patients (17). In the current study, there were 26 (41.9 %) cases with MDS with multilineage dysplasia (mld-MDS), while the expected distribution of the mld-MDS subtype is approximately 70 %, and in our case series, it was 41.9 %. The rate of MDS with single lineage dysplasia was 27.7 %, which was higher than the expected rate according to literature. The lower PLR value in mld-MDS cases may be related to the predominance of the defect in the thrombopoiesis part for the expected dysplasia in at least two series in these cases.

The reactive thrombocytosis is known to be associated with systemic inflammatory response. Therefore, many published studies have investigated the effect of PLR on hematologic and non-hematologic malignancies and reported that increased PLR is associated with poor prognosis and negative impact on survival (24-27). However, low PLR in multiple myeloma, one of the hematologic malignancies involving suppression of thrombopoiesis caused by inflammatory effect, was found to be associated with poor prognosis (28). This is a known effect of disease pathophysiology in MDS. Although the number of patients in our current data was limited, PLR was not found to be associated with survival or leukemic transformation in MDS.

Thrombocytopenia has been associated with a decrease in overall survival in many studies, which is consistent with our results. The rate of patients with severe thrombocytopenia who required platelet transfusion at the time of diagnosis was 8 %. The low platelet count in patients with MDS reflects a reduced bone marrow reserve and function. Therefore, low platelet count is considered a poor prognostic factor in many classification systems (4, 29). Another study stated that both low platelet count at the time of diagnosis and rapid decrease in platelet count during follow-up were poor prognostic factors (30). The finding of severe thrombocytopenia, especially in advanced stages such as RAEB-1 and RAEB-2, is more frequently expected (31).

The transformation to acute myeloid leukemia is a complication of MDS that leads to shortened survival in cases, while cases with transformation to acute myeloid leukemia are more likely to be refractory to treatment (2). In our series, patients with acute leukemia transformation had a significantly shortened survival rate. MDS cases with multiple series dysplasia are associated with decreased overall survival and are a risky group for leukemic transformation. Our data are also consistent with published data. Multilineage dysplasia in MDS has unfavorable survival compared to unilineage dysplasia. The published data show that cases with less cytopenia and less dysplasia at diagnosis have superior overall and progression-free survival (32).

Conclusion

According to our results, the decreased PLR was associated with mld-MSD subtype but not with survival in MDS cases. Although the number of patients was limited, we wanted to report our results because of the limited data on PLR values in MDS. The relationship between dysplasia and peripheral cytopenia in MDS has not been fully clarified. We believe that more comprehensive studies are needed to determine the value of PLR.

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