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ORIGINAL REPORT

Revised International Prognostic Scoring System (IPSS) Predicts Survival and Leukemic Evolution of Myelodysplastic Syndromes Significantly Better Than IPSS and WHO Prognostic Scoring System: Validation by the Gruppo Romano Mielodisplasie Italian Regional Database

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ABSTRACT

Purpose
The definition of disease-specific prognostic scores plays a fundamental role in the treatment decision-making process in myelodysplastic syndrome (MDS), a group of myeloid disorders characterized by a heterogeneous clinical behavior.

Patients and Methods
We applied the recently published Revised International Prognostic Scoring System (IPSS-R) to 380 patients with MDS, registered in an Italian regional database, recruiting patients from the city of Rome (Gruppo Romano Mielodisplasie). Patients were selected based on the availability of IPSS-R prognostic factors, including complete peripheral-blood and bone marrow counts, informative cytogenetics, and follow-up data.

Results
We validated the IPSS-R score as a significant predictor of overall survival (OS) and leukemia-free survival (LFS) in MDS ($P < .001$ for both). When comparing the prognostic value of the International Prognostic Scoring System (IPSS), WHO Prognostic Scoring System (WPSS), and IPSS-R, using the Cox regression model and the likelihood ratio test, a significantly higher predictive power for LFS and OS became evident for the IPSS-R, compared with the IPSS and WPSS ($P < .001$ for both). The multivariate analysis, including IPSS, WPSS, age, lactate dehydrogenase, ferritin concentration, Eastern Cooperative Oncology Group performance status, transfusion dependency, and type of therapy, confirmed the significant prognostic value of IPSS-R subgroups for LFS and OS. Treatment with lenalidomide and erythropoiesis-stimulating agents was shown to be an independent predictor of survival in the multivariate analysis.

Conclusion
Our data confirm that the IPSS-R is an excellent prognostic tool in MDS in the era of disease-modifying treatments. The early recognition of patients at high risk of progression to aggressive disease may optimize treatment timing in MDS.

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INTRODUCTION

Myelodysplastic syndromes (MDS) are a heterogeneous group of myeloid disorders, characterized by variable biologic and clinical behavior, ranging from indolent to aggressive diseases, with different probabilities of leukemic evolution and death.[1,2] This underlines the necessity for the identification of scores to distinguish patients at high risk of progression, where therapy is indicated, from those with a minor risk of evolution, where toxic therapies may lead to unjustified toxicity. The definition of prognostic scores, including the International Prognostic Scoring System (IPSS)[3] and later on the WHO Prognostic Scoring System (WPSS),[4,5] was a crucial step to define leukemic risk and patients' life expectancy.

Table 1. Patients' Clinical Characteristics

Characteristic	No. of Patients (N = 380)	%*
Hemoglobin, g/dL		
Median	9.9	
Range	3.9-16.3	
Absolute neutrophil count, × 10^9/L		
Median	1.9	
Range	0.1-44	
Platelets, × 10^9/L		
Median	152	
Range	2-962	
Bone marrow blasts, %		
Median	3	
Range	0-20	
Ferritin, μg/L		
Median	214	
Range	7-3,010	
Lactate dehydrogenase, IU/L		
Median	317	
Range	100-3,308	
FAB classification		
RA	253	67
RARS	23	6
RAEB	104	27
WHO classification		
RA	107	29
RT	12	3
RARS	20	5
RCMD	94	25
RAEB-I	57	15
RAEB-II	47	12
MDS-U	15	4
MDS del 5(q)	28	7
Cytogenetics		
Normal	232	61
Del(20q)	19	5
Single very good	11	3
Single intermediate/aneuploidy	13	3
Isolated del(5q) or double including del(5q)	40	10.5
Double independent clones	11	3
+8	18	5
Isolated −7 and 7q−	8	2
Complex (3 abnormalities)	13	3
Complex (≥ 4 abnormalities)	13	3
t(1;3), inv(3)	2	0.5
Hemoglobin, g/dL		
≥ 10	175	46
8-10	142	37
< 8	63	17
Platelets, × 10^9/L		
≥ 100	249	66
50-100	80	21
< 50	51	13
Absolute neutrophil count, × 10^9/L		
≥ 0.8	331	87
< 0.8	49	13
Bone marrow blasts, %		
0-2	161	42
> 2 to < 5	100	26
5-10	86	23
> 10 to 20	33	9

(continued on following page)

Table 1. Patients' Clinical Characteristics (continued)

Characteristic	No. of Patients (N = 380)	%*
Cytogenetics		
Very good	11	3
Good	291	77
Intermediate	49	13
Poor	16	4
Very poor	13	3
IPSS-R		
Very low	146	38
Low	124	33
Intermediate	67	18
High	27	7
Very high	16	4
IPSS		
Low	162	43
Intermediate-1	155	40
Intermediate-2	52	14
High	11	3
WPSS		
Very low	22	6
Low	211	55
Intermediate	65	17
High	66	17
Very high	16	4
ECOG PS	372	
0	188	51
1	146	39
2	38	10
RBC transfusion dependence		
Yes	221	58
No	159	42
Treatment type	377	
Supportive	92	24
ESA	186	49
Lenalidomide	23	6
Azacitidine	67	18
Cytoreductive	9	2

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; ESA, erythropoiesis-stimulating agent; FAB, French-American-British; IPSS, International Prognostic Scoring System; IPSS-R, Revised International Prognostic Scoring System; MDS, myelodysplastic syndrome; MDS-U, myelodysplastic syndrome unclassifiable; RA, refractory anemia; RAEB, refractory anemia with excess blasts; RARS, refractory anemia with ringed sideroblasts; RCMD, refractory cytopenia with multilineage dysplasia; RT, refractory thrombocytopenia; WPSS, WHO Prognostic Scoring System.

* Percentages were approximated to the closest full unit.

The major limit of these scores was that they considered mainly disease-related factors. Cytogenetics was included, but probably because of the limited patient numbers used for analysis, only three major cytogenetic risk groups were identified. More recently, newer prognostic scores, such as the MD Anderson Prognostic Risk Model[6] and the MDS Comorbidity Index,[7] had the merit of also evaluating patient-related factors, including age, performance status, and comorbidities.

In the last year, a major effort from several MDS cooperating groups led to the development of the Revised IPSS (IPSS-R).[8] They used large international databases of patients with MDS, including more than 7,000 patients, and integrated detailed disease-related and

patient-related factors. On the basis of the recently published comprehensive cytogenetic scoring system for primary MDS,[9] they better defined the role of cytogenetics as a major MDS prognostic determinant, with 16 specific abnormalities, grouped into five different risk groups.[8] Furthermore, they identified the severity of bone marrow infiltration and the depth of anemia, thrombocytopenia, and neutropenia as clinically and statistically relevant cut points. The IPSS-R defines five different patient groups, characterized by significantly different overall survival (OS) and leukemia-free survival (LFS) probabilities. Additional features predictive of survival and leukemic evolution include age, performance status, serum ferritin, lactate dehydrogenase (LDH), and β_2-microglobulin.[8]

We applied the IPSS-R to an independent group of 380 patients with MDS, registered in an Italian real-life database, recruiting patients from the city of Rome (Gruppo Romano Mielodisplasie [GROM]). We validated the new IPSS-R score and compared the OS and LFS predictive values of IPSS-R with those of the IPSS and WPSS. In addition, we analyzed the predictive value of IPSS-R integrating into the multivariate analysis IPSS, WPSS, age, Eastern Cooperative Oncology Group (ECOG) performance status, LDH, ferritin concentration, transfusion dependency, and type of treatment received by the patients.

PATIENTS AND METHODS

Our retrospective analysis included 380 patients with MDS, identified among all patients retrospectively registered in the GROM registry, including 13 hematology centers in the Rome area, which includes at present a total of 662 patients diagnosed with MDS between 2001 and 2011. MDS had been morphologically defined according to the French-American-British (FAB)[10] and WHO[11] classifications. Cytogenetic analysis had been performed at local participating centers by specialized laboratories. Cytogenetic classification was performed by grouping patients according to Schanz et al.[9] Criteria for patient selection for our analysis were the availability of detailed IPSS-R data, including complete peripheral-blood and bone marrow blast counts and informative cytogenetic analysis, and availability of follow-up data, date of leukemic evolution, and date of last follow-up or of death. Additional data required for patient inclusion were ECOG performance status, transfusion dependency, and type of therapy received by the patients. RBC transfusion dependence was defined as absence of a longer than 28-day transfusion-free period over 8 weeks.[12] The GROM regional registry has been approved by the local ethical committees of all participating centers.

Statistical Analysis

Differences in the distributions of prognostic factors in patient subgroups were analyzed using the χ^2 or Fisher's exact test and the Wilcoxon test. OS was defined as the time from registration to death or date of last follow-up. LFS was defined as time to bone marrow blast increase to $\geq 20\%$, according to the WHO classification,[11] and was calculated from the date of MDS diagnosis until the date of the first documentation of progressive disease or until death (whatever the cause), whichever occurred first. Patients still alive and known to be progression free were censored at last follow-up. Differences in survival were calculated using the log-rank test in univariate analysis and the Cox regression model in multivariate analysis. The probability of cumulative incidence of disease progression or transformation to acute myeloid leukemia (AML) was estimated using the appropriate nonparametric method, considering death as a competing risk and comparing groups using the Gray test. CIs were estimated using the Simon and Lee method. Cox proportional hazards regression model was used to examine the risk factors affecting time to event.

The likelihood ratio test was used to compare, two by two, the different prognostic models (IPSS-R *v* IPSS and IPSS-R *v* WPSS). The quantity of interest is the deviance difference between the compared models, under the null hypothesis that two models fit the data equally well and the deviance difference has an approximate χ^2 distribution with *df* equal to the difference in the number of parameters between the compared models.[13]

All significant variables identified by univariate analysis and clinical factors important for MDS were used to develop the multivariate model. Multivariate analysis for OS and LFS was performed including ferritin, LDH, age, transfusion dependency, therapeutic strategy, IPSS, WPSS, and IPSS-R. Step automatic procedures (backward and stepwise selection) were used to confirm the models.

CIs were estimated at the 95% level; all tests were two-sided, accepting $P \leq .05$ as indicative of a statistically significant difference. All statistical

Table 2. LFS, OS, and Predictive Value of IPSS-R Versus IPSS and WPSS

	LFS			OS		
Classification	Estimate (months)	95% CI (months)	Likelihood Ratio Test*	Estimate (months)	95% CI (months)	Likelihood Ratio Test*
IPSS			65.3			55.6
Low	NR	—		NR	—	
Intermediate-1	57.4	44.0 to NR		59.7	53.3 to NR	
Intermediate-2	19.0	14.0 to 48.1		27.1	18.4 to NR	
High	8.9	6.4 to NR		16.5	9.2 to NR	
WPSS			79.3			74.4
Very low	NR	—		NR	—	
Low	NR	—		NR	—	
Intermediate	46.6	30.4 to 59.7		46.6	30.4 to 59.7	
High	25.4	16.2 to 68.1		33.1	23.9 to 97.8	
Very high	9.0	5.9 to NR		14	6.4 to NR	
IPSS-R			88.2			85
Very low	NR	—		NR	—	
Low	75.1	55.4 to NR		75.1	55.7 to NR	
Intermediate	34.4	26.1 to 60.3		37.7	31.4 to 62	
High	12.9	6.6 to 52.6		18.4	12.6 to 52.6	
Very high	14	5.9 to NR		14	6.4 to NR	

Abbreviations: IPSS, International Prognostic Scoring System; IPSS-R, Revised International Prognostic Scoring System; LFS, leukemia-free survival; NR, not reached; OS, overall survival; WPSS, WHO Prognostic Scoring System.
*$P < .001$.

analyses were performed with the statistical software environment R (http://www.r-project.org/).

RESULTS

Data from 380 patients from the GROM database were evaluated. There were 182 women and 198 men, with a median age of 71 years (range, 22 to 89 years). Median peripheral-blood counts, bone marrow blasts, and ferritin and LDH values at the time of initial diagnosis were available for all patients and are listed in Table 1. Morphologic classification according to the FAB[10] and WHO[11] classifications, karyotype, and RBC transfusion dependence are also listed in Table 1. Most patients had a good performance status, with 90% of patients with an ECOG performance status of 0 to 1. Treatment included vitamins, erythropoiesis-stimulating agents (ESAs), and transfusion support in the majority of patients, whereas active treatment, including lenalidomide (Revlimid; Celgene Corporation, Summit, NJ), azacitidine (Vidaza; Celgene), or cytotoxic drugs, was administered to 26% of patients (Table 1). The IPSS and WPSS scores were applied, and the proportion of patients in each group is listed in Table 1. The distribution of MDS subtypes showed the prevalence of lower risk MDS subgroups.

We then calculated the IPSS-R[8] and reclassified patients into five risk categories. Table 1 shows the distribution of parameters used to calculate the IPSS-R. According to IPSS-R, most patients had a very low or low risk (38% and 33%, respectively), whereas 18% of the patients had an intermediate risk, and 7% and 4% of patients had a high and very high risk, respectively (Table 1). LDH concentration, as a parameter of disease activity, significantly correlated with patients' IPSS-R subgroup ($P = .007$; Appendix Fig A1, online only).

The prognostic value of the three scores was evaluated at a median follow-up time of 2.8 years (range, 0.1 to 12.2 years) from initial diagnosis. Median LFS was significantly different in patients subgroups classified according to IPSS, WPSS, and IPSS-R, as shown by the Kaplan-Meier method ($P < .001$ for all prognostic scores; Table 2 and Figs 1A to 1C). The difference in OS was also significant between the three different prognostic scores ($P < .001$ for all; Table 2 and Figs 2A to 2C). The significant prognostic value of IPSS-R for LFS and OS was also confirmed when evaluating separately patients treated with ESA, lenalidomide, and RBC transfusions and patients treated with disease-modifying treatment, including azacitidine and cytotoxic chemotherapy (Appendix Figs A2 and A3, online only).

When comparing the prognostic value of IPSS, WPSS, and IPSS-R, using the Cox regression model and the likelihood ratio test, a significantly higher predictive power for LFS became evident for the IPSS-R, compared with the IPSS and WPSS ($P < .001$; Table 2). Similarly, the IPSS-R predicted OS significantly better than the IPSS and WPSS ($P < .001$; Table 2).

Multivariate analysis, including age, LDH, ferritin concentration, ECOG performance status, transfusion dependency, and type of therapy, confirmed the significant prognostic value of IPSS-R subgroups for LFS and OS (Tables 3 and 4).

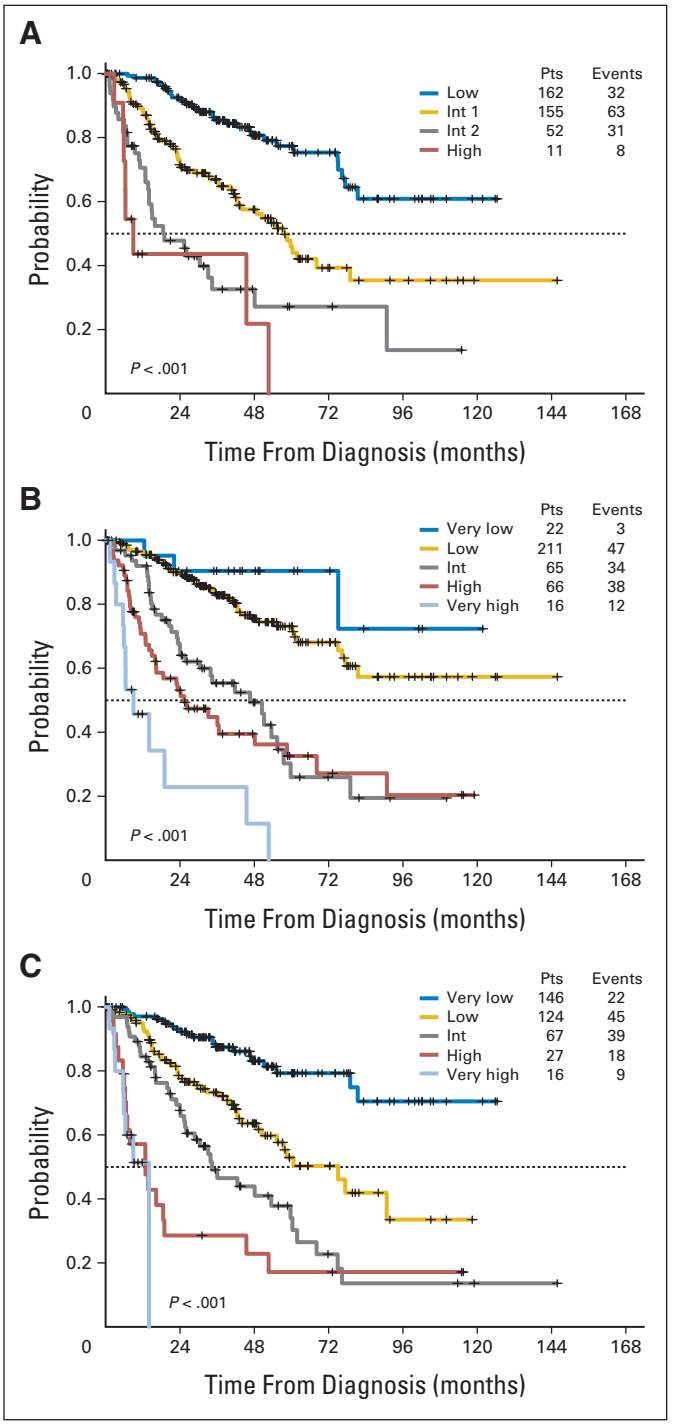

Fig 1. The probability of leukemia-free survival was significantly different in patients classified according to the (A) International Prognostic Scoring System (IPSS), (B) WHO Prognostic Scoring System, and (C) Revised IPSS, as shown by the Kaplan-Meier method ($P < .001$ for all prognostic scores). Number of patients (Pts) and number of events in each subgroup are detailed in the figure panels. Int, intermediate.

DISCUSSION

The recent publication of the IPSS-R provides an updated tool to more precisely define prognosis and life expectancy of patients with MDS.[8] This will be useful for risk-adapted patient management and will improve patient-physician communication, especially given the new therapeutic possibilities in MDS. We applied the IPSS-R to 380 patients with MDS from the Italian GROM registry, including patients treated in the city of Rome. Data refer to patients collected at the time

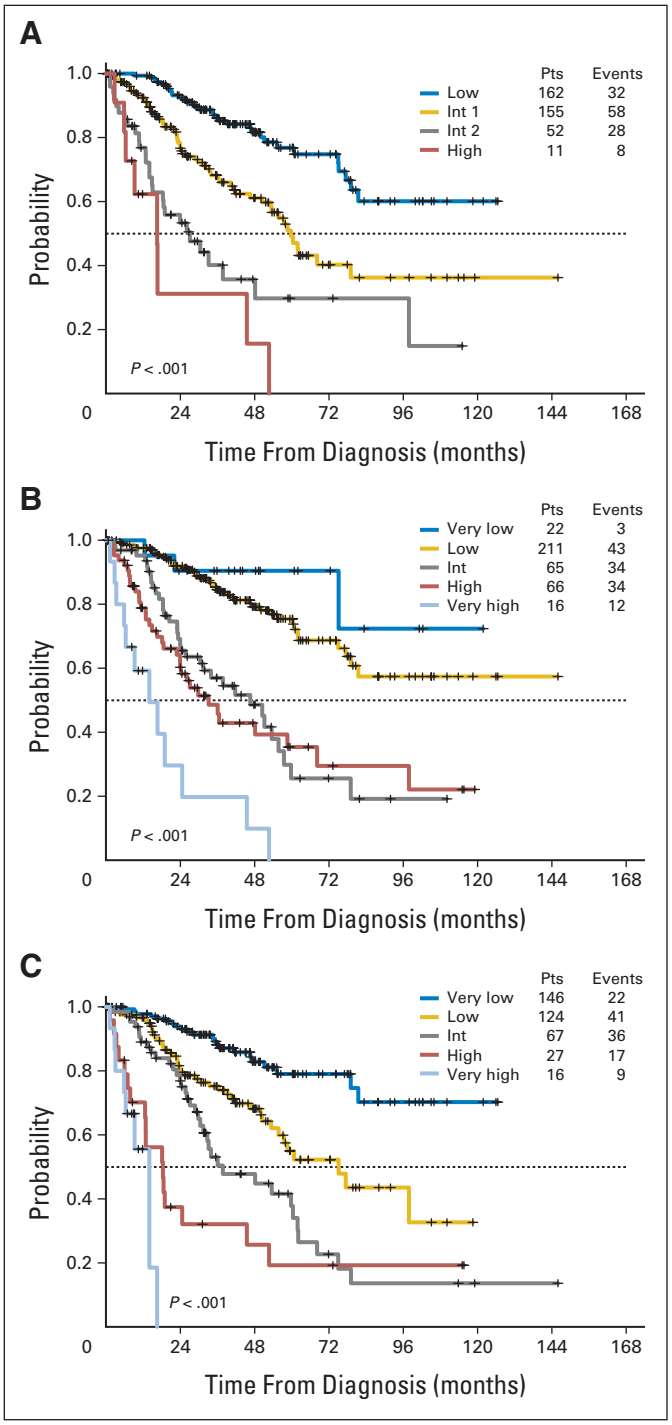

Fig 2. The difference in overall survival was significant in patients classified according to the (A) International Prognostic Scoring System (IPSS), (B) WHO Prognostic Scoring System, and (C) Revised IPSS, as shown by the Kaplan-Meier method ($P < .001$ for all prognostic scores). Number of patients (Pts) and number of events in each subgroup are detailed in the figure panels. Int, intermediate.

of initial diagnosis by 13 hematology centers, including nine local community hospitals and four university hospitals. There was no patient selection, and most of the patients had been observed at the centers where the diagnosis had been made, excluding potential confounding factors such as duration of MDS before patient referral.

Table 3. Multivariate Analysis for Leukemia-Free Survival

Parameter	P (χ^2)	Hazard Ratio	95% CI
Age, continuous variable	.0061	1.026	1.007 to 1.044
RBC transfusion dependence, no *v* yes	< .001	0.187	0.106 to 0.329
IPSS-R			
Very low *v* intermediate	< .001	0.258	0.147 to 0.452
Low *v* intermediate	.0217	0.580	0.364 to 0.924
High *v* intermediate	.0764	1.724	0.944 to 3.148
Very high *v* intermediate	.0036	3.262	1.473 to 7.228
Therapy			
ESA *v* supportive	.0284	0.542	0.313 to 0.937
Lenalidomide *v* supportive	.0024	0.145	0.041 to 0.504
Azacitidine *v* supportive	.5487	0.833	0.459 to 1.513
Chemotherapy *v* supportive	.8164	1.116	0.442 to 2.815

NOTE. International Prognostic Scoring System, Prognostic Scoring System, performance status, ferritin, and lactate dehydrogenase at the time of initial myelodysplastic syndrome diagnosis were not significant in the multivariate analysis for leukemia-free survival.
Abbreviations: ESA, erythropoiesis-stimulating agent; IPSS-R, Revised International Prognostic Scoring System.

In our study, MDS was morphologically defined according to the FAB[10] and WHO[11] classifications, and only patients with up to 20% blasts were included. This may explain the inferior proportion of patients in the high- and very high–risk groups in our registry (11%), compared with the original IPSS-R publication (24% of patients), which also includes refractory anemia with excess blasts in transformation.[8] Similar to IPSS-R, treatment-related MDSs have been excluded by our registry, because of the worse biologic and clinical features of these diseases, which have been inserted in the 2008 classification of acute leukemia.[11,14] Because patients were recruited from 2001 to 2011, we were able to include in the multivariable analysis the type of treatment administered to the patients, including not only vitamins, transfusion, and growth factor support, but also active treatment, such as lenalidomide, azacitidine, and cytotoxic therapy.

Table 4. Multivariate Analysis for Overall Survival

Parameter	P (χ^2)	Hazard Ratio	95% CI
Age, continuous variable	.0015	1.032	1.012 to 1.052
Ferritin, 100 μg/L increase	.0142	1.050	1.010 to 1.092
RBC transfusion dependence, no *v* yes	< .001	0.213	0.120 to 0.379
IPSS-R			
Very low *v* intermediate	< .001	0.285	0.161 to 0.504
Low *v* intermediate	.0364	0.594	0.365 to 0.968
High *v* intermediate	.1027	1.671	0.902 to 3.094
Very high *v* intermediate	< .001	5.128	2.235 to 11.767
Therapy			
ESA *v* supportive	.0107	0.477	0.270 to 0.842
Lenalidomide *v* supportive	.0021	0.139	0.039 to 0.487
Azacitidine *v* supportive	.2707	0.703	0.375 to 1.316
Chemotherapy *v* supportive	.8491	0.913	0.359 to 2.324

NOTE. International Prognostic Scoring System, Prognostic Scoring System, performance status, ferritin, and lactate dehydrogenase at the time of initial diagnosis were not significant in the multivariate analysis for overall survival.
Abbreviations: ESA, erythropoiesis-stimulating agent; IPSS-R, Revised International Prognostic Scoring System.

We were able to further validate the value of IPSS-R to predict survival and leukemic evolution and were able to confirm its significantly higher prognostic power compared with IPSS and WPSS. This higher predictive value is probably based on the extension to five cytogenetic groups, in addition to the definitions of the depth of cytopenias and of bone marrow blast infiltration, which are the major advances of the IPSS-R.[8]

As a result of the outstanding work by other groups,[12,15,16] the degree of anemia has recently replaced the concept of RBC transfusion dependence as a prognostic parameter of the WPSS, because it may significantly contribute to the high rate of nonleukemic mortality, mostly related to cardiac disease in MDS.[12] This was the rational for stratification of anemia according to three different hemoglobin thresholds in the IPSS-R. In addition, ferritin is known to reflect RBC transfusion burden and iron overload, but is also associated with disease-related factors such as severity of anemia and aggressiveness of MDS at time of diagnosis.[17,18] In our patients, ferritin was an independent prognostic factor in the multivariable analysis for OS, probably reflecting the negative impact of iron overload itself on the function of vital organs and on the number of cardiac deaths. However, the prognostic value of RBC transfusion dependence, which incorporates also features of disease progression, was superior to that of ferritin in predicting leukemic evolution.

IPSS-R also confirmed that patient age, performance status, and LDH are additive features for survival, but not for AML transformation.[8] Different from the original IPSS-R publication, in our patients, age was an independent predictor of both leukemic evolution and death. The reasons for this difference are not clear but may be the result of the inclusion in our analysis of patients who underwent active treatment.

In our patients, LDH concentration significantly correlated with IPSS-R risk groups and was not an independent predictor of OS or LFS. Elevated LDH at diagnosis or during follow-up is known to be associated with an increased probability of AML evolution and decreased probability of survival.[19,20] Among several different mechanisms underlying an increase in LDH in progressing MDS, ineffective hematopoiesis or the increased turnover and degradation of myeloid cells in the bone marrow, spleen, and other tissues preceding acceleration of the disease may explain the direct correlation to IPSS-R.

The precise definition of a prognostic score and of the probability of leukemic evolution is particularly important in the lower MDS risk groups, which represent the majority of patients with MDS, in whom new approaches, including allogeneic stem-cell transplantation in younger patients, may be addressed in a refined manner. In our study, treatment with ESA or lenalidomide, compared with supportive therapy, almost exclusively administered to low-risk patients, was a significant predictor of LFS, independent of the IPSS-R. These data show that these treatments may indeed improve survival of responding patients.[20-22] However, probably because of the low number of patients treated and the use of IPSS to classify the patients at the time of treatment start, azacitidine and cytotoxic therapy were not predictors of survival independent from IPSS-R.

Our data show that the IPSS-R is an excellent predictor of MDS prognosis in the era of disease-modifying treatments. In the future, the integration of comorbidity scores and time-dependent scores, which consider the evolutive nature of MDS, may further address the decision-making process for a correct treatment approach. The early recognition of patients at high risk of progression to aggressive disease may also optimize treatment timing, before worsening of comorbidities.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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Appendix

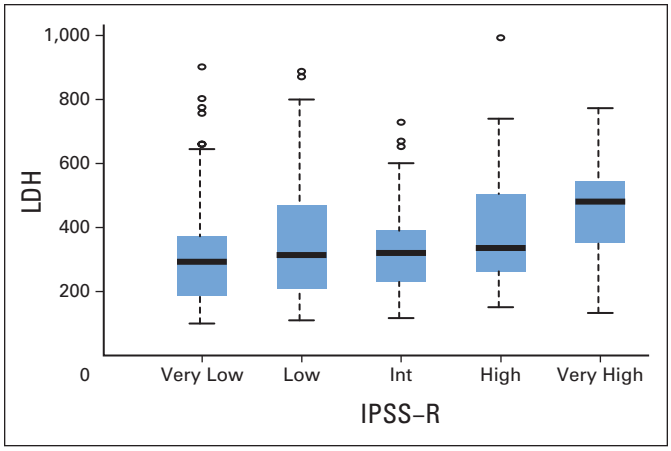

Fig A1. Lactate dehydrogenase (LDH) plasmatic concentration, as a parameter of disease activity, significantly correlates to patient groups according to the Revised International Prognostic Scoring System (IPSS-R; $P = .007$). Int, intermediate.

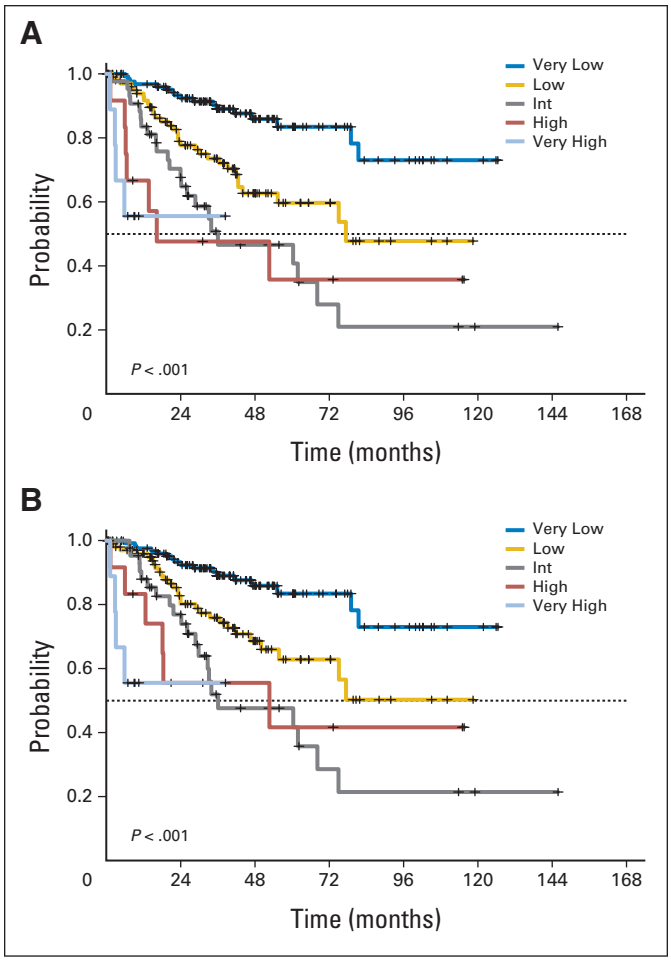

Fig A2. The Revised International Prognostic Scoring System has a significant prognostic role for (A) leukemia-free survival and (B) overall survival in patients receiving treatment including erythropoiesis-stimulating agents, lenalidomide, or RBC transfusions (n = 304). Int, intermediate.

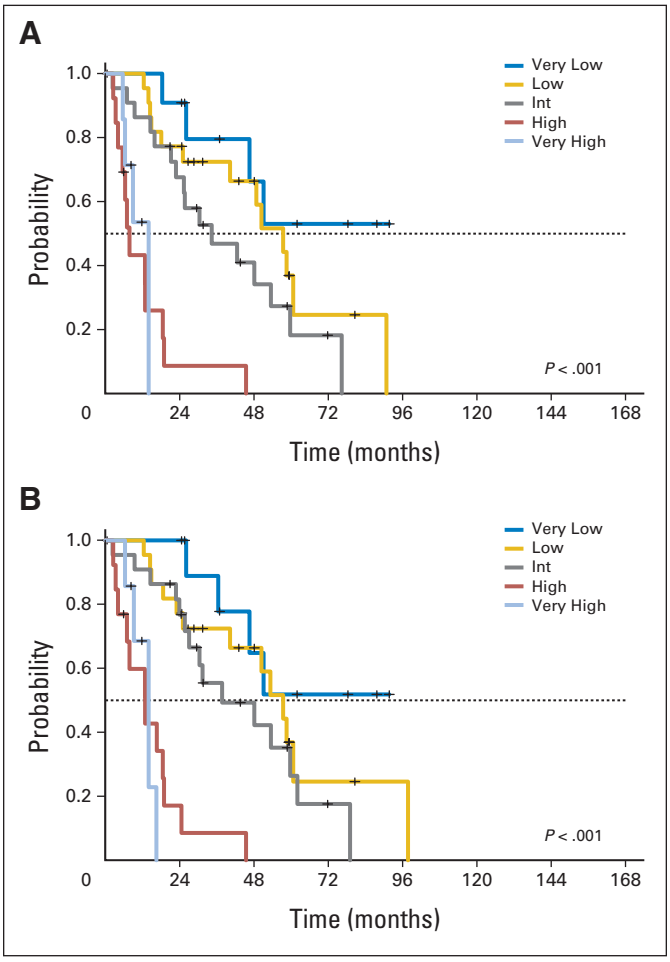

Fig A3. The significant prognostic role of the Revised International Prognostic Scoring System for (A) leukemia-free survival and (B) overall survival is confirmed in patients treated with disease-modifying treatment, including azacitidine or cytotoxic chemotherapy (n = 76). Int, intermediate.