Original Article

Risk Factors Associated with Progression of Myelodysplastic Syndrome: 13 Years of Experience from a Single Center

Miyelodisplastik Sendromun Progresyonu ile İlişkili Risk Faktörleri: Tek Merkezden 13 Yıllık Deneyim

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ABSTRACT

Aim: We aimed to assess the accuracy of the most widely-accepted prognostic classification systems in patients with myelodysplastic syndromes (MDS), and to investigate various parameters with respect to their association with MDS progression.

Material and Methods: Fifty-five patients diagnosed with MDS (January 1999 to December 2012) were reviewed retrospectively. Demographic characteristics, comorbidities, laboratory and pathological results, risk classifications (pathological and prognostic) at MDS diagnosis, treatment features, data regarding patient survival, and acute myeloid leukemia (AML) conversion were examined.

Results: Thirty-five male and 20 female patients (mean age: 70.95±9.80 years) were included. Twenty-four (43.46%) patients were defined to have had progression. Having an ECOG-PS score of ≥2 (OR: 6.939, 95%CI: 1.527-31.526; p=0.012) and being classified as 'high' or 'very high' risk according to the WPSS (OR: 10.115, 95%CI: 2.293-44.614; p=0.002) were found to be the only factors independently associated with MDS progression.

Conclusion: Although univariate differences were observed for various parameters, MDS progression was independently associated with ECOG-PS and WPSS class. It appears that singular classification systems are insufficient to predict MDS progression.

Keywords: Myelodysplastic syndrome, progression, prognostic factors, prognostic classification systems

ÖZET

Amaç: Miyelodisplastik sendrom (MDS) tanılı hastalarda en yaygın olarak kabul edilen prognostik sınıflandırma sistemlerinin doğruluğunu değerlendirmeyi ve MDS progresyonu ile ilişkisine göre çeşitli parametreleri araştırmayı amaçladık.

Gereç ve Yöntem: MDS tanısı konan 55 hasta (Ocak 1999-Aralık 2012) geriye dönük olarak incelendi. Demografik özellikler, komorbiditeler, laboratuvar ve patolojik sonuçlar, MDS tanısında risk sınıflamaları (patolojik ve prognostik), tedavi özellikleri, hasta sağkalımı ile ilgili veriler ve akut miyeloid lösemi (AML) dönüşümü incelendi.

Bulgular: Otuz beş erkek ve 20 kadın hasta (ortalama yaş: 70.95±9.80 yıl) dahil edildi. Yirmi dört (%43.4) hastada progresyon olduğu belirlendi. Sadece ECOG-PS skorunun ≥2 olması (OR: 6.939, %95 GA: 1.527-31.526; p=0.012) ve WPSS'ye göre 'yüksek' veya 'çok yüksek' riskli olarak sınıflandırmanın (OR: 10.115, %95) GA: 2.293-44.614; p=0.002), MDS progresyonu ile bağımsız olarak ilişkili faktörler olduğu belirlendi.

Sonuç: Çeşitli parametreler için tek değişkenli farklılıklar gözlemlenmesine rağmen, MDS progresyonu bağımsız olarak ECOG-PS ve WPSS sınıflandırması ile ilişkilendirilmiştir. Sınıflandırma sistemlerinin tek başına MDS progresyonunu tahmin etmede yetersiz olduğu görülmektedir.

Anahtar Kelimeler: Miyelodisplastik sendrom, progresyon, prognostik faktörler, prognostik sınıflandırma sistemleri

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Introduction

Hematopoietic cell transplantation is accepted Myelodysplastic syndrome (MDS) defines a group of diseases in which stem cell clonal disorders lead to bone marrow (BM) dysplasia and ineffective hematopoiesis. They have a high risk of progression to acute myeloid leukemia (AML) [1,2]. Annual MDS incidence is about three to four cases per 100,000 people, with a higher incidence in men and after the age of 80 years [3].

Since MDS demonstrates considerable clinical, pathological and cytogenetic heterogeneity, factors affecting survival and prognosis are highly variable [4]. Therefore, various classification systems have been developed, including pathological classification systems such as French-American-British co-operative group (FAB) and the World Health Organization (WHO) classifications. Also, various prognostic models have also been developed, such as the International Prognostic Scoring System (IPSS; and its revision, IPSS-R), the WHO classification-based Prognostic Scoring System (WPSS), and MD Anderson Cancer Center (MDACC) Risk Model [2,5-9]. Grading in these systems are made largely by considering chromosomal abnormalities, cytopenia, and BM blast percentages [10]. Patient comorbidities, physical performance status, various blood and BM parameters, treatment requirements at the time of diagnosis, and during the course of MDS are also likely to affect overall survival (OS) and progression [11-13]. The factors that determine the pathogenesis and progression of MDS have not been clarified [4] and considering that classification systems alone appear to be insufficient to predict the progression of this disease, it is evident that there is a need for further data to assess risk factors associated with progression in MDS [14].

In this study, we aimed to assess the accuracy of widely-accepted prognostic classification systems in MDS, and to investigate the roles of various parameters, many of which have not yet been included in these systems, in predicting MDS progression.

Methods

Study features and ethics

This retrospective study was conducted between January 1999 to December 2012 at the Department of Hematology, Faculty of Medicine, İstanbul University. The ethical approval of the study was obtained from the Clinical Research Ethics Committee of Istanbul University.

Participants

The files of 215 patients over the age of 18 who were diagnosed with MDS were reviewed retrospectively. Fifty-five patients whose files were sufficient for the study and who were followed up regularly in the outpatient clinic were included in the study. Patients with missing or inaccessible data were excluded.

Data collection instruments

Demographic characteristics of patients, comorbidity information, laboratory results, all histopathological information, and physical performance status were recorded. The results of classification systems listed below (at diagnosis of MDS), treatment, and follow-up data regarding survival and AML progression during disease course were obtained from hospital records.

MDS pathological classification

For MDS pathological grading, both the FAB classification [5,15] and the 2008 WHO classification [6] were used. There were 5 major groups according to the FAB classification system: Refractory anemia (RA), RA with ringed sideroblasts (RARS), RA with excess of blasts (RAEB), RAEB in transformation (RAEB-T), and chronic myelomonocytic leukemia (CMML) [5,15]. Using the 2008 WHO classification, MDS was grouped according to the findings of peripheral blood and BM as follows: Refractory cytopenia with unilineage dysplasia (RCUD), RARS, refractory cytopenia with multilineage dysplasia

(RCMD), RAEB-1, RAEB-2, MDS-unclassified (MDS-U), and isolated del(5q)-associated MDS [6].

MDS prognostic risk classification

Patients were classified in terms of prognostic risk using the IPSS, IPSS-R, WPSS, and MDACC models [7-9,16]. We used the 2011 revised version of the WPSS, that is, the original criterion of "transfusion requirement" was replaced by "severe anemia" (Hb<9g/dl in men, Hb<8g/dl in women) [9]. The patients were divided into 4 risk groups according to IPSS and MDACC (low, intermediate-1, intermediate-2, high), and 5 risk groups according to IPSS-R and WPSS (very low, low, intermediate, high, very high) [7-9,16].

Bone marrow assessment

Histopathological results of BM biopsy specimens were evaluated in terms of cellularity and dysplasia. Cellularity was categorized as “hypercellular, normocellular, hypocellular”; Dysplasia was categorized as “dysplasia in one, two or three cell line(s)” [17]. The European Myelofibrosis Network (EUMNET) scoring system was used to classify BM fibrosis which establishes 4 subgroups: MF-0, MF-1, MF-2, MF-3 [18].

Cytogenetic risk classification

Cytogenetic prognosis grouping was made according to the IPSS, and patients were divided into 3 risk groups as "good, moderate, poor" according to pre-specified chromosomal anomalies [1]. Patients with cytogenetically normal findings and those with del(5q), del(20q) or -Y were placed in the "good" subgroup, patients with complex (>2) abnormalities and chromosome 7 abnormalities were classified in the "poor" subgroup, and patients with other cytogenetic abnormalities were classified in the "moderate" subgroup.

Performance status assessment

The ECOG-PS was used to assess patients’ performance status at MDS diagnosis. In this scoring system, patients are classified according to their physical performance status in 6 degrees with the highest being 0 (fully active) and the lowest being 5 (dead) [19].

Progression criteria

Presence of at least one of the following 3 criteria was accepted to show MDS progression; (i) Conversion to AML, (ii) Death due to conversion to AML and/or BM failure, (iii) Later development of signs of BM failure that were not present at the beginning (i.e. Hb<9g/dl in men and <8g/dl in women, neutrophils count <0.8 x 10^9/L, platelet count <100 x 10^9/L). Progressive MDS cases were abbreviated as PG (presence of progression group), and non-progressive cases as non-PG (absence of progression group).

Statistical Analysis

All analyses were performed on SPSS version 25 (IBM, Armonk, NY, USA) with a significance threshold of <0.05 for p value. We employed the Shapiro-Wilk test to determine normality of distribution in numerical variables. Mean ± standard deviation or median (1st quartile-3rd quartile) summaries were used to describe numerical variables, in the presence and absence of normal distribution, respectively. Absolute and relative frequencies were reported for categorical variables. Numerical data were compared between groups by employing the independent samples t-test (normal distribution) or the Mann-Whitney U test (non-normal distribution). Chi-square tests were used to compare the distribution frequencies of categorical variables between groups, and the Fisher's exact test was utilized when assumptions for Pearson or continuity correction were not met. Variables’ prediction performance were assessed by using Receiver Operating Characteristic (ROC) curve analysis. Optimal cut-off points were determined by using Youden index. Multiple logistic regression analysis (forward conditional method) were performed to determine the best predictive factors associated with progression.

Results

Thirty-five male and 20 female patients were included in our study, and the mean age of the

patients was 70.95 ± 9.80 (range 49-92) years. 31 (56.4%) of the patients were in the non-PG and 24 (43.6%) in the PG group. The PG and non-PG groups were similar in terms of age (p=0.8) and sex (p=1.000). The duration of follow-up in the PG group was significantly shorter (p=0.049).

According to the WHO classification, the non-PG group had a significantly higher percentage of patients with RCUD, while the PG group had a significantly higher percentage of patients with RAEB-2 (overall comparison, p=0.049). The FAB classification also showed significant difference between groups. The non-PG group had a higher proportion of RA patients, while the PG group had a higher proportion of RAEB patients (p=0.008). Mean hemoglobin level (p=0.004), monocyte count (p=0.017), and platelet count (p=0.011) were significantly lower in the PG group, while these patients had significantly higher mean ferritin levels (p<0.001). BM blast percentage was significantly higher among patients in the PG group (p=0.008). BM dysplasia in three cell lines was found to be significantly more common in the PG group (75.0%) compared to the non-PG group (45.2%) (p=0.043). The two groups were similar in terms of BM cellularity (p=0.26) and BM fibrosis grade (p=0.167). Patients in the PG group were found to have required significantly more transfusions (p<0.001). Median IPSS (p=0.004), IPSS-R (p=0.001), WPSS (p<0.001), MDACC (p=0.002) scores were found to be significantly higher in PG. The percentage of patients classified as having high (and very high) risks according to IPSS, IPSS-R, WPSS and MDACC scores was significantly higher in the PG group compared to the non-PG group; however, while comparisons for IPSS (p=0.027), IPSS-R (p=0.024) and WPSS (p=0.013) demonstrated significant difference between groups, the MDACC results were statistically similar (p=0.067) (Table 1).

Evaluation of various parameters with regard to their performance to predict progression (ROC analysis) yielded the following significant results: IPSS with ≥intermediate-2 cut-off (AUC: 0.728, 95%CI: 0.592-0.864; p=0.004), IPSS-R with ≥high cut-off (AUC: 0.748, 95%CI: 0.618-0.878; p=0.002), WPSS with ≥high cut-off (AUC: 0.761, 95%CI: 0.628-0.894; p=0.001), MDACC with ≥intermediate-2 cut-off (AUC: 0.702, 95%CI: 0.562-0.841; p=0.011). In particular, WPSS with ≥ high cut-off had 81.8% sensitivity and 83.3% negative predictive value (NPV) (Table 2, Figure 1).

Next, we performed multiple logistic regression analysis to determine the best predictive factors associated with progression. All parameters demonstrating significant difference in univariate analyses and previously suggested risk factors were included in the model. Patients with high ECOG-PS score (≥2) were found to have a 6.939-fold higher risk of progression than other patients (OR: 6.939, 95%CI: 1.527-31.526; p=0.012). Patients with high or very high WPSS were found to have a 10.115-fold higher risk of progression than other patients (OR: 10.115, 95%CI: 2.293-44.614; p=0.002) (Table 3, Figure 2, Figure 3). These results indicated that the ECOG-PS and WPSS combination was the best combination that could be used to predict progression. Other variables included in the model, age (p=0.733), sex (p=0.634), fibrosis grade (p=0.099), cytogenetics (p=0.484), dysplasia (p=0.513), IPSS (p=0.554), IPSS-R (p=0.354), and MDACC (p=0.974), were found to be non-significant.

Discussion

About two-thirds of patients with MDS die from bleeding, recurrent infections, and severe anemia due to progressive BM failure. Progression to AML is also associated with an extremely poor outcome and short survival [20]. Therefore, in our study, we identified BM failure and/or conversion to AML and/or death as the progression criteria of MD. We then aimed to identify various predictors that may be most associated with progression. We found that MDS progression could be associated with being classified as having RAEB-2 (WHO classification) and RAEB

Table 1. Summary of patient characteristics with regard to progression

		Progression		
	Total (n=55)	No (n=31)	Yes (n=24)	p
Age	70.95 ± 9.80	70.65 ± 9.06	71.33 ± 10.86	0.8
Sex				
Male	35 (63.6%)	20 (64.5%)	15 (62.5%)	1.000
Female	20 (36.4%)	11 (35.5%)	9 (37.5%)	
Comorbidity	31 (56.4%)	17 (54.8%)	14 (58.3%)	1.000
Diabetes mellitus	6 (10.9%)	5 (16.1%)	1 (4.2%)	0.216
Hypertension	10 (18.2%)	4 (12.9%)	6 (25.0%)	0.304
Ischemic heart disease	9 (16.4%)	4 (12.9%)	5 (20.8%)	0.48
COPD	4 (7.3%)	2 (6.5%)	2 (8.3%)	1.000
Other	7 (12.7%)	4 (12.9%)	3 (12.5%)	1.000
Malignancy	7 (12.7%)	3 (9.7%)	4 (16.7%)	0.69
Type of MDS, WHO				
RCUD	5 (9.1%)	5 (16.1%)	0 (0.0%)	
RCMD	15 (27.3%)	11 (35.5%)	4 (16.7%)	
RARS	4 (7.3%)	3 (9.7%)	1 (4.2%)	
Isolated del(5q)	4 (7.3%)	3 (9.7%)	1 (4.2%)	0.049
RAEB-1	7 (12.7%)	2 (6.5%)	5 (20.8%)	
RAEB-2	17 (30.9%)	6 (19.4%)	11 (45.8%)	
MDS/MPN	3 (5.5%)	1 (3.2%)	2 (8.3%)	
Type of MDS, FAB				
RA	22 (40.0%)	18 (58.1%)	4 (16.7%)	
RARS	5 (9.1%)	4 (12.9%)	1 (4.2%)	
RAEB	23 (41.8%)	7 (22.6%)	16 (66.7%)	0.008
RAEB-T	2 (3.6%)	1 (3.2%)	1 (4.2%)	
CMML	3 (5.5%)	1 (3.2%)	2 (8.3%)	
ECOG performance status				
0	15 (27.3%)	9 (29.0%)	6 (25.0%)	
1	22 (40.0%)	16 (51.6%)	6 (25.0%)	0.085
2	16 (29.1%)	5 (16.1%)	11 (45.8%)	
3	2 (3.6%)	1 (3.2%)	1 (4.2%)	
Hemoglobin (gr/dL)	9.17 ± 2.27	9.92 ± 1.94	8.20 ± 2.34	0.004
MCV (fL)	96.69 ± 13.71	95.17 ± 15.31	98.66 ± 11.32	0.354
WBC (/µl)	3300 (2360-5440)	3420 (2800-6060)	3125 (2075-5150)	0.175
Neutrophil (/µl)	1460 (900-2370)	1750 (1000-3000)	1295 (580-2030)	0.082
Lymphocyte (/µl)	1600 (1040-2340)	1400 (1090-2390)	1760 (1005-2260)	0.95
Monocyte (/µl)	330 (130-580)	380 (200-690)	185 (65-435)	0.017
Platelet (*10^3/µl)	107 (68-188)	141 (84-230)	87.5 (37-133)	0.011
LDH (IU/L)	233 (177-367)	228 (177-383)	234 (175.5-347)	0.96
Ferritin (ng/mL)	525 (143-1258)	160 (87-668)	1155 (412-1801)	<0.001
Bone marrow blast (%)	4 (2-12)	3 (2-7)	8 (3.5-14.5)	0.008
Bone marrow cellularity				
Hypercellular	46 (83.6%)	27 (87.1%)	19 (79.2%)	
Normocellular	7 (12.7%)	4 (12.9%)	3 (12.5%)	0.261
Hypocellular	2 (3.6%)	0 (0.0%)	2 (8.3%)	
Dysplasia (in … cell line(s))				
1	9 (16.4%)	8 (25.8%)	1 (4.2%)	
2	14 (25.5%)	9 (29.0%)	5 (20.8%)	0.043
3	32 (58.2%)	14 (45.2%)	18 (75.0%)	
Fibrosis grade				
MF-0	6 (10.9%)	4 (12.9%)	2 (8.3%)	
MF-1	34 (61.8%)	22 (71.0%)	12 (50.0%)	0.167
MF-2	11 (20.0%)	3 (9.7%)	8 (33.3%)	
MF-3	4 (7.3%)	2 (6.5%)	2 (8.3%)	

Cytogenetic				
Good	25 (45.5%)	17 (54.8%)	8 (33.3%)	
Moderate	16 (29.1%)	8 (25.8%)	8 (33.3%)	0.262
Poor	14 (25.5%)	6 (19.4%)	8 (33.3%)	
Transfusion need	30 (54.5%)	10 (32.3%)	20 (83.3%)	<0.001
Chelating agent use	4 (7.3%)	3 (9.7%)	1 (4.2%)	0.624
IPSS	1 (0-2)	0.5 (0-1.5)	1.5 (1-2.5)	0.004
Low	15 (27.3%)	12 (38.7%)	3 (12.5%)	
Intermediate-1	17 (30.9%)	11 (35.5%)	6 (25.0%)	0.027
Intermediate-2	11 (20.0%)	5 (16.1%)	6 (25.0%)	
High	12 (21.8%)	3 (9.7%)	9 (37.5%)	
IPSS-R	4 (2-6.5)	3 (2-5)	6 (3.75-7.25)	0.001
Very low	5 (9.1%)	5 (16.1%)	0 (0.0%)	
Low	15 (27.3%)	11 (35.5%)	4 (16.7%)	
Intermediate	9 (16.4%)	6 (19.4%)	3 (12.5%)	0.024
High	10 (18.2%)	4 (12.9%)	6 (25.0%)	
Very high	16 (29.1%)	5 (16.1%)	11 (45.8%)	
WPSS	3 (1-4)	1.5 (1-3)	4 (3-5)	<0.001
Very low	7 (13.5%)	6 (20.0%)	1 (4.5%)	
Low	10 (19.2%)	9 (30.0%)	1 (4.5%)	
Intermediate	7 (13.5%)	5 (16.7%)	2 (9.1%)	0.013
High	16 (30.8%)	6 (20.0%)	10 (45.5%)	
Very high	12 (23.1%)	4 (13.3%)	8 (36.4%)	
MDACC	6 (4-8)	5 (3-8)	8 (6-10)	0.002
Low	15 (27.3%)	12 (38.7%)	3 (12.5%)	
Intermediate-1	15 (27.3%)	9 (29.0%)	6 (25.0%)	0.067
Intermediate-2	12 (21.8%)	6 (19.4%)	6 (25.0%)	
High	13 (23.6%)	4 (12.9%)	9 (37.5%)	
Chemotherapy	3 (5.5%)	1 (3.2%)	2 (8.3%)	0.575
Follow-up time, month	22 (8-33)	26 (10-38)	12.5 (6.5-28)	0.049
AML transformation	12 (21.8%)	-	12 (50.0%)	-
Mortality	16 (29.1%)	-	16 (66.7%)	-

Data are given as mean ± standard deviation or median (1st quartile-3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables

COPD: Chronic obstructive pulmonary disease, MDS: myelodysplastic syndromes, WHO: World Health Organization, RCUD: Refractory cytopenia with unilineage dysplasia, RCMD: Refractory cytopenia with multilineage dysplasia, RARS: Refractory anemia with ringed sideroblasts, RAEB: Refractory anemia with excess of blasts, MPN: Myeloproliferative neoplasms, FAB: French-American-British, RA: Refractory anemia, RARS: Refractory anemia with ringed sideroblasts, RAEB-T: Refractory anemia with excess of blasts in transformation, CMML: Chronic myelomonocytic leucaemia, ECOG: Eastern Cooperative Oncology Group, MCV: Mean corpuscular volume, WBC: White blood cell, LDH: Lactate dehydrogenase, MF: Myelofibrosis, IPSS: International Prognostic Scoring System, IPSS-R: International Prognostic Scoring System-revised, WPSS: WHO classification-based Prognostic Scoring System, MDACC: MD Anderson Cancer Center, AML: Acute myeloid leukemia

(FAB classification). In addition, we observed that the likelihood of progression appeared to increase in the presence of higher risk category in IPSS, IPSS-R, and WPSS. As a result of multiple logistic regression analysis, we found that having an ECOG-PS score of ≥2 and a WPSS classification of ≥high were the only factors independently associated with progression.

The prognosis of MDS patients, with respect to OS and risk of transformation to AML, is primarily defined by the IPSS and the IPSS-R scores [2,21]. IPSS-R has been shown to have improved accuracy over IPSS. In this study, IPSS(-R) scores were not found to be strongly associated with prognostic prediction, especially relative to ECOG-PS and WPSS. Median OS for high-risk MDS patients (IPSS: intermediate-2 and high-risk; IPSS-R: intermediate [with >3.5 points], high or very-high-risk score) ranges from a few months to 1.2 years [21]. The recent study by Papageorgiou et al. showed that IPSS or IPSS-R independently predicted shortened LFS and

Table 2. Performance of the variables to predict progression

	Cut-off	Sensitivity	Specificity	Accuracy	PPV	NPV	AUC (95.0% CI)	p
ECOG-PS	≥ 2	50.0%	80.6%	67.3%	66.7%	67.6%	0.621 (0.466-0.776)	0.127
Fibrosis grade	≥ MF-2	41.7%	83.9%	65.5%	66.7%	65.0%	0.624 (0.472-0.776)	0.118
Cytogenetic	Moderate & Poor	66.7%	54.8%	60.0%	53.3%	68.0%	0.618 (0.468-0.769)	0.135
IPSS	≥ Intermediate-2	62.5%	74.2%	69.1%	65.2%	71.9%	0.728 (0.592-0.864)	0.004
IPSS-R	≥ High	70.8%	71.0%	70.9%	65.4%	75.9%	0.748 (0.618-0.878)	0.002
WPSS	≥ High	81.8%	66.7%	73.1%	64.3%	83.3%	0.761 (0.628-0.894)	0.001
MDACC	≥ Intermediate-2	62.5%	67.7%	65.5%	60.0%	70.0%	0.702 (0.562-0.841)	0.011

PPV: Positive predictive value, NPV: Negative predictive value, AUC: Area under ROC curve, CI: Confidence intervals, ECOG: Eastern Cooperative Oncology Group, IPSS: International Prognostic Scoring System, IPSS-R: International Prognostic Scoring System-revised, WPSS: WHO classification-based Prognostic Scoring System, MDACC: MD Anderson Cancer Center

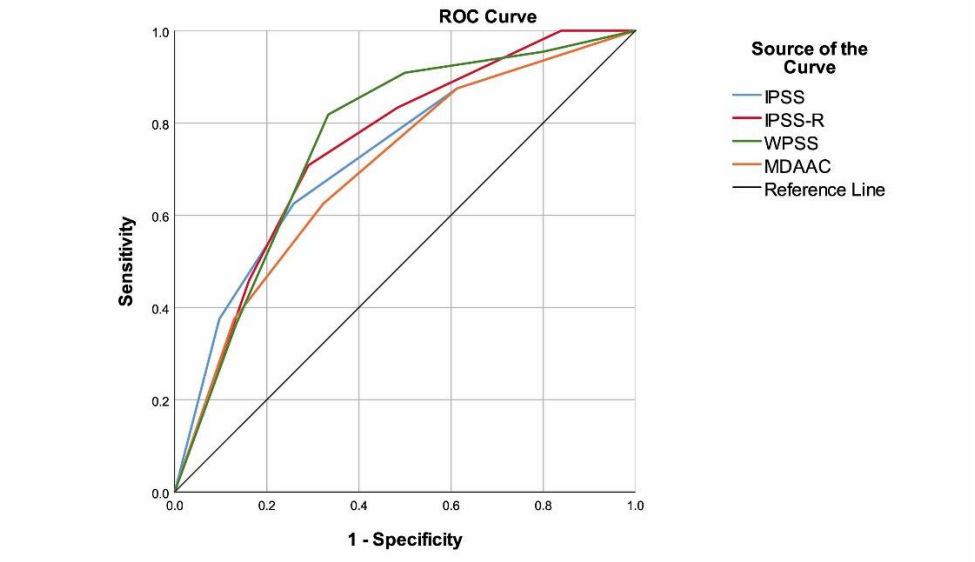

Figure 1. ROC curve of the risk scores to predict progression

Table 3. The best predictive factors of the progression, multiple logistic regression analysis

	β coefficient	Standard Error	p	Exp(β)	95% CI for Exp(β)	
ECOG-PS, ≥ 2	1.937	0.772	0.012	6.939	1.527	31.526
WPSS, ≥ High	2.314	0.757	0.002	10.115	2.293	44.614
Constant	-2.335	0.703	0.001	0.097		

Dependent variable: Progression; Nagelkerke R^2=0.430

CI: Confidence Interval, ECOG: Eastern Cooperative Oncology Group, WPSS: WHO classification-based Prognostic Scoring System

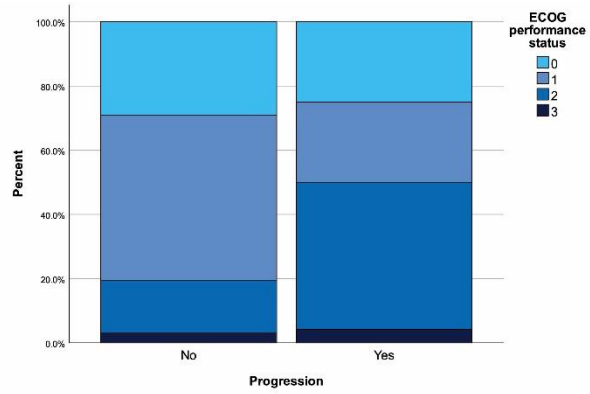

Figure 2. ECOG performance status score with regard to progression

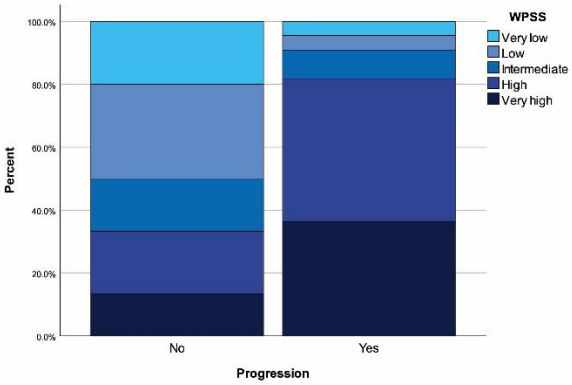

Figure 3. WPSS risk groups with regard to progression

OS [21]. Apart from these two, the other 2 classification systems developed and accepted as prognostic determinants are WPSS and MDACC models [16,22]. We believe the outcomes of our study may be associated with the fact that WPSS performs a dynamic risk assessment and has prognostic value not only at the time of diagnosis but also at other times [23]. Porta and colleagues studied OS and AML conversion time in 5326 MDS patients with respect to IPSS-R and WPSS classes. They found that according to, median OS was 121, 67, 35, 20, and 9 months in very low, low, intermediate, high and very high risk IPSS-R classes, respectively. Also, after excluding the "very low risk" group, median time for 25% of patients to develop AML was found to be 188, 34, 17 and 9 months, respectively. They also showed that according to WPSS classes median OS was 98, 76, 44, 21 and 9 months in very low, low, intermediate, high and very high risk, respectively, while median times for 25% of patients to develop AML (except very low) were 174, 72, 18 and 8 months, respectively.

They found the prognostic power of the WPSS was comparable to that of IPSS-R [22]. Comparing the IPSS and WPSS outcomes, it appears that the relatively steep decline regarding length of OS and time until AML conversion from the "intermediate" to the "high risk" groups of the WPSS may have had a role in establishment of statistical significance in the present study. The multivariable analysis results of our study support the relationship of the WPSS system with MDS progression. In our study, RAEB-2 was found to be significantly associated with progression and WHO-RAEB-2 significantly increased the WPSS score. Taken together, these provide support for the importance of blast percentage in determining prognosis, as this parameter is the primary parameter that distinguishes RAEB-2 from other WHO subclasses. However, before drawing direct conclusions regarding this matter, the non-homogeneous distribution of patient characteristics in MDS and the limited patient counts in several subgroups must be considered.

The MDACC is another prognostic system that assesses treated and untreated MDS patients, as well as patients with proliferative CMML and treatment-associated MDS [16,23]. Notwithstanding its reliable performance and wide inclusion criteria, the relative complexity of this model has limited its use in routine clinical practice [23]. The studies by Komrokji et al. and Nazha et al. also supported the prognostic value of MDACC in MDS [24,25]. Although we did not find an independent relationship between MDACC and MDS progression, ECOG-PS (which is included in the MDACC) was independently associated with MDS progression, further supporting the utility of MDACC in prognostic assessment while also showing the need for further data to improve patient risk stratification in MDS. When we evaluated ECOG-PS's prognostic value as a separate parameter, it was found that half of the patients with progression had an ECOG-PS score of 2 or higher. Perhaps more importantly, 80% of the non-PG group had an ECOG-PS score of <2. Similar to our study, the logistic regression analysis performed in one study showed that having a poor ECOG-PS (score ≥2) was an independent predictor of shortened LFS and OS, independent of IPSS-R risk class [21]. This relationships was also supported by another study in which an ECOG-PS score of 2 or higher was independently associated with shorter survival [26].

The FAB and WHO classifications are two widely accepted models in the pathological classification of MDS. The WHO classification was revised in 2016 [27,28], but since we used data obtained between 1999 and 2012 in our study, we classified patients according to the WHO 2008 classification. In a comprehensive study involving 5326 patients, OS for the types defined according to the WHO classification were as follows: median OS was 99 months for RCUD, RARS, and del5q (considered a single category), 66 months for RCMD, 28 months for RAEB-1, and 18 months for RAEB-2. The median time that surpassed until 25% of patients developed AML was 123 months for RCMD, 23 months for RAEB-1, and 9 months for RAEB-2 [22]. In the study by Ohyashiki et al., the conversion of RAEB-1 to AML was reported at a frequency of 37.5%, while the conversion rate of RAEB-2 to AML was 50% [29]. A recent study from Japan reported that MDS patients with high ferritin levels were significantly more likely to have RARS according to the FAB classification and were significantly less likely to have RA when compared to those with low ferritin levels [10]. Considering that high ferritin level is associated with worse survival in MDS, the ferritin elevation in these groups could be a factor contributing to survival [30]. We found that patients with RAEB-2 (WHO classification) and patients with RAEB (FAB classification) were significantly more likely to be in the PG group rather than the non-PG group. Furthermore, patients with RCUD (WHO classification) and patients with RA (FAB classification) were significantly more common in the PG group than in the non-PG group. We can say that these results are relatively consistent with the results of previous studies. Undoubtedly, the combination of the excess blast percentage with the presence of dysplasia in one or more cell lines has an important role in this relationship.

The limitations of our study can be listed as follows: the fact that it was a single-center study and the small number of participants limits the generalizability of the results. The retrospective analysis limited both the addition of new data and the use of the revised version of the WHO classification (2016) and comparison with other studies in this respect. In addition, since some patients had been diagnosed prior to access to advanced methods, we could not examine the effects of molecular genetics on the clinical course of MDS. The heterogeneity of the patient population is true for all studies evaluating patients with MDS, and therefore, is unavoidable; however, our data were further limited by the heterogeneous distribution of patients into prognostic subgroups. This may have influenced the statistical analyses.

Multivariable analysis showed that having an ECOG-PS score of ≥2 and being classified with ≥high risk according to the WPSS were independent predictors of MDS progression. Compared to the non-PG group, patients with progression had lower hemoglobin, monocyte, and platelet values, while BM blast percentage, transfusion need and ferritin levels were higher. In addition, the presence of dysplasia in more than one cell line was also found to be associated with progression. The development of different systems to predict the progression of MDS disorders, possibly with inclusion of genetic studies, will be beneficial to increase the accuracy of available classification systems, to determine the most appropriate and early treatment regimens, and ultimately, to improve survival.

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