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Factors affecting prognosis in myelodysplastic syndrome: an 11 years' experience from a tertiary care center

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ABSTRACT

Aims: Myelodysplastic syndrome (MDS) is a clonal bone marrow neoplasia characterized by morphological findings of dysplasia in hematopoietic cells, peripheral cytopenia(s), ineffective hematopoiesis, recurrent genetic abnormalities, and an increased risk of transformation to acute myeloid leukemia (AML). The International Prognostic Scoring System (IPSS) is the most commonly used prognostic classification system for MDS. Classification was made by a combination of morphology, cytopenia, and genetic studies. In this study, we aimed to examine the parameters that affect prognosis in MDS patients, show their effects on mortality, and evaluate their positive or negative effects on the course of the disease.

Methods: Two hundred twenty-nine patients who applied to Erciyes University Faculty of Medicine, Department of Hematology, and were diagnosed with MDS according to WHO classification between 2010 and 2020 were included in this retrospective study. Age, gender, comorbiditites, laboratory parameters, bone marrow biopsy materials, and genetic mutation analysis data were available. The bone marrow aspiration and biopsy examinations of each patient were evaluated and categorized according to the WHO classification. The prognosis was evaluated according to the data of the patients, survival-exitus, and survival after MDS-AML transformation. Risk scoring was analyzed with three different scoring systems (IPSS, WPSS, and R-IPSS).

Results: Of the 229 MDS patients included in the study, 57% (n=131) were male. The mean age of the patients was 67 years. Age, MDS-AML transformation times, disease duration, cellularity, and pathology blast rate were found to be statistically significant between the groups ($p<0.05$). Leukocyte, neutrophil, platelet, hematocrit, lymphocyte, monocyte, CRP, erythropoietin, ferritin, and LDH data were found to be statistically significant regarding survival ($p<0.05$). Age, IPSS risk status 3, and W-PSS risk status 3 were found to be independent risk factors affecting survival.

Conclusion: Age, IPSS high risk, and WPSS high risk status were found to be independent risk factors affecting survival. Although our study revealed important data in the analysis of MDS patients, single-center analysis of patients and retrospective analysis revealed the need for further studies.

Keywords: Mortality, myelodysplastic syndrome, prognosis

INTRODUCTION

Myelodysplastic syndromes (MDS) include a group of hematologic malignancies characterized by clonal hematopoiesis, cytopenia in one or more series (i.e., anemia, neutropenia, and/or thrombocytopenia), and abnormal cellular maturation.[1] MDS shares clinical and pathological features with acute myeloid leukemia (AML), but has a lower percentage of blasts in peripheral blood and bone marrow (by definition, blasts in bone marrow <20%). Patients with MDS are at risk of conversion to AML, which varies greatly according to subtypes and is frequently seen in advanced age.[2] As in many diseases, some models and scoring have been developed to predict prognosis and shape treatment in MDS. Over time, scoring systems and genetic-based models have improved in parallel with the rapid advances in the field of genetics.[3]

There are classification systems to indicate prognosis in MDS. The World Health Organization (WHO) classification system is based on a combination of morphology, immunophenotype, genetic, and clinical features.[4] The French-American-British (FAB) classification system partially subdivides patients with MDS according to the percentage of blasts in the bone marrow (BM). The International Prognostic Scoring System (IPSS) is the most widely used prognostic classification system for MDS. Classification was made with a combination of morphology, cytopenia, and genetic

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studies.[5] In the Revised IPSS (R-IPSS), BM blast percentage, cytogenetics, hemoglobulin, platelet count, and neutrophil count were included.[6] The WHO Prognostic Scoring System (WPSS) was designed to include information on the need for erythrocyte transfusion, which has been shown to be an independent prognostic factor for patients with MDS.[7,8]

In this study, we aimed to examine the parameters affecting prognosis in patients diagnosed with MDS and to evaluate their positive or negative effects on the disease course. We planned to compare our current data with the currently used prognostic systems and present them in the literature.

METHODS

The study was carried out with the permission of Erciyes University Clinical Researches Ethics Committee (Date: 08.09.2021, Decision No: 2021/571). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The study included 229 patients over the age of 18 who were admitted to Erciyes University Faculty of Medicine, Department of Internal Medicine, Division of Hematology between January 2010 and December 2020 in a total period of 11 years and diagnosed with MDS according to WHO classification. The files of 229 patients were analyzed retrospectively.

Our patients had a bone marrow biopsy, genetic examinations, and flow cytometric examinations. Each patient's age, gender, comorbidities, laboratory data, bone marrow aspiration and biopsy examinations, blood product replacement status, cytogenetic abnormalities, and genetic examinations were evaluated and classified according to the WHO classification. Defining thresholds for anemia, leukopenia, and thrombocytopenia was based on the values defined in the R-IPSS classification. For the MDS-AML conversion threshold, the blast count threshold accepted by WHO was taken as 20%. In order to define the need for blood product transfusion, patients who received transfusions once every 8 weeks for at least 4 months from the time of diagnosis were considered to be in need of blood products, and those who did not comply with this condition were considered not in need. The use of azacitidine, decitabine, oxymetholone, eltrombopag, granulocyte colony stimulating factor, lenalidomide, and erythropoietin in the treatment of the patients was recorded, and the status of allogeneic bone marrow transplantation was added to the study. The effects of these treatments on overall survival and treatment response were grouped and recorded.

Three different scoring systems, including IPSS, WPSS, and R-IPSS, were used for prognosis evaluation.5-8 The final status and mortality of the patients, dependent on and independent of the transformation from MDS to AML, were recorded. The risk group in which the patients were placed according to their scores in the scoring systems was recorded.

In the data analysis section, descriptive statistics were presented with frequency, percentage, mean, and standard deviation values. In the study, X^2 (chi-square) analysis was used for proportional comparisons according to the characteristics of the patients, and Fisher's test was used for corrections. An independent sample t-test and an analysis of variance test were applied for comparisons of patients' measurements according to survival levels and durations. The Sidak test was applied to determine the groups found to be different in the analysis of variance. Logistic regression analysis was applied to analyze the multiple risk factors affecting the survival level of the patients in the study. Odds ratios and 95% confidence intervals (CI) were calculated for risk factors. Survival analysis was performed using Kaplan-Meier analysis. P values less than 0.05 were considered statistically significant (α=0.05). Analyses were performed with the SPSS 22.0 package program.

RESULTS

Demographic Data

Forty-three percent (n=98) of the patients were female, and 57% (n=131) were male. The mean age was 67 years. The mean age of female patients was 64.1 years, and the mean age of male patients was 69.5 years. Seventeen percent (n=39) had no comorbidity, 41% (n=97) had a single comorbidity, and 42% (n=93) had more than one comorbidity.

Twenty-one percent (n=49) had RCUD (refractory cytopenias with single-strand dysplasia), 3% (n=8) had RARS (refractory anemia with ring sideroblasts), and 19% (n=44) had RCMD (refractory cytopenia with multiple-strand dysplasia). 28% (n=63) were grouped as RAEB-1 (RAEB-1 with increased blast rate), 19% (n=44) as RAEB-2 (RAEB-2 with increased blast rate), 3% (n=7) as isolated 5q deletion, and 7% (n=14) as unclassified.

Transformation Status

Of the patients, 61% (n=140) had no conversion, 34% (n=78) had conversion with a survival of less than 1 year, and 5% (n=11) had a survival of 1-3 years. In the study, it was determined that age differed according to survival time. It was found that the age of patients with a survival time between 1-3 years was higher than the other groups (p=0.04). In the study, it was found that the duration of conversion from MDS to AML differed according to survival time. It was found that the duration of AML conversion from MDS was lower in patients with a survival period of less than 1 year compared to the other groups (p=0.01). In the study, it was determined that the duration of the disease differed according to the survival time. It was found that the disease duration of patients with a survival of less than 1 year was lower than the other groups (p=0.01). In the non-transformation group, the cellularity levels of the patients were found to be lower than the other groups (p=0.02). In the group with a survival of 1 year or less, the pathology blast rate of the patients was found to be higher than the other groups (p=0.01) (**Table 1**).

Table 1. Examination of patient measurements according to MDS survival time

	No transformation (X±S.D.)	Less than 1-year survival (X±S.D.)	1-3 Year survival (X±S.D.)	P
Age (years)	66.4±14.03	67.15±13.36	72.18±6.78	0.04*
MDS-AML transformation time	61.14±20.53	20.54±10.39	31.00±20.4	0.01*
Duration of illness	61.29±20.37	29.24±10.34	48.91±18.46	0.01*
Cellularity	55%±0.19	64%±0.21	74%±0.18	0.02*
Pathology blast rate	3%±0.02	9%±0.05	5%±0.03	0.01*

MDS: Myelodysplastic syndrome, AML: Acute myeloid leukemia *Significant relation at 0.05 level

Laboratory Data

Leukocyte, neutrophil, lymphocyte, and hemoglobulin levels did not differ according to survival time. Platelet and hematocrit levels differed according to survival time, and the group with a survival of less than 1 year was found to be lower than the other groups (p=0.01) (Table 2). It was observed that monocyte levels were different according to survival time, and the measurements of the group without transformation were lower (p=0.01)

Table 2. Analysis of complete blood count according to MDS survival time

	No Transformation (X±S.D.)	Less than 1 Year (X±S.D.)	1-3 Years (X±S.D.)	P
Leucocyte (µ/L)	5.40±6.47	6.09±11.13	6.56±6.2	0.18
Neutrophil (µ/L)	3.14±4.74	2.95±7.32	4.18±4.92	0.08
Hemoglobulin (g/dl)	10.35±2.54	9.21±2.13	11.22±2.55	0.17
Platelet (µ/L)	189.13±160.75	122.65±121.98	248.27±234.44	0.01*
Hemotocrit (%)	31.77±7.53	27.74±6.35	34.78±8.26	0.03*
Lymphocyte (µ/L)	1.39±0.84	1.42±0.98	1.45±0.69	0.13
Monocyteµ/L)	0.58±1.47	1.24±3.20	0.69±0.61	0.01*
Eritropoetin (u/mL)	75.44±134.34	138.06±210.51	341.73±885.27	0.01*
Fibrinogen (mg/dl)	331.81±105.45	347.76±117.01	334.18±128.21	0.53
CRP (mg/L)	19.85±39.89	37.63±111.26	20.64±29.86	0.02*
Ferritin (ng/mL)	559.55±777.98	867.54±857.1	582.55±580.05	0.04*
Lactate dehydrogenase (u/L)	292.77±164.86	683.42±896.03	760.09±599.88	0.01*
Albumin (g/dl)	4.04±0.57	3.87±0.67	3.8±0.33	0.25

*Significant relation at 0.05 level

Erythropoietin (EPO) levels were found to be different in the groups. The EPO level was found to be higher in the group with a survival time between 1 and 3 years (p=0.01). Fibrinogen and albumin levels did not differ according to survival time (p>0.05).

Ferritin and CRP levels were found to be different according to survival time, and the measurements of the group with a survival time of less than 1 year were found to be higher (p values of 0.04 and 0.02, respectively). Lactate dehydrogenase (LDH) levels were found to be different according to the survival time, and the measurements of the group with a survival time of less than 1 year were lower (p=0.01).

Treatment and Survival

In the treatment analysis according to MDS survival status, the total number of patients who received azacitidine was 58, 72% (42) of whom were exited and 28% (16) of whom survived. The total number of patients who received decitabine was 21, 95% (20) of whom were exited and 5% (1) of whom survived. The total number of patients who received oxymetholone was 7, 43% (3) of them had an exitus, and 57% (4) of them survived. The total number of patients receiving eltrombopag was 2, 50 (1%) of whom exited and 50 (1%) of whom survived. The total number of patients who received GCSF was 38, 71 (27.2%) of whom exited, and 29 (11.1%) survived. The total number of patients who received erythropoietin was 54, 63 (34%) of whom exited, and 37 (20%) survived. The total number of patients who received lenalidomide was 58, 75(3) % of whom exited, and 25(1) % survived.

MDS Risk Classifications and Survival

In our survival analysis according to MDS risk classification and treatment, survival response to treatment was evaluated according to WHO classification and R-IPSS classification (Table 3). IPSS Risk Status: It was found that patients in the middle-2 and high groups had a higher rate of survival below 1 year (p=0.02). R-IPSS Risk Status-3: patients in the high group had a higher survival rate of less than 1 year (p=0.01). W-PSS Risk Status-2; it was determined that patients in the high group had a higher survival rate of less than 1 year (p=0.01).

Table-3. Scoring risk distribution table according to MDS transformation status

	No Transformation	Less than 1 Year	1-3 Years	P
IPSS risk status				0.01*
Low	27.9%	1.3%	0.0%	
Medium-1	50.0%	11.5%	72.7%	
Medium-2	20.7%	51.3%	27.3%	
High	1.4%	35.9%	0.0%	
R-IPSS risk status				0.02*
Low	27.9%	1.3%	0.0%	
Low	24.3%	1.3%	9.1%	
Middle	51.4%	20.5%	45.5%	
High	12.9%	56.4%	45.5%	
WPSS risk status				0.01*
Very Low	20.7%	0.0%	0.0%	
Low	24.3%	3.8%	18.2%	
Middle	49.3%	29.5%	63.6%	
High	5.7%	64.1%	18.2%	
Very High	0.0%	2.6%	0.0%	

IPSS: The International Prognostic Scoring System , R-IPSS: Revised IPSS, WPSS: The WHO Prognostic Scoring System *Significant relation at 0.05 level

Evaluation of Independent Variables Affecting Survival

The data were evaluated by logistic regression analysis to investigate the independent risk factors affecting MDS survival. Age, IPSS risk status 3, and WPSS risk status 3 were found to be independent risk factors affecting survival. Other factors were found to be significant in univariate analyses but not in the multivariate model. If the significant variables are interpreted, patients younger than 60 years of age reduce the probability of survival level by 2.77 (95% CI 1.64-3.65) times. Patients with an IPSS risk score in the middle 2 reduce the survival level probability by 3.81 times (95% CI 1.39-5.28). Patients with a high WPSS risk score have a 3.67-fold (95% CI 1.22-5.07) lower probability of survival. At least 43% of survival was explained by the variables in the model, and the overall success rate of the model was 92% (Table 4).

Table-4. MDS survival independent risk factors logistic regression analysis table

MODEL	Wald	P	Odds Rate	95% GA Lower Limit	95% GA Upper Limit
Age (60<)	8.93	0.01*	2.77	1.64	3.65
IPSS Risk Status (MeHigh)	-7.58	0,01*	3.81	1.39	5.28
WPSS Risk Status (High)	-7.83	0.01*	3.67	1.22	5.07
ModelX2: 29,35; Success rate=92%					
Cox & Snell R2=0,43					

IPSS: The International Prognostic Scoring System , WPSS: The WHO Prognostic Scoring System

DISCUSSION

Myelodysplastic syndromes (MDS) include a group of hematological malignancies characterized by clonal hematopoiesis, cytopenia in one or more series (i.e., anemia, neutropenia, and/or thrombocytopenia), and abnormal cellular maturation.[1] In a multicenter retrospective analysis conducted by Stuart L. Goldberg et al.[9] on 2253 MDS patients, the proportion of male and female patients was 46.5% and 53.5%, respectively. Sekeres Mikkael A. et al.[10] in a multicenter cross-sectional analysis of 670 to 827 MDS patients in 4514 people, showed that 55% were male and 45% were female. In another study by Xiaomei Ma et al.[11] and Gregory et al.[12] on 7131 MDS patients, men had a significantly higher incidence rate than women. In our study, 43% of the patients were female and 57% were male. The median age of our patients was 67 years. In the results of the HAEMACARE project by Milena Sant et al.[13] on the incidence of hematologic malignancies in Europe according to morphologic subtype, the mean age was found to be 64 years in the data analyzed from a total of 97,521 patients.

Scores such as IPSS, R-IPSS, and WPSS used in MDS patients are effective in predicting prognosis.[5-8] In a single-center retrospective study conducted by Bektaş et al.[14] on 101 MDS patients in a tertiary care university hospital between 2003 and 2011, as the International Prognostic Scoring System (IPSS), World Health Organization Classification Based Prognostic Scoring System (WPSS), and revised IPSS (IPSS-R) risk categories increased, leukemia-free survival and overall survival decreased ($p<0.001$). When IPSS, WPSS, and IPSS-R prognostic systems were compared by Cox regression analysis, WPSS was the best at predicting leukemia-free survival ($p<0.001$), and WPSS ($p<0.001$) and IPSS-R were the best at predicting overall survival ($p=0.037$). All three prognostic systems were successful in predicting overall survival and leukemia-free survival ($p<0.001$). In a multicenter cohort study by Porta et al.[15] on 5326 MDS patients, WPSS and IPSS-R scores demonstrated an increase in mortality and leukemic transformation risk with increasing risk. In our study, it was determined that patients in the IPSS, medium-2, and high groups had a higher mortality rate. Similarly, R-IPSS and W-PSS at the time of diagnosis showed that patients in the high and very high groups had a higher mortality rate. Our study and other studies show in parallel that when leukemia-free survival and overall survival of patients are analyzed according to risk groups using IPSS, WPSS, and IPSS-R scoring systems, survival is directly affected as the risk group increases and stands out as direct predictive parameters for prognosis.

Low white blood cell count, low neutrophil count, and low platelet count, which are used as parameters in MDS prognostic risk scoring systems in the study by Guillermo-Montalban Bravo et al.[16] have very critical importance under the title of cytopenia. In the MDS study by Robert P. Hasserjian[17] persistent and unexplained cytopenia, which has a very important place in the diagnosis, was mentioned. A decrease in platelet values had a direct impact on disease prognosis in a single-center retrospective study by Strapatsas et al.[18] on 334 MDS patients. When the literature data and our study are evaluated together, leukocyte types and platelets have a direct effect on the diagnosis, survival, and prognosis of MDS. However, a point where the literature data and our study do not agree is that although hemoglobin values were low in our study, they were not found to be significant. The reason for this difference in our study may be the difference in the timing of blood product replacement and the lack of data availability in our retrospective study.

In a retrospective analysis of 47 patients diagnosed with MDS between 2002 and 2019, Belohlavkova et al.[19] analyzed the importance of LDH, CRP, and ferritin on MDS prognosis. Univariate analysis showed the impact of elevated LDH on survival ($p=0.041$): four-year survival was 70% versus 32% in patients with elevated LDH. CRP elevation was present in 47% of patients. The significance of the CRP value for survival could not be demonstrated in the study ($p=0.92$; $p=0.20$). Two values were taken as limits for ferritin. The limit for high levels was >1000 ng/mL. Patients with higher ferritin levels had similar four-year survival compared to patients with ferritin levels below 1000 ng/ml (46% vs. 48%; $p=0.76$). The importance of ferritin for survival has not been shown ($p=0.55$). Çelik et al.[20] showed that decreased fibrinogen levels decreased survival in patients with ACIT, including MDS. In our study, LDH, ferritin, and CRP levels were found to differ according to survival status. However, no relationship was observed between fibrinogen levels and survival.

In the study titled Recent Advances in the Treatment of Low-Risk Non-Del (5q) Myelodysplastic Syndromes by Almeida et al.[21] (2016), he drew attention to the importance of hypomethylated agents azacitidine and decitabine and mentioned the importance of erythrocyte stimulating agents, thrombopoietin receptor agonists, and GCSF used in patients. Malcovati et al.[22] mentioned the importance of hypomethylating agents, erythrocyte stimulating agents, thrombopoietin receptor agonists, and GCSF in the study titled Diagnosis and Treatment of Primary MDS in Adults. In the analysis conducted by Valeria Santini et al.[23] in 529 MDS patients divided according to 3 clinical groups and an IPSS risk group, the use of lenalidomide increased the mean survival compared to the placebo group. When our study was compared with other studies, the excess heterogeneity affected the treatment survival rates in the analysis of 229 MDS patients in our unit followed up in a retrospective 11-year period according to the risk group. Samples and study groups taken from the literature were categorized as high or low risk. Our study is not a study with the aim of consumable treatment and survival, but the treatment response according to risk status was analyzed according to survival, and the serious treatment response of patients with an increasing risk group decreased. Data analysis of treatment response and controls in our study, which included all MDS patients evaluated and followed up in our unit, was seriously complicated by confounders including patient compliance, a lack of file data, and treatment heterogeneity.

Limitations

This study has some limitations. First of all, the single-center experience limits the generalizability of the results. Retrospective and incomplete data is another limitation. Lack of complete genetic characteristics was another important limitation.

CONCLUSION

This single-center, retrospective study of 229 MDS patients analyzed the demographic, clinical, laboratory, survival, and treatment data of the patients; however, when the data are analyzed, heterogeneity in patients stands out.

Age, IPSS risk status, and WPSS risk status level were found to be independent risk factors affecting survival. Although our study reveals important data in the evaluation and analysis of MDS patients, single-center analysis of patients, and lack of data recording in the files, the number of patients participating in the study and retrospective examination revealed the need for further studies.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Erciyes University Clinical Researches Ethics Committee (Date: 08.09.2021, Decision No: 2021/571).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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