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ORIGINAL REPORT

# Scoring System Prognostic of Outcome in Patients Undergoing Allogeneic Hematopoietic Cell Transplantation for Myelodysplastic Syndrome

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## ABSTRACT

### Purpose
To develop a system prognostic of outcome in those undergoing allogeneic hematopoietic cell transplantation (allo HCT) for myelodysplastic syndrome (MDS).

### Patients and Methods
We examined 2,133 patients with MDS undergoing HLA-matched (n = 1,728) or -mismatched (n = 405) allo HCT from 2000 to 2012. We used a Cox multivariable model to identify factors prognostic of mortality in a training subset (n = 1,151) of the HLA-matched cohort. A weighted score using these factors was assigned to the remaining patients undergoing HLA-matched allo HCT (validation cohort; n = 577) as well as to patients undergoing HLA-mismatched allo HCT.

### Results
Blood blasts greater than 3% (hazard ratio [HR], 1.41; 95% CI, 1.08 to 1.85), platelets 50 $\times$ $10^9$/L or less at transplantation (HR, 1.37; 95% CI, 1.18 to 1.61), Karnofsky performance status less than 90% (HR, 1.25; 95% CI, 1.06 to 1.28), comprehensive cytogenetic risk score of poor or very poor (HR, 1.43; 95% CI, 1.14 to 1.80), and age 30 to 49 years (HR, 1.60; 95% CI, 1.09 to 2.35) were associated with increased hazard of death and assigned 1 point in the scoring system. Monosomal karyotype (HR, 2.01; 95% CI, 1.65 to 2.45) and age 50 years or older (HR, 1.93; 95% CI, 1.36 to 2.83) were assigned 2 points. The 3-year overall survival after transplantation in patients with low (0 to 1 points), intermediate (2 to 3), high (4 to 5) and very high ($\geq$ 6) scores was 71% (95% CI, 58% to 85%), 49% (95% CI, 42% to 56%), 41% (95% CI, 31% to 51%), and 25% (95% CI, 4% to 46%), respectively ($P < .001$). Increasing score was predictive of increased relapse ($P < .001$) and treatment-related mortality ($P < .001$) in the HLA-matched set and relapse ($P < .001$) in the HLA-mismatched cohort.

### Conclusion
The proposed system is prognostic of outcome in patients undergoing HLA-matched and -mismatched allo HCT for MDS.

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## INTRODUCTION

Myelodysplastic syndrome (MDS) is a progressive disorder characterized by defective myeloid progenitor cell maturation resulting in blood cytopenias and increased likelihood of progression to acute myelogenous leukemia.[1,2] Among available therapies, only allogeneic hematopoietic cell transplantation (allo HCT) is considered curative.[3-6] The decision to proceed with allo HCT, however, is complicated by several factors, including the potential for transplantation-related mortality (TRM), disease heterogeneity, and patient comorbidities and preference.[7,8]

Several prognostic tools, such as the standard (IPSS) and revised International Prognostic Scoring System (IPSS-R), use disease-specific factors to

 

determine patient prognosis.[9,10] The IPSS-R includes updated cytogenetic classifications, incorporates patient age, and offers greater prognostic value over the IPSS.[11,12] Despite this, the IPSS is typically used to determine disease-specific transplantation eligibility and has been integrated into the National Comprehensive Cancer Network guidelines.[13] The rationale for this algorithm is based in part on analyses using Markov decision modeling to predict benefit of allo HCT in populations based on IPSS score. The first of these analyses demonstrated that younger patients with intermediate-2– or high-risk MDS benefited from myeloablative allo HCT at diagnosis, whereas patients with lower-risk disease did not.[14] Koreth et al[15] updated these findings in a cohort of patients undergoing reduced-intensity conditioning allo HCT, with similar results. The IPSS-R has also been independently validated as offering prognostic information for post–allo HCT outcomes.[11] Thus, both the IPSS and IPSS-R may be used to determine disease-specific variables that would indicate a benefit from transplantation.

A major limitation to both the IPSS and IPSS-R is that they are not specific to patients undergoing transplantation and do not take into account other factors that may enter into a decision to pursue allo HCT. To address these problems, we used data from the Center for Blood and Marrow Transplant Research (CIBMTR) registry to identify disease-, patient-, and transplantation-specific variables that are associated with outcome in patients undergoing allo HCT for MDS. The primary objective of this study was to develop a risk-stratification tool prognostic of survival after transplantation. We applied this tool to patients undergoing HLA-matched, HLA-mismatched sibling, or unrelated-donor allo HCT. We then sought to determine if this tool was also prognostic of relapse, TRM, or disease-free survival (DFS) in these populations.

## PATIENTS AND METHODS

### Data Source

The CIBMTR is a combined research program of the Medical College of Wisconsin and the National Marrow Donor Program. The CIBMTR comprises a voluntary network of more than 450 transplantation centers worldwide that contribute data on consecutive allo and autologous HCTs to a centralized statistical center. Observational studies conducted by the CIBMTR are performed in compliance with all applicable federal regulations pertaining to the protection of human research participants. Protected health information used in the performance of such research is collected and maintained in the capacity of the CIBMTR as a public health authority under the Health Insurance Portability and Accountability Act Privacy Rule. Additional details regarding the data source are described elsewhere.[16]

### Patients

Patients age 18 years or older who underwent HLA-matched or -mismatched related-donor or URD allo HCT for MDS reported to the CIBMTR from 2000 to 2012 were included. Patients undergoing haploidentical, syngeneic, umbilical cord blood, or more than two HLA loci– or allele–mismatched URD transplantation or with missing donor data were excluded from this analysis (n = 663). Pediatric patients (n = 262) were also excluded. An additional 84 patients were removed because of missing date of diagnosis, unknown graft-versus-host disease (GVHD) prophylaxis, or missing complete 100-day follow-up data. Patients who had bone marrow or blood blasts of 20% or greater at any time before transplantation but who were reported as having MDS were excluded (n = 11). A total of 1,728 patients met these criteria and underwent HLA-matched allo HCT. An additional 405 patients underwent one to two HLA loci–mismatched allo HCT and formed the HLA-mismatched set.

Cytogenetics were stratified based on the MDS Comprehensive Cytogenetic Scoring System.[12] The prognostic subgroups were defined based on the following karyotype results: the very good subgroup included del(11q) and −Y; the good subgroup included normal karyotype, del(5q), del(12p), and del(20q); the intermediate subgroup included del(7q), +8, i(17q), +19, and other independent clones; the poor subgroup included inv(3), translocations involving 3q, del(3q), and complex karyotype (three abnormalities); and the very poor subgroup included very complex karyotype more than three abnormalities). Monosomal karyotype (MK) was defined as monosomy of two or more chromosomes or one single autosomal monosomy in the presence of other structural abnormalities.[17] Advanced MDS was defined as having either bone marrow blasts of 5% or greater at HCT or French-American-British classification of refractory anemia with excess blasts-1 or refractory anemia with excess blasts-2.[18] Continuous variables were stratified using the maximum-likelihood method and confirmed with false-discovery rate control.[19] Overall survival (OS) and DFS were calculated from the day of transplantation to the day of death or either death or relapse, respectively, using the Kaplan-Meier method.

### Statistical Analysis

A total of 1,728 patients who underwent HLA-matched allo HCT and met selection criteria were randomly assigned to a training data set comprising 67% (n = 1,151) of the cohort and a validation data set including the remaining 33% (n = 577). The training data set was used to develop a prognostic scoring system, and the validation data set was used to assess the prognostic ability of the scoring system. A Cox proportional hazards model with a stepwise selection procedure was used to select significant covariates for OS. Maximum likelihood from the Cox model was used to establish cutoffs for continuous variables. Forward-selection and backward-elimination procedures were used to confirm the significant covariates. Interaction between significant covariates was examined, and proportional hazards assumption was examined. On the basis of the magnitude of the hazard ratios (HRs) associated with variables, a weighted score was assigned to factors positively associated with OS in the training cohort. HRs between 1.25 and 1.79 were assigned 1 point, whereas HRs of 1.8 or greater were assigned 2 points. Scores were grouped based on associated HRs into good-, intermediate-, high-, and very high–risk groups. Patients with missing data were included in the multivariable Cox model analysis but were excluded from analysis of the final risk score in the training and validation sets. Cause-specific HRs are reported in the analysis of secondary end points with competing events. These results were confirmed using the Fine and Gray method to account for competing risks.[20] Concordance indices were calculated for the proposed prognostic scoring system as well as the IPSS and IPSS-R using the validation cohort as previously described.[21]

## RESULTS

### Patients

Patient data for the HLA-matched validation and training sets and for the HLA-mismatched set are listed in Table 1 and Appendix Table A1 (online only), respectively. The median follow-up of survivors was 52 months (range, 3 to 169) in the HLA-matched training cohort, 48 months (range, 3 to 145) in the HLA-matched validation cohort, and 46 months (range, 4 to 145) in the HLA-mismatched cohort. The percentage of patients for whom follow-up data were reported was 98%, 90%, and 88% at 1, 3, and 5 years, respectively, in the combined training and validation cohorts. To validate uniformity between the training and validation cohorts, we calculated the incidence of relapse and TRM as well as OS and DFS in each group. OS at 1, 3, and 5 years was 59%, 43%, and 39%

**Table 1.** Demographic and Clinical Characteristics of HLA-Matched Validation and Training Cohorts

| Characteristic | No. (%) Training (n = 1,151) | Validation (n = 580) | *P* |
|---|---|---|---|
| Age, years | | | .67 |
| Median | 56 | 56 | |
| Range | 18-77 | 19-77 | |
| Male sex | 693 (60) | 352 (61) | .85 |
| KPS, % | | | .88 |
| 90-100 | 702 (61) | 361 (62) | |
| < 90 | 386 (34) | 188 (32) | |
| Missing | 63 (5) | 31 (5) | |
| Secondary disorder | | | .93 |
| No | 898 (78) | 448 (77) | |
| Yes | 222 (19) | 116 (20) | |
| Missing | 31 (3) | 16 (3) | |
| Cytogenetic status | | | .92 |
| MK positive | 195 (17) | 94 (16) | |
| Very good | 9 (< 1) | 7 (1) | |
| Good | 440 (38) | 233 (40) | |
| Intermediate | 272 (24) | 131 (23) | |
| Poor | 128 (11) | 62 (11) | |
| Very poor | 21 (2) | 13 (2) | |
| Missing | 86 (7) | 40 (7) | |
| Blast in marrow before HCT, % | | | .84 |
| ≤ 2 | 497 (43) | 239 (41) | |
| 2-5 | 236 (21) | 121 (21) | |
| 5-10 | 209 (18) | 105 (18) | |
| > 10 | 90 (8) | 45 (8) | |
| Missing | 119 (10) | 70 (12) | |
| Blast in blood before HCT, % | | | .67 |
| ≤ 3 | 877 (76) | 448 (77) | |
| > 3 | 89 (8) | 38 (7) | |
| Missing | 185 (16) | 94 (16) | |
| Platelet count before HCT, × $10^9$/L | | | .84 |
| ≤ 50 | 489 (42) | 242 (42) | |
| > 50 | 658 (57) | 335 (58) | |
| Missing | 4 (< 1) | 3 (< 1) | |
| ANC before HCT, /μL | | | .50 |
| ≥ 800 | 682 (59) | 347 (60) | |
| < 800 | 420 (36) | 215 (37) | |
| Missing | 49 (4) | 18 (3) | |
| Elevated LDH before HCT | | | .87 |
| No | 677 (59) | 346 (60) | |
| Yes | 327 (28) | 165 (28) | |
| Missing | 147 (13) | 69 (12) | |
| IPSS at diagnosis | | | .71 |
| Low | 28 (2) | 13 (2) | |
| Intermediate-1 | 412 (36) | 215 (37) | |
| Intermediate-2 | 381 (33) | 202 (35) | |
| High | 98 (9) | 40 (7) | |
| Missing | 232 (20) | 110 (19) | |
| Pretransplantation therapy | | | .55 |
| Hypomethylating agents only | 378 (33) | 189 (33) | |
| Chemotherapy only | 71 (6) | 33 (6) | |
| Both | 23 (2) | 19 (3) | |
| None | 646 (56) | 325 (56) | |
| Missing | 33 (3) | 14 (2) | |
| Conditioning regimen intensity | | | .89 |
| Myeloablative | 662 (58) | 334 (58) | |
| Reduced | 338 (29) | 174 (30) | |
| *Nonmyeloablative* | 127 (11) | 63 (11) | |
| Missing | 24 (2) | 9 (2) | |
| Graft type | | | .64 |
| Bone marrow | 221 (19) | 106 (18) | |
| Peripheral blood | 930 (81) | 474 (82) | |
| Ex vivo T-cell depletion | 29 (3) | 11 (2) | .93 |
| ATG or alemtuzumab | 335 (29) | 174 (30) | .09 |
| Type of donor | | | .92 |
| Sibling | 491 (43) | 246 (42) | |
| Unrelated | 660 (57) | 334 (58) | |

Abbreviations: ANC, absolute neutrophil count; ATG, antithymocyte globulin; HCT, hematopoietic cell transplantation; IPSS, International Prognostic Scoring System; KPS, Karnofsky performance status; LDH, lactate dehydrogenase; MK, monosomal karyotype.

in the training cohort and 60%, 47%, and 39% in the validation cohort, respectively ($P$ = not significant). The 3-year incidences of relapse and TRM were 25% (95% CI, 22% to 28%) and 34% (95% CI, 31% to 37%) in the training cohort and 25% (95% CI, 22% to 29%) and 31% (95% CI, 27% to 35%)in the validation cohort, respectively ($P$ = not significant).

### *Development of Prognostic Scoring System*

We constructed a Cox proportional hazards model using the HLA-matched training set that included the following variables: patient age; sex; and Karnofsky performance status; disease stage at transplantation; comprehensive cytogenetic risk status; bone marrow and peripheral blood blast percentages; hemoglobin, neutrophil, and platelet counts at diagnosis and pretransplantation; lactate dehydrogenase at transplantation; pretransplantation therapy (hypomethylating agents, chemotherapy, neither, or both); time from diagnosis to transplantation; year of transplantation; conditioning regimen and regimen intensity (myeloablative *v* reduced intensity); donor–recipient sex match or mismatch; GVHD prophylaxis; graft type (bone marrow *v* peripheral blood); presence of secondary MDS; and URD versus related donor.

Table 2 summarizes the variables relevant to OS identified in the multivariable analysis of the 1,151 patients in the HLA-matched training cohort. This multivariable model identified five independent predictors of survival: age, Karnofsky performance status less than 90%, cytogenetics, blood blasts greater than 3% at the time of HCT, and platelet count $50 \times 10^9$/L or less at the time of HCT. On the basis of an HR of 1.8 or higher, a weighted score of 2 was assigned to older age (> 50 years) and monosomal karyotype, whereas other factors were assigned a score of 0 or 1 based on an HR of less than 1.25 and 1.25 to 1.79, respectively (Appendix Table A2, online only). The overall score ranged from 0 to 7, with increasing scores indicating greater risk. On the basis of these data, we created a four-category system: low, score of 1 or lower; intermediate, score of 2 to 3; high, score of 4 to 5; and very high, score of 6 or higher. The HR for death (using the low-risk group as reference) was 1.76 (95% CI, 1.24 to 2.49) for the intermediate-risk group, 2.87 (95% CI, 1.99 to 4.14) for the high-risk group, and 6.75 (95% CI, 4.28 to 10.67) for the very high–risk group (overall $P < .001$; Table 3).

Important variables that were not associated with OS in the multivariable analysis included donor source (sibling *v* unrelated), conditioning intensity, GVHD prophylaxis, and bone marrow blasts at the time of transplantation. Factors associated with worse

  

**Table 2.** Multivariable Analysis of Factors Associated With OS in HLA-Matched Training Cohort

| Factor | No. of Patients | HR for Death (95% CI) | *P* |
|---|---|---|---|
| Patient age, years | | | .003 |
| 18-29 | 77 | 1 (reference) | |
| 30-49 | 289 | 1.60 (1.09 to 2.35) | |
| ≥ 50 | 785 | 1.93 (1.36 to 2.83) | |
| KPS, % | | | .014 |
| 90-100 | 702 | 1 (reference) | |
| < 90 | 386 | 1.25 (1.06 to 1.28) | |
| Cytogenetics | | | < .001 |
| Very good, good, or intermediate | 720 | 1 (reference) | |
| Poor or very poor | 149 | 1.43 (1.14 to 1.80) | |
| MK | 195 | 2.01 (1.65 to 2.45) | |
| Blood blast before HCT, % | | | .005 |
| ≤ 3 | 877 | 1 (reference) | |
| > 3 | 89 | 1.41 (1.08-1.85) | |
| Platelet count before HCT, × $10^9$/L | | | < .001 |
| > 50 | 658 | 1 (reference) | |
| ≤ 50 | 489 | 1.37 (1.18 to 1.61) | |

Abbreviations: HCT, hematopoietic cell transplantation; HR, hazard ratio; KPS, Karnofsky performance status; OS, overall survival.

OS on univariable but not on multivariable analysis were RBC transfusion dependence (HR, 1.23; 95% CI, 1.05 to 1.44; $P = .009$), presence of secondary MDS (HR, 1.22; 95% CI, 1.01 to 1.47; $P = .04$), and advanced disease at transplantation (HR, 1.25; 95% CI, 1.07 to 1.47; $P = .005$). Although higher percentage of bone marrow blasts was associated with presence of blood blasts, bone marrow blast percentage alone was not prognostic of survival.

### *Validation of Prognostic Scoring System*

We then used the scoring system to calculate a risk score for individuals in the training cohort for whom complete data on all five variables were available (n = 839). On the basis of these data, we applied the score to the HLA-matched validation cohort (Table 3). Complete data for all variables were missing for 150 patients. We analyzed relapse and TRM incidence and OS in the patients with missing data versus those with complete data and found no difference in any of these outcomes. Therefore, the 150 patients with missing data were excluded, leaving 427 patients in the analysis. Among these 427 patients, the scoring system was associated with OS ($P < .001$; Table 3). The 3-year OS in the HLA-matched validation cohort was 71% (95% CI, 58% to 85%) in low-risk, 49% (95% CI, 42% to 56%) in intermediate-risk, 41% (95% CI, 31% to 51%) in high-risk, and 25% (95% CI, 4% to 46%) in very high–risk patients (Fig 1A).

Because the training set was developed based on OS and not other outcomes, we combined the 839 patients from the training cohort with the 427 patients from the validation cohort for analysis of secondary objectives (Table 4). In the combined HLA-matched cohort, the scoring system was associated with relapse ($P < .001$), TRM ($P < .001$), and DFS ($P < .001$).

### *Application of MDS Scoring System in HLA-Mismatched Cohort*

The prognostic score was applied to an additional cohort of 405 patients undergoing one to two HLA loci–mismatched allo HCT. Complete data were available for 289 patients, who were analyzed in this set. When compared with the HLA-matched cohort, HLA-mismatched patients were more likely to have poor-risk karyotype (11% *v* 16%; $P < .001$), undergo reduced-intensity conditioning (31% *v* 39%; $P = .003$), receive a bone marrow graft (19% *v* 25%; $P = .009$), or receive antithymocyte globulin or alemtuzumab with conditioning (29% *v* 43%; $P < .001$; Appendix Table A1). The 1-, 3-, and 5-year OS were 46%, 34%, and 27% in the HLA-mismatched cohort, respectively. In the HLA-mismatched cohort, the 3-year incidence of TRM was 42% (95% CI, 37% to 47%), and relapse was 25% (95% CI, 21% to 30%). The prognostic score was prognostic of relapse in this cohort ($P = .04$) but not TRM ($P = .82$), DFS ($P = .21$), or OS ($P = .13$; Fig 1B).

### *Comparison of Proposed Scoring System With IPSS and IPSS-R*

To determine if the proposed scoring system was superior to the IPSS or IPSS-R prognostic tool, we compared the three scoring systems in the HLA-matched validation set. We first generated a cross table of proposed patient classifications (rows), with IPSS-R classifications represented in colors on the *x*-axis (Fig 2). We found that the systems generally agreed on patients at very high risk; however, the proposed system resulted in significant reclassification of patients in the low-, intermediate-, and high-risk classifications. To quantify which prognostic system better fit actual outcomes, we calculated a concordance index including 384 patients for whom complete data were available for the IPSS, IPSS-R, and proposed systems. Concordance indices describe the probability that predicted and observed survival times are similar among ranked pairs within a given system.[22] As the prognostic capability

**Table 3.** OS by Prognostic Score in HLA-Matched Training and Validation Cohorts

| | Training Cohort | | | Validation Cohort | | |
|---|---|---|---|---|---|---|
| Risk Group | No. of Patients | HR (95% CI) | *P* | No. of Patients | HR (95% CI) | *P* |
| Low (0-1) | 98 | 1.00 | | 47 | 1.00 | |
| Intermediate (2-3) | 459 | 1.76 (1.24 to 2.49) | .0017 | 258 | 1.66 (1.01 to 2.71) | .045 |
| High (4-5) | 237 | 2.87 (1.99 to 4.14) | < .001 | 104 | 2.29 (1.35 to 3.87) | .002 |
| Very high (≥ 6) | 45 | 6.75 (4.28 to 10.67) | < .001 | 18 | 5.02 (2.48 to 10.15) | < .001 |
| Overall *P** | | | < .001 | | | < .001 |

Abbreviations: HR, hazard ratio; OS, overall survival.
*Wald test.

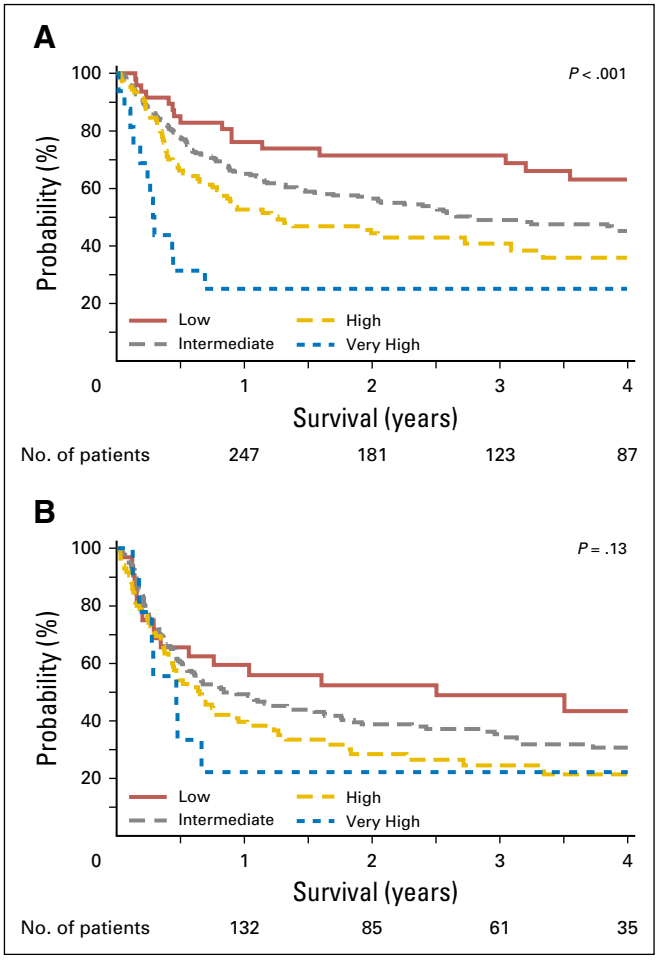


**Fig 1.** Overall survival in the (A) HLA-matched and (B) -mismatched cohorts by prognostic scoring system risk classification.

of a system improves, the concordance index will approach 1. We found the concordance index for the proposed scoring system to be 0.575, compared with 0.538 and 0.554 for the IPSS and IPSS-R, respectively, indicating a modest improvement in prognostic capability using the proposed model.

## DISCUSSION

Here we present a scoring tool prognostic of outcome in patients undergoing allo HCT for MDS. Using multivariable analysis, we identified pretransplantation thrombocytopenia, MDS comprehensive cytogenetic score, patient age, performance status, and increased blood blasts as having prognostic relevance to survival. Selection of patients for allo HCT is largely based on the IPSS and, more recently, the IPSS-R tools. Although both of these systems are prognostic of outcome after allo HCT, they were not generated specifically from patients undergoing transplantation and do not take into account non–disease-specific factors. A recent large-scale evaluation of the prognostic utility of the IPSS-R in patients undergoing transplantation conducted by the European Society for Blood and Marrow Transplantation (EBMT) found similar outcomes between the very good–, good-, and intermediate-risk groups as well as the poor- and very poor–risk groups.[23] These findings indicate that although the IPSS-R may account for disease-specific causes of death after transplantation, a system developed based on patient factors may offer more specificity to patients facing potential transplantation. Here we note that the proposed system generally agrees with the IPSS-R in the very high–risk subcategory; however, a significant portion of patients in high- and very high–risk IPSS-R groups were represented in the low- and intermediate-risk proposed scoring subcategories. The 3-year survival in patients classified as high risk with the IPSS-R was 75%; it was 57% in those classified as low or intermediate risk with the proposed system. The proposed system offers improved prognostic capability, particularly for patients in the low-, intermediate-, and high-risk subgroups. Similar to the IPSS-R, we identified cytogenetics as a major factor prognostic of outcome. As in the EBMT analysis and that conducted by Della Porta et al,[11] we found MK to offer prognostic relevance beyond the other karyotype classifications.[23-26] Outcomes in patients with MK are poor, indicating this group may benefit from strategies designed to prevent relapse after allo HCT.

More recently, Armand et al[27] defined the disease risk index (DRI) using a large data set of patients undergoing transplantation at Dana-Farber Cancer Institute. The DRI offers prognostic information for patients undergoing allo HCT based on disease risk and stage. In the context of MDS, the DRI defines two groups of MDS-specific risk based on cytogenetics. The authors additionally found that the HCT comorbidity score defined by Sorror et al[28] offered further prognostic information related to patient fitness before transplantation. In contrast, here we offer a single score that takes into account both patient- and disease-related factors to form a single prognostic score.

An important finding in this study is the absence of an association between conditioning intensity and outcome. An obvious limitation to this conclusion is bias introduced from the

**Table 4.** Relapse, TRM, and DFS in Combined HLA-Matched Training and Validation Cohorts by Prognostic Score

| | | Relapse | | TRM | | DFS | |
|---|---|---|---|---|---|---|---|
| Risk Score | No. of Patients | HR (95% CI) | *P* | HR (95% CI) | *P* | HR (95% CI) | *P* |
| Low | 139 | 1.00 | | 1.00 | | 1.00 | |
| Intermediate | 696 | 2.09 (1.3 to 3.36) | .002 | 1.40 (0.99 to 1.97) | .0582 | 1.63 (1.23 to 2.15) | < .001 |
| High | 332 | 3.71 (2.28 to 6.04) | < .001 | 1.92 (1.33 to 2.79) | < .001 | 2.53 (1.89 to 3.39) | < .001 |
| Very high | 60 | 7.49 (4.11 to 13.66) | < .001 | 4.43 (2.71 to 7.27) | < .001 | 5.47 (3.75 to 7.98) | < .001 |
| Overall *P* | | | < .001 | | < .001 | | < .001 |

Abbreviations: DFS, disease-free survival; HR, hazard ratio; TRM, treatment-related mortality.

  

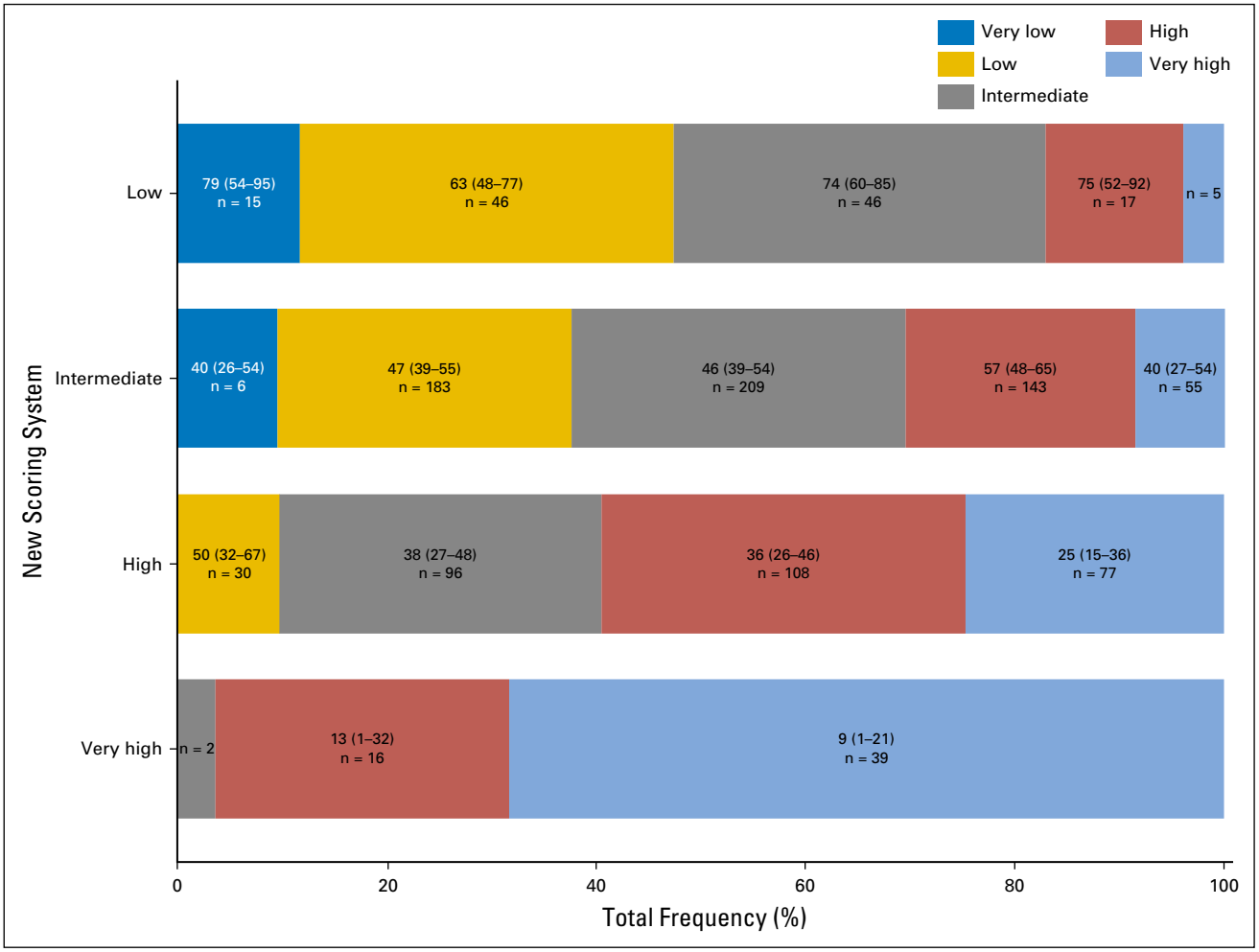


**Fig 2.** Categorization of patients according to the proposed prognostic system versus the revised International Prognostic Scoring System (IPSS-R). Colored bars represent IPSS-R risk stratification on the *x*-axis, within the stratification based on the new scoring system represented in rows. The 3-year survival (%; range) and number of patients for each IPSS-R group within the new scoring system is provided. Survival was omitted for groups with fewer than 10 patients.

use of retrospective registry data, where patients perceived as having greater disease-specific risk are encouraged to undergo myeloablative therapy. We did not find any significant demographic or disease-specific differences between patients undergoing reduced-intensity versus myeloablative conditioning; however, it is impossible to control for all variables in a cohort such as was analyzed here. Nevertheless, recent findings from a prospective, randomized study conducted by the EBMT (the RICMAC [Reduced Versus Standard Conditioning in MDS/Secondary Acute Myelogenous Leukemia] trial) seem to confirm that myeloablative conditioning does not confer a survival benefit.[29] It remains an open question whether specific, high-risk disease subsets would preferentially benefit from higher-intensity conditioning. Missing from this analysis are data on somatic mutations identified by genomic technologies that have more recently become relevant in MDS prognostication.[8] As these data become more relevant to therapeutic decisions, the next generation of prognostic tools will need to account for this information. A second limitation in this study is the use of Karnofsky performance status, which is subjective and can vary between clinicians or at different times during the transplantation evaluation. More-objective tools evaluating patient fitness, including the HCT comorbidity index, should be used as they become available in large patient data registries. Finally, although this scoring system demonstrated improved prognostic capacity over the IPSS-R, the magnitude of this benefit was limited, suggesting that incorporation of genomic aberrations will refine systems in the future.

Despite the limitations identified, the scoring system presented here is of use to clinicians evaluating patients with MDS. The scoring system uses readily available clinical data and can be calculated quickly, facilitating patient consultation with respect to allo HCT, and may also be used to identify high-risk populations where interventions such as post–allo HCT maintenance therapies may be of benefit.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

## AUTHOR CONTRIBUTIONS

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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

**Scoring System Prognostic of Outcome in Patients Undergoing Allogeneic Hematopoietic Cell Transplantation for Myelodysplastic Syndrome**

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## *Appendix*

**Table A1.** Demographic and Clinical Characteristics of HLA-Matched and -Mismatched Cohorts

| Variable | No. (%) Matched (n = 1,731) | No. (%) Mismatched (n = 405) | *P* |
|---|---|---|---|
| Age, years | | | .13 |
| Median | 56 | 55 | |
| Range | 18-77 | 18-73 | |
| Male sex | 1,045 (60) | 231 (57) | |
| KPS, % | | | .12 |
| 90-100 | 1,063 (61) | 253 (62) | |
| < 90 | 574 (33) | 140 (35) | |
| Missing | 94 (5) | 12 (3) | |
| Secondary disorder | | | .44 |
| Yes | 338 (20) | 85 (21) | |
| Missing | 47 (3) | 7 (2) | |
| Cytogenetic status | | | < .001 |
| MK positive | 289 (17) | 52 (13) | |
| Very good | 16 (< 1) | 1 (< 1) | |
| Good | 673 (39) | 134 (33) | |
| Intermediate | 403 (23) | 97 (24) | |
| Poor | 190 (11) | 66 (16) | |
| Very poor | 34 (2) | 5 (1) | |
| Missing | 126 (7) | 50 (12) | |
| Blast in marrow before HCT, % | | | .06 |
| ≤ 2 | 736 (43) | 162 (40) | |
| 2-5 | 357 (21) | 90 (22) | |
| 5-10 | 314 (18) | 73 (18) | |
| > 10 | 135 (8) | 47 (12) | |
| Missing | 189 (11) | 33 (8) | |
| Blast in blood before HCT, % | | | .10 |
| ≤ 3 | 1,325 (77) | 316 (78) | |
| > 3 | 127 (7) | 38 (9) | |
| Missing | 279 (16) | 51 (13) | |
| Platelet count before HCT, $\times 10^9$/L | | | .06 |
| ≤ 50 | 731 (42) | 197 (49) | |
| > 50 | 993 (57) | 206 (51) | |
| Missing | 7 (< 1) | 2 (< 1) | |
| ANC before HCT, /μL | | | .71 |
| ≥ 800 | 1,029 (59) | 235 (58) | |
| < 800 | 635 (37) | 151 (37) | |
| Missing | 67 (4) | 19 (5) | |
| Elevated LDH before HCT | 1,023 (59) | 243 (60) | .58 |
| No | 492 (28) | 119 (29) | |
| Yes | 216 (12) | 43 (11) | |
| Missing | | | |
| IPSS at diagnosis | | | .31 |
| Low | 41 (2) | 7 (2) | |
| Intermediate-1 | 627 (36) | 130 (32) | |
| Intermediate-2 | 583 (34) | 138 (34) | |
| High | 138 (8) | 34 (8) | |
| Missing | 342 (20) | 96 (24) | |
| Pretransplantation therapy | | | .71 |
| Hypomethylating agents only | 567 (33) | 132 (33) | |
| Chemotherapy only | 104 (6) | 19 (5) | |
| Both | 42 (2) | 7 (2) | |
| None | 971 (56) | 234 (58) | |
| Missing | 47 (3) | 13 (3) | |
| Conditioning regimen intensity | | | .003 |
| Myeloablative | 996 (58) | 215 (53) | |
| Reduced | 543 (31) | 156 (39) | |
| Nonmyeloablative | 159 (9) | 34 (8) | |
| Missing | 33 (2) | 0 | |
| Donor–recipient sex match | | | .48 |
| Male–Male | 693 (40) | 153 (38) | |
| Male–Female | 397 (23) | 89 (22) | |
| Female–Male | 342 (20) | 77 (19) | |
| Female–Female | 281 (16) | 81 (20) | |
| Missing | 18 (1) | 5 (1) | |
| Graft type | | | .009 |
| Bone marrow | 327 (19) | 100 (25) | |
| Peripheral blood | 1,404 (81) | 305 (75) | |
| Ex vivo T-cell depletion | 40 (2) | 13 (3) | .20 |
| ATG or alemtuzumab | 510 (29) | 174 (43) | < .001 |

Abbreviations: ANC, absolute neutrophil count; ATG, antithymocyte globulin; HCT, hematopoietic cell transplantation; IPSS, International Prognostic Scoring System; KPS, Karnofsky performance status; LDH, lactate dehydrogenase; MK, monosomal karyotype.

**Table A2.** Calculation of Prognostic Scoring System

| Prognostic Variable | Score Value 0 | 1 | 2 |
|---|---|---|---|
| Age, years | 18-29 | 30-49 | ≥ 50 |
| KPS, % | 90-100 | < 90 | |
| Comprehensive cytogenetic score* | Intermediate, good, or very good | Poor or very poor | MK |
| Blood blasts at transplantation, % | ≤ 3 | > 3 | |
| Platelet count at transplantation, $\times 10^9$/L | > 50 | ≤ 50 | |

Abbreviations: KPS, Karnofsky performance status; MK, monosomal karyotype.
*Very good, −Y and del(11q); good, normal, del(5q), del(12p), del(20q), and double including del(5q); intermediate, del(7q), +8, +19, i(17q), and any one or two abnormalities; poor, −7, inv(3), t(3q), del(3q), double including −7/del(7q), any three abnormalities; very poor, more than three abnormalities.