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Personalized Prediction Model to Risk Stratify Patients With Myelodysplastic Syndromes

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abstract

PURPOSE Patients with myelodysplastic syndromes (MDS) have a survival that can range from months to decades. Prognostic systems that incorporate advanced analytics of clinical, pathologic, and molecular data have the potential to more accurately and dynamically predict survival in patients receiving various therapies.

METHODS A total of 1,471 MDS patients with comprehensively annotated clinical and molecular data were included in a training cohort and analyzed using machine learning techniques. A random survival algorithm was used to build a prognostic model, which was then validated in external cohorts. The accuracy of the proposed model, compared with other established models, was assessed using a concordance (c)index.

RESULTS The median age for the training cohort was 71 years. Commonly mutated genes included *SF3B1*, *TET2*, and *ASXL1*. The algorithm identified chromosomal karyotype, platelet, hemoglobin levels, bone marrow blast percentage, age, other clinical variables, seven discrete gene mutations, and mutation number as having prognostic impact on overall and leukemia-free survivals. The model was validated in an independent external cohort of 465 patients, a cohort of patients with MDS treated in a prospective clinical trial, a cohort of patients with paired samples at different time points during the disease course, and a cohort of patients who underwent hematopoietic stem-cell transplantation.

CONCLUSION A personalized prediction model on the basis of clinical and genomic data outperformed established prognostic models in MDS. The new model was dynamic, predicting survival and leukemia transformation probabilities at different time points that are unique for a given patient, and can upstage and downstage patients into more appropriate risk categories.

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INTRODUCTION

Myelodysplastic Syndromes (MDS) are clonal hematopoietic disorders that lead to bone marrow failure and a risk of progression to acute myeloid leukemia (AML).[1] The outcomes of patients with MDS are heterogeneous, with some alive more than a decade following diagnosis and others dying within a few months. Accurately predicting outcome can help patients manage expectations for their disease trajectory and help physicians identify appropriate therapies.[2,3]

Established prognostic models rely primarily on clinical variables that are derived from bone marrow pathology and peripheral blood counts and divide patients into a handful of risk categories.[4] The most commonly used models in clinical practice and for clinical trial eligibility are the International Prognostic Scoring System (IPSS) and the revised IPSS (IPSS-R).[5,6] The recent addition of molecular data to these scoring systems has enhanced the accuracy of these models, allowing upstaging and downstaging of patients into more appropriate risk categories, although the increment in improving their accuracy is modest.[7,8] Furthermore, these prognostic models, many of which were developed in untreated patients, may underestimate or overestimate the actual survival of a patient, affecting treatment recommendations and prediction of disease course.[7,8]

In this study, we took advantage of a machine learning algorithm that can take into account clinical, pathologic, and molecular variables, as well as their interactions with each other, and developed and validated a prediction model that can provide a personalized prognosis that is specific for a given patient.

METHODS

Patient Cohort

Peripheral blood and bone marrow samples from patients diagnosed with MDS according to 2016 WHO criteria[9] (criteria were reviewed and updated for patients who were diagnosed before 2016) and evaluated at the Cleveland Clinic and Munich Leukemia laboratory between 2001 and 2018 were included in the

ASSOCIATED CONTENT

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

Build and validate a personalized prediction model using artificial intelligence.

Knowledge Generated

A personalized genoclinical model outperformed established prognostic models in myelodysplastic syndromes. The new model was dynamic, predicting survival and leukemia transformation probabilities at different time points that are unique for a given patient.

Relevance

The new model can be used as a stand-alone model or in conjunction with other established models to improve the predictability of outcomes in patients with myelodysplastic syndromes. It can also be used as a risk stratification tool for clinical trials enrollment.

training cohort. The training cohort was used to build the model that was subsequently validated in an independent cohort of patients with MDS treated at the Moffitt Cancer Center between 2005 and 2018. Karyotypes were classified using the International System for Cytogenetic Nomenclature Criteria. The IPSS and IPSS-R were calculated as described previously.[5,6]

All patients signed informed consent for their samples and data to be used in future studies, and the study was approved by each participating center's Institutional Review Board committee in accordance with Declaration of Helsinki. More details regarding the patient cohorts and samples are summarized in the Methods section of the Data Supplement (online only).

DNA Sequencing and Analysis

Targeted deep sequencing was performed on 38 genes that are commonly reported in commercial laboratories' genomic panels and have shown to have clinical impact in MDS and other myeloid malignancies. Annotation of the mutations was blinded from the clinical variables and performed by individuals not associated with the study. Detailed sequencing information is provided in the Methods section in the Data Supplement.

Statistical Analyses

Overall survival (OS) was defined as the time from diagnosis until death from any cause or censoring at the time that the patient was last known to be alive. Patients who underwent an allogeneic stem-cell transplant were censored at the time of the transplant. Stepwise Cox proportional hazard analyses were conducted to evaluate the prognostic impact of each mutation on OS and AML transformation in univariate analyses and after controlling for age and IPSS-R score. For AML transformation, death without AML transformation was considered to be a competing risk. A Bonferroni correction was used to identify significant mutations (a P value $< .002$ is considered significant instead of .05). To build the new model, clinical and mutational data were entered into random survival forest algorithm.[10] The algorithm randomly bootstraps the original data into two thirds, where the model is developed, and one third, where the model is internally validated. The process is repeated multiple times to assure reproducibility of the final result. Furthermore, the algorithm includes all the variables and takes into account the relationship between each variable and other variables and the desired outcome (Data Supplement). Missing variables are imputed using an internal function built into the algorithm (more details are given in the Methods section in the Data Supplement). To produce an easy-to-use and reliable model, only variables with a significant impact on the desired outcome were included using variable importance analysis (Data Supplement). The top variables that affected the desired outcome were chosen to build the final model. Given a significant overlap between the top variables that affected OS and leukemia transformation, we decided to have one combined model rather than two separate models to ease the communication and implementation of the final model. The performance of the proposed model, compared with other models, was assessed by Harrell concordance index (c-index). More details regarding the statistical analyses are included in the Statistical Analysis section in the Data Supplement.

RESULTS

Patient Characteristics

Data on 1,471 patients were used to build the new model. The clinical characteristics of the cohort are summarized in Table 1. The median age was 71 years (range, 19-99 years). Cytogenetic risk categories per IPSS-R included 65 patients (4%) with very good, 1,060 (72%) with good, 193 (13%) with intermediate, 60 (4%) with poor, and 93 (6%) with very poor risk. Risk stratification per IPSS-R included 749 (51%) with very low or low risk, 336 (23%) with intermediate, 182 (19%) with higher or very high risk, and 7% not calculated because of missing values. The clinical and mutational characteristics for the validation cohort compared with the training cohort as well the

treatment modalities in each cohort are summarized in the Data Supplement. The validation cohort has more patients with higher-risk disease and differs in the presence of some mutations compared with the training cohort (Data Supplement).

Molecular Landscape of MDS and Mutations Associations

To identify mutations associated with OS and AML transformation and to standardize the definition of mutation number or sample, we focused the analyses on 24 genes that were mutated in at least 30 patients in the study cohort (these genes are commonly included in commercial laboratory panels and have been shown to affect outcomes in our study and others[11,12]; Fig 1 and the Data Supplement). We identified at least one mutation of these genes in 1,149 patients (78%) with a median number of mutations per sample being 2 (range, 0-8). Gene mutation frequencies were consistent with those reported in previous studies.[11,12] We then evaluated the correlation of these genes with each other. Strong correlations were observed for *TP53* mutations and complex karyotype, *TP53* and chromosome seven abnormalities, and *STAG 2* or *RUNX1* with *ASXL1* mutations (Fig 1). *SF3B1* mutations were mutually exclusive with *TP53* mutations, complex karyotype, chromosome seven abnormalities, and *ASXL1*/*SRSF2*/*U2AF1* (Fig 1).

Impact of Mutations on OS

With a median follow-up of 43.6 months, the median OS was 32.2 months (range, 0.03-221.8 months). The impact of mutations on OS in univariate analyses and after adjustment for age and IPSS-R scores is summarized in Table 2. Using the Bonferroni correction, 10 mutations (*ASXL1*, *EZH2*, *IDH2*, *KRAS*, *NRAS*, *RAD21*, *RUNX1*, *SRSF2*, *STAG2*, and *TP53*) had a significant negative prognostic impact on OS, whereas only *SF3B1* was associated with favorable outcomes (Table 2 and Fig 2). Only seven mutations (with the exception of *KRAS*, *RUNX1*, and *SRSF2*) remained significant after adjustment for age and IPSS-R scores (Table 2 and Fig 2). In a multivariate analysis that included age, IPSS-R risk categories, and significant mutations in univariate analysis versus all 24 gene mutations regardless of their significance, the prognostic impact of some of these mutations fluctuated depending on the variables included in the model. For example, only mutations in *ASXL1*, *EZH2*, *KRAS*, *NRAS*, *RAD21*, *SF3B1*, and *TP53* were significant when only significant mutations in univariate analysis were added to the multivariate analysis, whereas more mutations (*ASXl1*, *CBL*, *EZH2*, *NRAS*, *RA21*, *SF3B1*, *TET2*, and *TP53*) were significant when adding all the 24 genes (Data Supplement).

We also investigated the impact of variant allelic frequency (VAF) of each mutation on OS. When VAF was used as a continuous variable, only *EZH2* (hazard ratio [HR] 6.27; 95% CI, 2.12 to 18.50; $P < .001$) had a negative adjusted (for age, IPSS-R risk categories, and the Bonferroni correction) impact on OS (Data Supplement).

Impact of Mutations on AML Transformation

A total of 231 patients (16%) had AML transformation during their disease course. The leukemia transformation rate in our cohort correlates with previous reports.[6,11] The impact of mutations on leukemia transformation in univariate analysis and after adjustment with age and IPSS-R is summarized in Table 2. In a multivariate analysis that included age, IPSS-R risk categories, and significant mutations in univariate analysis (after the Bonferroni correction) versus all 24 gene mutations regardless of their significance, the prognostic impact of some of these mutations on leukemia transformation also changed depending on the variables included in the model. For example, only mutations in *ASXL1, IDH2, PHF6, PTPN11, RAD21, RUNX1, SF3B1, STAG2*, and *TP53* were significant when only significant mutations in univariate analysis were added to the multivariate analysis, whereas more mutations (*ASXl1, IDH2, RAD21, RUNX1, SF3B1, SRSF2, STAG2*, and *TP53*) were significant when adding all the 24 genes (Data Supplement).

We also investigated the impact of VAF (as a continuous variable) on AML transformation. Only mutations in *ASXL1* (HR 1.08; 95% CI, 1.05 to 1.11; $P < .001$), *NPM1* (HR 12.02; 95% CI, 1.40 to 103; $P = .023$), *RUNX1* (HR 3.07; 95% CI, 0.26 to 35.8; $P = .019$), and *TET2* (HR 4.67; 95% CI, 1.38 to 15.83; $P = .013$) led to a higher likelihood of AML transformation (Data Supplement).

Mutation Number As an Independent Prognostic Variable

Mutation number can measure the mutational load of MDS, although its number depends on the number of genes that are included in the panel. Using the 24 genes that were mutated in ≥ 30 patients in our cohort, we found that the number of mutations had a significant impact on OS and leukemia transformation (Fig 3). This impact remained significant even after adjustment for age and IPSS-R categories (OS, HR 1.13; 95% CI, 1.07 to 1.19; $P < .001$) and (AML transformation, HR 1.45; 95% CI, 1.33 to 1.57; $P < .001$). More importantly, mutation number retained its prognostic impact even after the removal of *SF3B1* (OS, HR 1.29; 95% CI, 1.23 to 1.35; $P < .001$) (leukemia-free survival, HR 1.59; 95% CI, 1.48 to 1.71; $P < .001$) and *TP53* mutations (OS, HR 1.20; 95% CI, 1.14 to 1.26; $P < .001$) (AML transformation, HR 1.50; 95% CI, 1.39 to 1.62; $P < .001$).

Personalized Prediction Model

Variables that affected OS and leukemia transformation are shown in Figure 4 (ranked from the most to the least important). As expected, cytogenetic risk groups per IPSS-R were the most important variable for survival, whereas blast percentage was most important for AML transformation. Although there is a partial interaction between blast percentage and 2016 WHO criteria, both variables remained significant for OS and leukemia transformation and affected the final model accuracy. A total of seven mutations,

TABLE 1. Patient Clinical Characteristics

Parameter	Training Cohort (N = 1,471)
Median age, years (range)	71 (19-99)
Sex, female, No. (%)	486 (33)
MDS etiology, No. (%)	
Primary MDS	1,315 (89)
Secondary MDS	56 (4)
Therapy-related MDS	100 (7)
Patients who transformed to AML, No. (%)	231 (16)
Patients who received bone marrow transplant, No.	130
2016 WHO subtypes, No. (%)	
MDS with del5q abnormality	62 (4)
MDS MLD	358 (24)
MDS SLD	78 (5)
MDS with excess blasts—1	315 (21)
MDS with excess blasts—2	258 (18)
MDS-SLD/MLD-RS	351 (24)
MDS-U	49 (3)
Clinical characteristics	
Median white blood cell count, k/μL (range)	4.2 (0.6-82.6)
Median hemoglobin, g/dL (range)	9.9 (3.9-15.6)
Median platelets, k/μL (range)	120 (4-975)
Median absolute neutrophil count, k/μL (range)	2.1 (0-65.1)
Median absolute monocyte count, k/μL (range)	1.52 (0-6.5)
Median absolute lymphocyte count, k/μL (range)	5 (0-62)
Median bone marrow blast percentage (range)	4 (0-19)
Median peripheral blood blast percentage (range)	0 (0-15)
Bone marrow blasts, % < 5%, No. (%)	838 (57)
Bone marrow blasts, 5%-10%, No. (%)	408 (28)
Bone marrow blasts, > 10%, No. (%)	225 (15)
Cytogenetics per IPSS, No. (%)	
Good	1,045 (71)
Intermediate	246 (17)
Poor	180 (12)
Cytogenetics per IPSS-R, No. (%)	
Very good	65 (4)
Good	1,060 (72)
Intermediate	193 (13)
Poor	60 (4)
Very poor	93 (6)
IPSS risk categories, No. (%)	
Low	391 (27)
Intermediate-1	626 (43)
Intermediate-2	280 (19)
High	70 (5)
Missing[a]	104 (7)
IPSS-R risk categories, No. (%)	
Very low	318 (22)
Low	431 (29)
Intermediate	336 (23)
High	190 (13)
Very high	92 (6)
Missing[a]	104 (7)

Abbreviations: AML, acute myeloid leukemia; IPSS, International Prognostic Scoring System; IPSS-R, revised IPSS; MDS, myelodysplastic syndromes; MDS-U, MDS unclassifiable; MLD, multilineage dysplasia; RS, ring sideroblast; SLD, single lineage dysplasia.

[a]Missing is related to missing one or more of the clinical variables such as hemoglobin, platelets, or absolute neutrophil counts that are required for calculating the IPSS and IPSS-R scoring systems.

along with mutation number, affected OS and AML transformation (Fig 4). The final model internal cross-validation showed the c-index score of 0.74 (95% CI, 0.73 to 0.75) for OS and 0.81 (95% CI, 0.80 to 0.82) for leukemia transformation in the training cohort and 0.71 (95% CI, 0.73 to 0.75) and 0.84 (95% CI, 0.73 to 0.75) compared with IPSS 0.66 (95% CI, 0.62 to 0.67) and IPSS-R 0.67 (95% CI, 0.62 to 0.68) in the validation cohort, respectively (Fig 4), which included patients diagnosed at an independent center, who underwent sequencing analyses that used a different set of genes and sequencing method. The new model outperformed the IPSS and IPSS-R even when mutations were added to the scoring systems as described previously[7,8] (Fig 4). Furthermore, the proposed model was very well-calibrated in the training and validation cohorts for OS and leukemia transformation (Data Supplement).

To translate this model into a useful clinical tool, we built an online calculator[13] that can generate the survival and leukemia transformation probabilities at different time points in a patient's disease course using available clinical, laboratory, and molecular data.

Clinical Implications of the Proposed Model

As shown in Figure 4D, OS survival rates varied substantially even among patients in the same IPSS-R risk

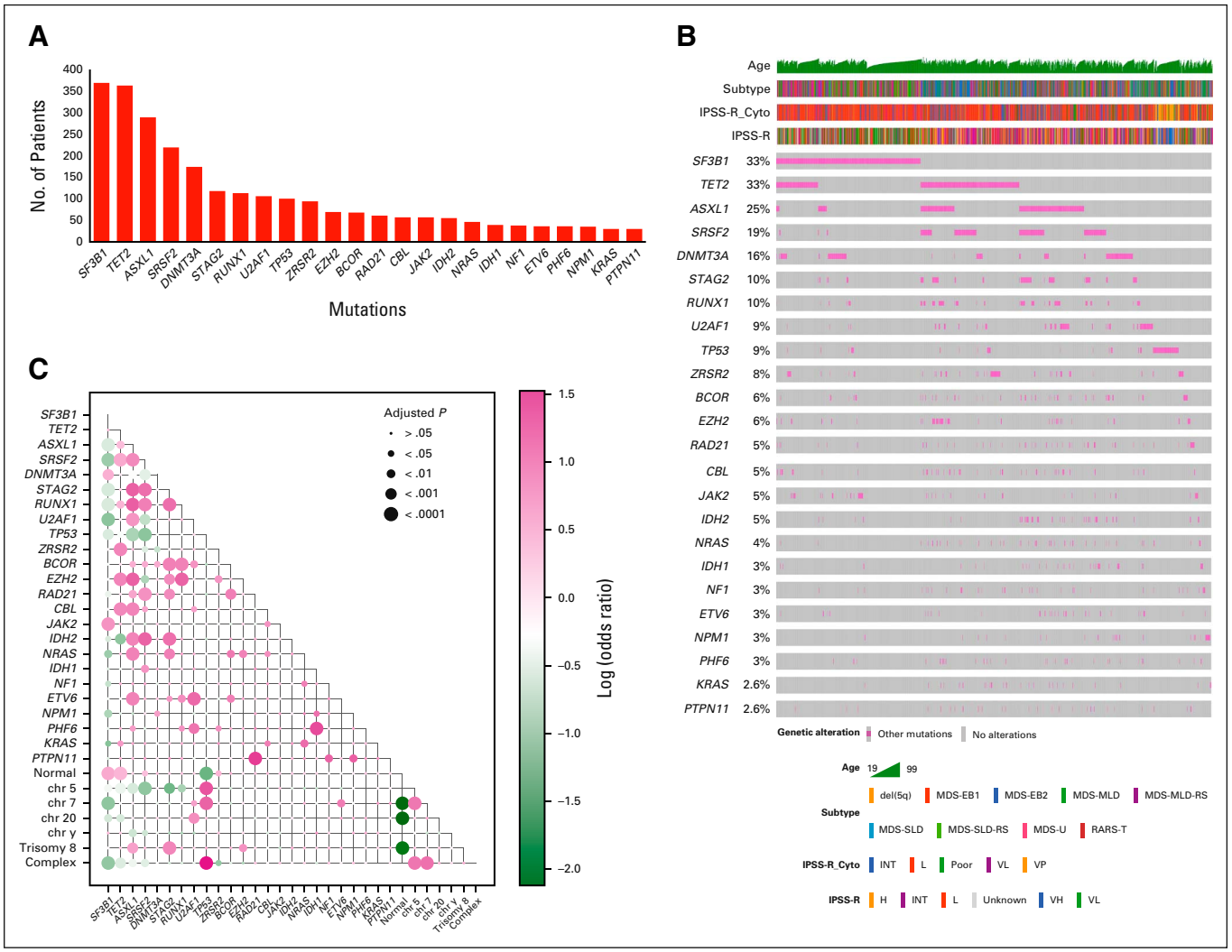

FIG 1. Genomic landscape of the training cohort: (A) the graph represents frequencies of recurrent gene mutations in this cohort, (B) the mosaic plot represents distributions of recurrent gene mutations in 1,471 patients, and (C) exclusivity and co-occurrence between different gene mutations. The circles were sized and colored according to their log (odds) from Fisher's exact test and person correlation (pink color represents co-occurrence, and green color represents exclusivity). H, high; INT, intermediate; IPSS-R, revised International Prognostic Scoring System; L, low; MDS, myelodysplastic syndromes; MDS-EB, MDS-excess blasts; MDS-U, MDS unclassifiable; MLD, multilineage dysplasia; OS, overall survival; RARS, refractory anemia with ring sideroblasts; RARS-T, RARS with thrombocytosis; RS, ring sideroblast; SLD, single lineage dysplasia; VH, very high; VP, very poor; VL, very low.

group. Applying the new model, patients with a survival probability < 50% at 18 months (patients with a median OS < 18 months) were considered higher-risk. Using the new model, 306 patients (20%) in the training cohort were identified as a higher-risk group; among them, 148 (48%) were classified as lower-risk per IPSS and 107 (35%) per IPSS-R (score ≤ 3.5)[14] (Fig 4D). Similarly, 73 patients (16%) in the validation cohort were classified as a higher-risk and 28 (39%) of them were classified as lower-risk per IPSS and 33 (45%) per IPSS-R (Fig 4D).

Validations of the New Model in Different Settings

To further assure the reproducibility of our model in different settings, we validated it in three different cohorts. First, we obtained clinical and mutational data from patients who participated in the prospective, phase II, North American Intergroup S1117 trial in which patients with higher-risk MDS and chronic myelomonocytic leukemia received azacitidine monotherapy or azacitidine combined with either lenalidomide or vorinostat. The study cohort and outcomes were described previously and are summarized in the Methods section in the Data Supplement. After excluding patients with chronic myelomonocytic leukemia, we identified 75 MDS patients with available clinical and genomic data. The clinical and mutational characteristics of this patient cohort are summarized in the Data Supplement. The cohort did not include absolute monocyte counts or absolute lymphocyte counts (not collected), and 37 patients (49%) had no karyotype results reported by the participating centers despite IPSS scores being reported for

TABLE 2. Impact of Mutations on OS and Leukemia Transformation in Cox Regression Model

		OS					Leukemia Transformation				
			Unadjusted		Adjusted			Unadjusted		Adjusted	
Variable	No.	No. of Events	HR (95% CI)	*P*	HR (95% CI)	*P*	No. of Events	HR (95% CI)	*P*	HR (95% CI)	*P*
ASXL1	289	195	1.78 (1.51 to 2.10)	< .001	1.41 (1.19 to 1.67)	< .001	82	2.42 (1.85 to 3.17)	< .001	2.17 (1.63 to 2.89)	< .001
BCOR	68	39	1.53 (1.11 to 2.11)	.01	1.24 (0.89 to 1.72)	.20	20	2.38 (1.50 to 3.76)	< .001	2.02 (1.24 to 3.29)	.005
BCORL1	25	11	0.80 (0.44 to 1.46)	.47	0.91 (0.50 to 1.66)	.76	3	0.79 (0.26 to 2.44)	.68	1.08 (0.34 to 3.40)	.89
CBL	57	35	1.54 (1.09 to 2.16)	.013	1.64 (1.17 to 2.31)	.004	10	1.05 (0.54 to 2.03)	.89	1.07 (0.54 to 2.13)	.85
CEBPA	14	7	1.38 (0.66 to 2.91)	.39	0.97 (0.46 to 2.05)	.93	2	1.05 (0.24 to 4.54)	.95	0.72 (0.17 to 3.15)	.67
DNMT3A	174	91	0.89 (0.71 to 1.11)	.30	0.92 (0.74 to 1.14)	.44	33	1.21 (0.83 to 1.76)	.32	1.33 (0.91 to 1.95)	.13
ETV6	36	25	1.34 (0.90 to 2.00)	.15	1.26 (0.85 to 1.88)	.26	10	1.80 (0.97 to 3.32)	.062	1.71 (0.90 to 3.27)	.10
EZH2	69	55	1.91 (1.45 to 2.52)	< .001	1.57 (1.19 to 2.08)	.002	18	1.73 (1.05 to 2.85)	.031	1.63 (0.98 to 2.71)	.059
FLT3	18	14	1.74 (1.03 to 2.96)	.039	2.23 (1.31 to 3.79)	.003	7	2.68 (1.26 to 5.69)	.01	2.85 (1.21 to 6.70)	.017
GATA2	13	6	1.23 (0.55 to 2.76)	.61	1.19 (0.53 to 2.66)	.68	3	1.72 (0.59 to 4.97)	.32	1.65 (0.57 to 4.74)	.36
IDH1	39	26	1.43 (0.96 to 2.11)	.076	1.52 (1.03 to 2.26)	.036	8	1.31 (0.65 to 2.63)	.45	1.34 (0.66 to 2.73)	.41
IDH2	55	40	1.70 (1.24 to 2.34)	.001	1.32 (0.96 to 1.82)	.09	24	3.71 (2.41 to 5.71)	< .001	3.48 (2.21 to 5.49)	< .001
JAK2	57	30	0.90 (0.62 to 1.30)	.57	0.90 (0.62 to 1.30)	.57	8	0.74 (0.35 to 1.57)	.43	0.84 (0.39 to 1.83)	.67
KDM6A	15	9	0.91 (0.47 to 1.75)	.77	1.10 (0.57 to 2.13)	.77	2	0.71 (0.19 to 2.70)	.62	0.85 (0.22 to 3.29)	.81
KIT	13	6	1.30 (0.58 to 2.89)	.53	1.26 (0.56 to 2.83)	.58	2	1.13 (0.30 to 4.28)	.86	1.13 (0.29 to 4.45)	.86
KRAS	30	23	2.08 (1.37 to 3.14)	< .001	1.83 (1.21 to 2.78)	.004	6	1.34 (0.57 to 3.13)	.50	1.05 (0.44 to 2.51)	.91
NF1	38	25	1.46 (0.98 to 2.18)	.063	1.55 (1.04 to 2.32)	.031	8	1.34 (0.65 to 2.73)	.43	1.23 (0.59 to 2.55)	.59
NPM1	35	24	1.83 (1.22 to 2.75)	.004	1.38 (0.91 to 2.09)	.12	10	1.92 (0.98 to 3.76)	.059	1.95 (1.00 to 3.80)	.051
NRAS	46	35	2.73 (1.94 to 3.85)	< .001	1.84 (1.30 to 2.60)	< .001	13	2.24 (1.26 to 4.00)	.006	1.50 (0.80 to 2.81)	.20
PHF6	36	26	1.43 (0.97 to 2.12)	.072	1.24 (0.84 to 1.85)	.28	13	2.50 (1.44 to 4.36)	.001	2.26 (1.25 to 4.06)	.007
PTPN11	29	22	1.83 (1.19 to 2.79)	.005	1.84 (1.20 to 2.81)	.005	14	3.94 (2.18 to 7.12)	< .001	4.24 (2.25 to 7.99)	< .001
RAD21	61	46	2.24 (1.66 to 3.02)	< .001	1.80 (1.33 to 2.44)	< .001	24	3.27 (2.16 to 4.96)	< .001	2.98 (1.85 to 4.79)	< .001
RUNX1	113	86	2.37 (1.89 to 2.97)	< .001	1.44 (1.13 to 1.83)	.003	43	3.28 (2.35 to 4.58)	< .001	2.43 (1.67 to 3.53)	< .001
SF3B1	369	147	0.48 (0.40 to 0.58)	< .001	0.62 (0.51 to 0.75)	< .001	25	0.32 (0.21 to 0.48)	< .001	0.44 (0.28 to 0.67)	< .001
SRSF2	219	146	1.70 (1.42 to 2.04)	< .001	1.22 (1.01 to 1.48)	.035	61	2.16 (1.61 to 2.89)	< .001	1.99 (1.43 to 2.77)	< .001
STAG2	118	88	2.48 (1.98 to 3.11)	< .001	1.50 (1.18 to 1.90)	< .001	43	3.23 (2.28 to 4.56)	< .001	2.57 (1.79 to 3.70)	< .001
TET2	363	183	0.88 (0.75 to 1.04)	.15	0.73 (0.61 to 0.86)	< .001	63	1.11 (0.83 to 1.49)	.47	1.16 (0.85 to 1.59)	.34
TP53	100	74	3.10 (2.43 to 3.95)	< .001	1.98 (1.53 to 2.56)	< .001	19	1.35 (0.84 to 2.19)	.22	0.72 (0.43 to 1.22)	.22
U2AF1	106	68	1.46 (1.14 to 1.87)	.003	1.31 (1.02 to 1.68)	.034	27	1.80 (1.20 to 2.70)	.004	1.69 (1.11 to 2.56)	.014
U2AF2	8	5	2.57 (1.07 to 6.22)	.036	1.74 (0.72 to 4.24)	.22	2	2.24 (0.54 to 9.20)	.26	1.55 (0.32 to 7.63)	.59
WT1	11	6	1.06 (0.48 to 2.38)	.88	0.91 (0.40 to 2.05)	.82	4	2.71 (1.07 to 6.84)	.035	2.09 (0.72 to 6.01)	.17
ZRSR2	94	48	0.84 (0.63 to 1.12)	.24	0.85 (0.63 to 1.14)	.27	17	1.10 (0.68 to 1.81)	.69	1.24 (0.75 to 2.04)	.40

Abbreviations: HR, hazard ratio; OS, overall survival.

all patients. We compared our model with the IPSS scoring system only to assure the accuracy of the comparison.

When applying our model to this patient cohort, the c-index for our model was 0.68 compared with 0.57 for the IPSS scoring system. Although this trial targeted patients with higher-risk MDS per the IPSS scoring system, our model identified 24 patients (32%) as being higher-risk (considering patients with a survival probability of < 50% at 18 months) and 51 (68%) as lower-risk. In total, 37 patients (64%) with higher-risk disease per the IPSS (26 of 39 with intermediate-2 risk and 11 or 19 in high-risk categories) were downstaged by our model, whereas 3 of 17 patients in the Intermediate-1 risk group were upstaged to a higher-risk category. Interestingly, the median OS for the patients who were downstaged using our model was 26.1 months (95% CI, 12.5 to 45.6) compared with 16 months (95% CI, 12.3 to 35.3; $P = .33$) for patients without changes in their risk category. Furthermore, the median OS for patients who were identified as higher-risk by our model and by the IPSS scoring system (unchanged category) was 12.5 months for patients (n = 7) who received azacitidine treatment compared with 25.8 months for patients who received azacitidine plus lenalidomide (n = 9) and 14.9 months for patients who received azacitidine plus vorinostat (n = 8). However, the median OS for patients who were downstaged by our model was 28, 16.6, and 36.1 months, respectively.

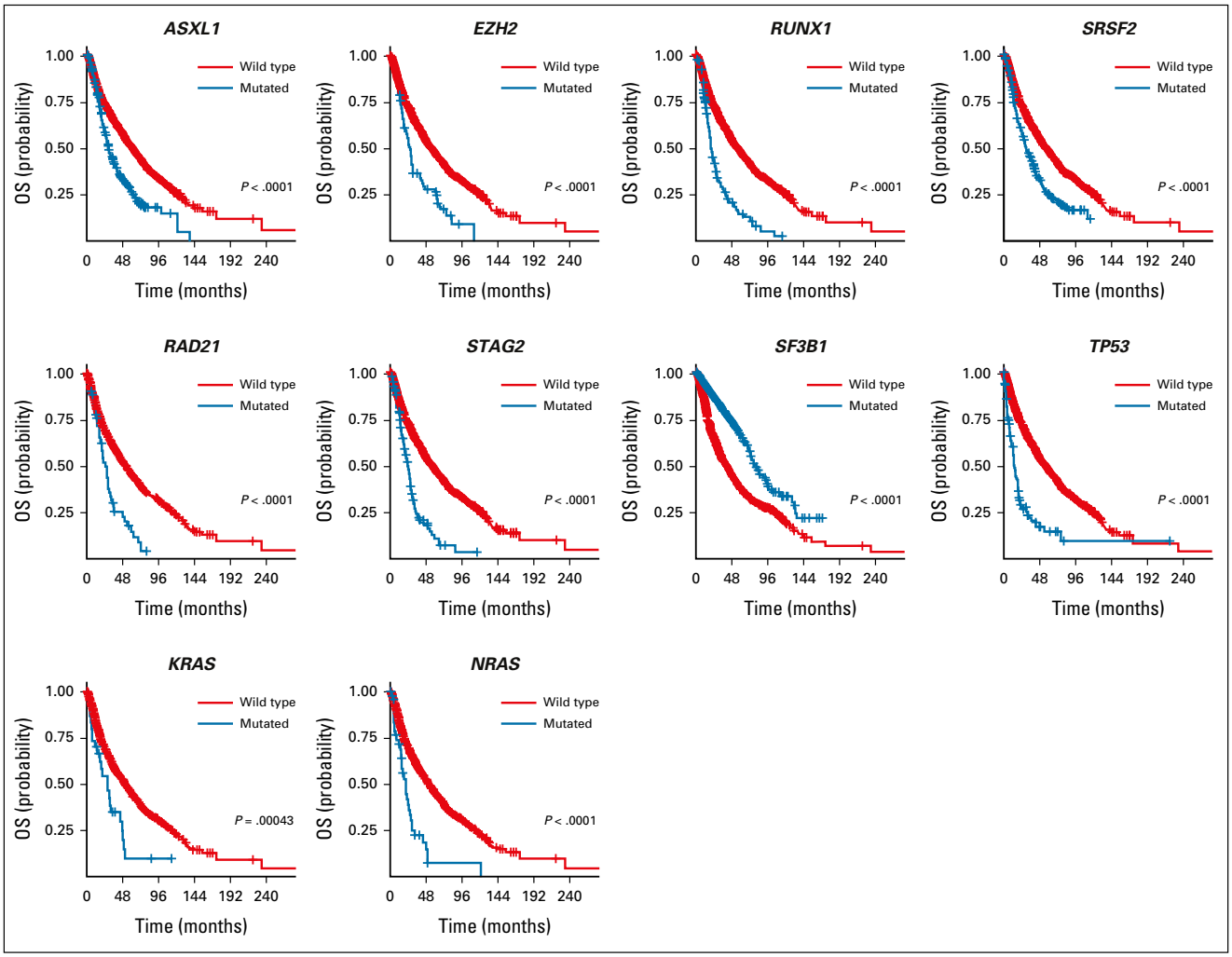

FIG 2. Impact of mutations on OS. Kaplan-Meier curves comparing the OS of patients with a mutated gene (blue) compared with a wild type (red). Only significant mutations after Bonferroni correction are shown. OS, overall survival.

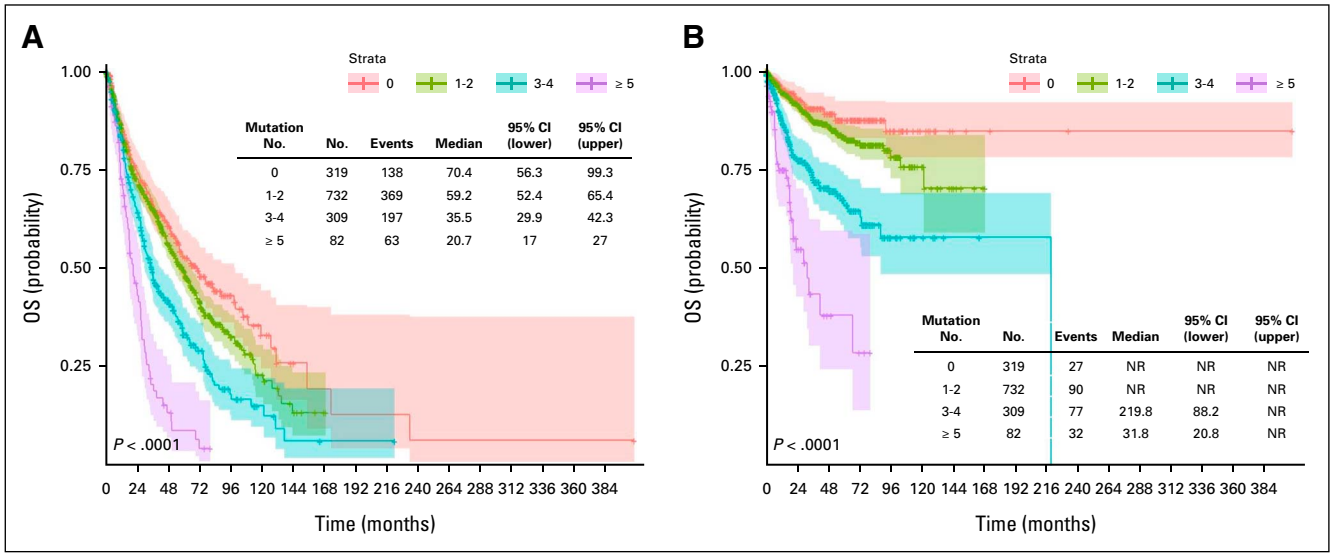

FIG 3. OS and leukemia-free survival on the basis of mutation number: (A) Kaplan-Meier curves for OS on the basis of mutation number and (B) Kaplan-Meier curves for leukemia-free survival on the basis of mutation number. NR, no response; OS, overall survival.

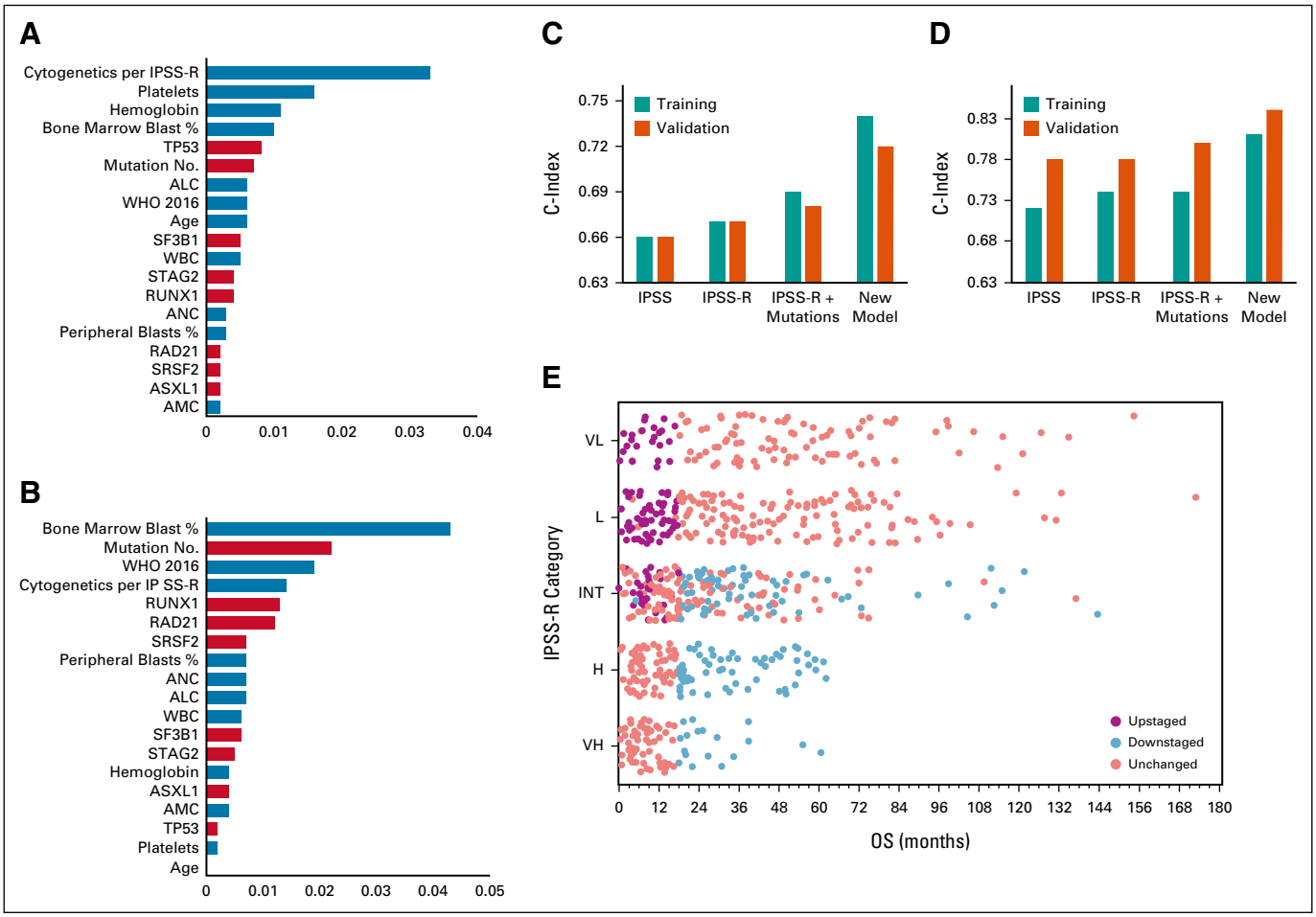

FIG 4. New model variables and performance matrix: (A) variable importance analysis showing the top variables from the most important to the least important that affect OS in the new model, the blue color represents clinical variables, and the orange color represents mutations; (B) variable importance analysis showing the top variables from the most important to the least important that affect leukemia transformation in the new model; the concordance index of the new model compared with that of IPSS and IPSS-R for (C) OS and (D) leukemia transformation in the training and validation cohorts; and (E) survival time from diagnosis to death in the training cohort on the basis of the IPSS-R risk categories; dots represent patients and their survival in each risk categories (only patients who died are included in this figure). Purple dots represent patients who were upstaged by the new model, and blue dots represent patients who were downstaged by the new model. ALC, absolute lymphocyte count; AMC, absolute monocyte count; ANC, absolute neutrophil count; H, high; INT, intermediate; IPSS, International Prognostic Scoring System; IPSS-R, revised IPSS; L, low; OS, overall survival; VL, very low; VH = very high.

These findings suggest that patients with lower-risk disease by our model had a shorter survival when they received azacitidine plus lenalidomide, whereas truly higher-risk patients might have benefitted from the combination, although small numbers precluded significant conclusions.

We also validated our model in a cohort of patients with paired samples from different time points during the disease course and another cohort of patients who underwent allogeneic hematopoietic stem-cell transplantation (HCT). More details on the characteristics of these cohorts and the performance of our model compared with the IPSS/IPSS are summarized in the Data Supplement.

DISCUSSION

In this study, we developed a prognostic model that uses clinical and mutational data to provide estimates of the risk of death or progression to AML that are specific for a given patient. The proposed model significantly outperformed the IPSS and IPSS-R scoring systems (the most widely used systems in clinical practice and trial eligibility). To assure the reproducibility and generalizability of the model and its applicability in routine or real-world patients, our training cohort represents a diverse MDS population treated at centers in the United States and Europe and was validated in an independent cohort and a cohort of patients with MDS who were enrolled on a prospective clinical trial. In these cohorts, our model significantly outperformed the IPSS and IPSS-R scoring systems and indicated a possible different impact of treatment on the basis of the new classification by our model. We also validated our model in a patient cohort with paired samples at different time points and demonstrated the stability of our model performance over time compared with the IPSS/IPSS-R scoring systems. Although

our model c-index was better compared with that of the IPSS/IPSS-R when applied to a cohort who received HCT, the drop in the performance of all models may be related to the lack of clinical and mutational variables that affect transplant-related outcomes, such as graft versus host disease. We have previously shown that transplant-related factors such as donor age, graft type, conditioning regimen, and others have a significant impact on the personalized prediction for patients with MDS before the transplant.

Recent efforts to improve the accuracy of established clinical prognostic scoring systems included the addition of molecular data or the development of gene-only prognostic models.[7,8,12,15] These approaches have shown that the addition of selected gene mutations to established models such as the IPSS and IPSS-R can improve their predictive power and can upstage or downstage patients into more appropriate risk categories. Another study tried to build a gene-only model after controlling for clinical variables, but the model underperformed compared with a genoclinical model.[12] The incremental improvement in the model's performance when molecular data were added was modest, though, suggesting that ad hoc inclusion of other variables, analyzed using traditional statistical methods, is not enough.

Our study has some limitations. Recent studies have shown that patient-reported outcomes and frailty scores have a significant impact on OS and that adding such variables can improve the accuracy of prognostication. Such data were not available for inclusion in the final model. Although our patient cohort is large, the significant impact of infrequent mutations on outcomes can be too small and misleading. Thus, we focused our analyses on the top 24 genes that are mutated in more than 30 patients and the seven genes that were included in our final model were among the top 10 mutated genes in our cohort and other previous reports.[11,12] Although we controlled for patients who proceeded with HCT by censoring at the time of transplant, we did not control for specific treatment modalities, since not all patients had treatment data recorded in our data set. The impact of treatments (such as hypomethylating agents) on the performance of the model is minimal and only seen in a subset of higher-risk patients. Furthermore, our model was validated in four different validation cohorts at different settings including patients who received hypomethylating agents on a clinical trial. Finally, our model includes age as an important prognostic variable although younger patients with MDS generally have a greater loss of life (in years) than older patients. Thus, including age in prognostic scores may lead to less intensive treatment in younger patients since they have better OS.

In conclusion, we built and validated a personalized prediction model that can provide survival and leukemia transformation probability at MDS diagnosis and throughout a patient's disease course. The model outperformed other existing models that are used in clinical practice, for clinical trial eligibility, and the timing of transplant. This model can be used as a stand-alone model or in conjunction with the IPSS/IPSS-R scoring systems to improve their accuracy.

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REFERENCES

1. Tefferi A, Vardiman JW: Myelodysplastic syndromes. N Engl J Med 361:1872-1885, 2009
2. Greenberg PL, Stone RM, Al-Kali A, et al: Myelodysplastic syndromes, version 2.2017, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 15:60-87, 2017
3. Fenaux P, Haase D, Sanz GF, et al: Myelodysplastic syndromes: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 25: iii57-iii69, 2014 (suppl 3)
4. Nazha A: The MDS genomics-prognosis symbiosis. Hematology Am Soc Hematol Educ Program 2018:270-276, 2018
5. Greenberg P, Cox C, LeBeau MM, et al: International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood 89:2079-2088, 1997
6. Greenberg PL, Tuechler H, Schanz J, et al: Revised international prognostic scoring system for myelodysplastic syndromes. Blood 120:2454-2465, 2012
7. Nazha A, Narkhede M, Radivoyevitch T, et al: Incorporation of molecular data into the Revised International Prognostic Scoring System in treated patients with myelodysplastic syndromes. Leukemia 30:2214-2220, 2016
8. Nazha A, Al-Issa K, Hamilton BK, et al: Adding molecular data to prognostic models can improve predictive power in treated patients with myelodysplastic syndromes. Leukemia 31:2848-2850, 2017
9. Arber DA, Orazi A, Hasserjian R, et al: The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood 127: 2391-2405, 2016
10. Ishwaran H, Kogalur UB, Chen X, et al: Random survival forests for high-dimensional data. Stat Anal Data Mining 4:115-132, 2011
11. Papaemmanuil E, Gerstung M, Malcovati L, et al: Clinical and biological implications of driver mutations in myelodysplastic syndromes. Blood 122:3616-3627, 2013
12. Haferlach T, Nagata Y, Grossmann V, et al: Landscape of genetic lesions in 944 patients with myelodysplastic syndromes. Leukemia 28:241-247, 2014
13. Personalized Prediction Model for Myelodysplastic Syndromes. https://azizn38.shinyapps.io/final/
14. Pfeilstocker M, Tuechler H, Sanz G, et al: Time-dependent changes in mortality and transformation risk in MDS. Blood 128:902-910, 2016
15. Bejar R, Stevenson K, Abdel-Wahab O, et al: Clinical effect of point mutations in myelodysplastic syndromes. N Engl J Med 364:2496-2506, 2011

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Personalized Prediction Model to Risk Stratify Patients With Myelodysplastic Syndromes

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