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Impact of a Novel Prognostic Model, Hematopoietic Cell Transplant -Composite Risk (HCT-CR), on Allogeneic Transplant Outcomes in Patients with Acute Myeloid Leukemia and Myelodysplastic syndrome

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Abstract

Outcomes after allogeneic stem-cell transplantion (AHSCT) are influenced by both disease and patient related factors. Here we developed a novel prognostic model, Hematopoietic Cell Transplant -Composite Risk (HCT-CR), by combining the refined disease risk index (DRI-R) and hematopoietic stem-cell transplant comorbidity/age index (HCT-CI/Age) to predict post-transplant survival for patients with acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS). The analysis included 942 AML/MDS patients treated with AHSCT. Patients were stratified into 4 HCT-CR risk groups: **Low-risk** - Patients with low/intermediate DRI-R and HCT-CI/Age </=3 (N=272); **Intermediate-risk** - Patients with low/intermediate DRI-R and HCT-CI/Age >3 (N=168); **High-risk** - Patients with high/very high DRI-R and HCT-CI/Age </=3 (N=284); and **Very high-risk** - Patients with high/very high DRI-R and HCT-CI/Age >3 (N=184). Compared with low-risk group, intermediate, high and very high-risk group had significantly increased risk of death [adjusted HR of 1.37 (P0.04), 2.08 (P<0.001) and 2.92 (P<0.001), respectively]. The concordance test showed that the HCT-CR model provided better discriminative capacity for OS prediction compared with all prior models independently, including cytogenetic risk group, DRI-R and HCT-CI/Age model (C-indices 0.62, 0.55, 0.60 and 0.54, respectively) (P<0.001). In conclusion, combining disease and patient-related factors provides better survival stratification for patients with AML/MDS receiving AHSCT.

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Authorship contribution

P.K. contributed with study design, data analysis, interpretation and wrote the manuscript; S.P. interpretation of the study results, reviewed and approved the manuscript; D.R.M contributed with data analysis, interpretation of the results, wrote, reviewed and approved the manuscript; J.M.R.P contributed with manuscript writing, reviewed and approved the manuscript; G.R., J.C, A.C contributed with data collection, reviewed and approved the manuscript; G.A, A.A., B.S.A, J.S.I., C.M.H., Q.B, I.K, P.K., B.O, B.S.A, U.P, R.E.C contributed with treatment of patients, reviewed and approved the manuscript; S.O.C. contributed with study design, data collection and interpretation of results, and manuscript writing.

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Keywords

Acute myeloid leukemia; Myelodysplastic syndrome; Refined-disease risk index; Hematopoietic stem-cell transplant comorbidity-age index; Cytogenetic risk

INTRODUCTION

Allogeneic hematopoietic stem-cell transplantation (AHSCT) has demonstrated curative potential for patients with acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), in particular for patients with high-risk disease, which otherwise have dismal survival.(1, 2) Over the past decade, several important advances have been made to overcome limitations of AHSCT, including better understanding of prognosis for patients undergoing transplantation, as well as the use of alternative donors, especially the use of haploidentical donors for transplantation.(3–6) However, procedure-related mortality and survival may vary greatly depending on patient, disease as well as transplant characteristics, and it remains a major challenge to better assess survival based on multiple different factors influencing transplant outcomes.

Several prognostic models have been developed to estimate the risks, predict outcomes and help with decision-making and prognostic counseling before transplant.(7–10) Among these, the hematopoietic stem cell transplantation comorbidity index (HCT-CI) is the most commonly used for the prediction of transplant-related mortality.(9) Even though, its predictive accuracy has improved with the incorporation of age in the model (comorbidity/age index; HCT-CI/Age)(8), the predictive ability for post-transplant survival remains suboptimal,(11–14) in part due to both HCT-CI and HCT-CI/Age being based solely on patient's organ function at the time of transplant but disease related characteristics which reflect disease aggressiveness and its inherent resistance to therapy are not accounted for in the models. Moreover, the comorbidity index models were developed in patients receiving AHSCT from HLA-matched related and unrelated donors. Whether they can be used in transplantation using other donor types remains to be clarified.

The disease risk index (DRI)(15) and the refined-DRI (DRI-R)(16), on the other hand, have been created based exclusively on disease specific characteristics and remission status before transplant to help predict post-transplant survival and to diminish heterogeneity of the study population when outcomes of several diseases are reported together. However, both the DRI and DRI-R models do not capture patient characteristics, which could have major influence on a process of transplant patient selection and prediction of procedure-related mortality.

Here we hypothesized that a prognostic scheme that includes both patient comorbidities and disease characteristics would be more suitable for both patient selection and post-transplant outcome prediction. Therefore, in this study, we proposed to develop a new composite risk model of the DRI-R(16) which represents disease characteristics and HCT-CI/Age(8) by using the large database of patients with AML and MDS who underwent AHSCT with various donor types at The University of Texas MD Anderson Cancer Center (UTMDACC). The goal was to help transplant physicians more accurately account for the impact of age,

comorbidities as well as disease characteristics when estimating survival outcomes and making treatment decisions for patients receiving AHSCT.

METHODS

Patient population and transplant procedures

The study included consecutively treated patients, 18 years of age or older with a diagnosis of AML and MDS who received first AHSCT from HLA-matched related (MRD), HLA-matched unrelated (MUD), HLA one antigen mismatched related (MMRD), HLA mismatched unrelated (MMUD) and T-cell replete haploidentical (HAPLO) donor transplants at UTMDACC between 2005-2016.

Donor types were defined according to previously described criteria.(17) Conditioning regimens varied; most patients received fludarabine in combination with an alkylating agent, either busulfan or melphalan. The cytogenetic risk groups were determined at diagnosis according to the transplantation-specific cytogenetics grouping scheme for patients with AML(18) and MDS(19).

All patients provided written informed consent for transplant in accordance with the Declaration of Helsinki. The Institutional Review Board of UTMDACC approved a retrospective data review protocol for this analysis.

Outcomes and Statistical analysis

Primary outcome was overall survival (OS), while progression-free survival (PFS), non-relapse mortality (NRM; defined as death related to transplant during continuous complete remission) and relapse incidence were assessed as secondary outcomes. OS and NRM were computed from date of AHSCT to last known vital sign. Patients alive at the last follow-up date were censored. PFS was computed from date of AHSCT to date of disease progression, death or the last evaluation date. Patients who were alive and did not experience progression of disease at the last follow-up date were censored. Relapse incidence was computed from date of AHSCT to date of disease relapsed; patients who did not experience the event were censored. The Kaplan-Meier method was used to estimate all survival measures. Differences in survival between groups were assessed using the log-rank test. Associations between OS and potential prognostic factors were determined using univariable and multivariable Cox proportional hazards regression models. All variables of interest were tested for the proportional hazard assumption and interaction terms. The cumulative incidence of relapse and NRM were evaluated by the competing risks method where death was the competing risk for relapse and relapse was the competing risk for NRM. Differences in cumulative incidence between subgroups were assessed using Gray's test.(20)

The analyses were done using the complete-case method without data imputation. All P values were 2-sided at a significance level of 0.05.

Model development

The disease risk groups were categorized as low, intermediate, high and very high risk according to the DRI-R (Supplemental Table 1).(16) Age and comorbidities were assessed to calculate the HCT-CI/Age score.(8)

Patients from the whole cohort were then randomly assigned into a training cohort, comprising two-third of the patients, and validation cohort, comprising the remaining one-third of the patients.

To stratify patients into risk groups of a hematopoietic cell transplant – composite risk (HCT-CR), the classification and regression trees (CART) analysis for OS incorporating the impact of HCT-CI/Age and DRI-R was applied to patients in the whole dataset using split criteria of p value <0.05.

The CART analysis using the same condition was also applied to patients in the training cohort to confirm the reproducibility of the model.

Post-transplant outcomes including OS, PFS, and cumulative incidence of NRM and relapse of patients in each risk group were assessed. Univariable and multivariable Cox regression analysis were used to calculated crude and adjusted hazard ratio (HR) for OS of each risk group. Potential prognostic factors adjusted in the multivariable models were age (>60 vs. </=60), gender, donor type, conditioning regimen intensity (reduced intensity vs. myeloablative), stem cell source (peripheral blood vs. bone marrow) and transplant protocol (standard of care vs. on protocol).

Internal validation

Two methods of internal validation were used to test the stability of the HCT-CR model. The first validation was done using bootstrap resampling method. In the bootstrap procedure, new 500 data sets of all patients with risk group information were created by random sampling of the original data with replacement. In each new bootstrap data set, a patient might be represented once, multiple times or not at all.(21, 22) Multivariable Cox proportional hazards regression with the same condition as in the original data set was then calculated for the new data sets in order to obtain the bootstrap parameter estimates.

The discrimination power of the HCT-CR model on OS was compared with that of the DRI-R, HCT-CI/Age and cytogenetic risk model by the Harrell's C-concordance index: a C-index of 0.50 indicates a model that does not discriminate better than chance alone and a C-index of 1.00 indicates perfect discrimination. Moreover, goodness of fit of each model was compared with the HCT-CR model using the likelihood ratio test.

To confirm the model stability, the second method of internal validation using Cox regression analysis using the same condition was applied to data in a validation cohort.

RESULTS

The analysis included 942 patients, 492 male (52%) and 450 female (48%) with a median age of 53 years (range 18–65 years). Five hundred and forty-six patients (58%) were in first

or second complete remission. Cytogenetic data at diagnosis was available in 928 (98.5%) patients and was favorable, intermediate and adverse cytogenetic risk in 63 (7%), 523 (56%) and 342 (37%), respectively. Fifty-five (6%), 399 (43%), 392 (42%) and 82 (9%) patients had low, intermediate, high and very high DRI-R, respectively. The HCT-CI/Age was available in 922 (98%) patients with the median score of 3 (range 0-18). Donor types included MRD (n=377, 40%), MUD (n=416, 44%), MMUD (n=68, 7%), HAPLO (n=73, 8%) and MMRD (N=8, 1%). The sources of hematopoietic stem cells were peripheral blood for 589 patients (63%) and bone marrow for 353 patients (37%). Seven hundred and eighty-seven patients (84%) received myeloablative-conditioning chemotherapy. Baseline patient characteristics are summarized in Table 1. Missing data of all variables were less than 5%.

Transplant outcomes

Median follow-up duration for 436 survivors was 48 months. Nine hundred and seventeen patients (97%) engrafted with a median time to neutrophil and platelet engraftment of 12 days and 14 days, respectively.

For the entire group, the cumulative incidence of NRM was 17% and 22% at 1 and 5 years, respectively. At 5 years post-transplant, OS, PFS and cumulative incidence of relapse were 42%, 39% and 39%, respectively.

Development of the HCT-CR model

Total 908 of 942 patients (96.4%) had data on both DRI-R and HCT-CI/Age available. Six hundred and 308 patients were randomly assigned into training and validation set, respectively.

To develop the HCT-CR model using CART analysis for OS in the training cohort, patients were stratified into 4 risk groups; patients with low or intermediate DRI-R and HCT-CI/Age </=3 (low-risk, N=163); patients with low or intermediate DRI-R and HCT-CI/Age >3 (intermediate-risk, N=132); patients with high or very high DRI-R and HCT-CI/Age </=3 (high-risk, N=172); and patients with high or very high DRI-R and HCT-CI/Age >3 (very high-risk, N=133) (Figure 1).

The similar 4 risk groups were created when CART analysis was performed in all patients cohort.

Impact of the HCT-CR model on transplant outcomes

Applying the HCT-CR model to all patients, patients were stratified into 4 risk groups: low (N=272), intermediate (N=168), high (N=284) and very high-risk (N=184), with significantly different survival. The 5-year OS rates for patients in low, intermediate, high and very high-risk group were 57%, 48%, 34%, and 26%, respectively (P<0.001) (Figure 2A). Results for PFS were consistent with those observed for OS. The probability of 5-year PFS rates were 55%, 46%, 30% and 23% for these 4 risk groups, respectively (P<0.001) (Supplemental Figure 1). Post-transplant survival and cumulative incidence of NRM and relapse are summarized in Table 2.

Compared with the low HCT-CR risk group, patients with intermediate, high and very high-risk group had a significantly increased risk of death with HR of 1.42 (95%CI 1.06-1.91; P=0.02), 2.11 (95%CI 1.65-2.70; P<0.001), and 3.02 (95%CI 2.32-3.92; P<0.001), respectively. Results for the association between OS and cytogenetic risk groups, DRI-R groups, HCT-CI/Age and HCT-CR groups are presented in Table 3 and Figure 2.

The significant association between OS and the HCT-CR groups persisted after adjusting for potential confounders [adjusted HR 1.37 (95%CI 1.02-1.85, P=0.04) for intermediate, 2.08 (95%CI 1.62-2.67, P<0.001)) for high and 2.92 (2.23-3.82, P<0.001) for very high risk group when compared with low risk group] (Table 4).

Model Validation and Performance

The stability of the hematopoietic cell transplant - composite risk model was confirmed in a bootstrap resampling procedure. Among 500 new datasets, on average, patients in intermediate, high and very high-risk group had significantly increased risk of death after transplant when compared with low risk group with HR of 1.39, 2.11 and 2.98, respectively (Table 4).

Results from the concordance test showed that the HCT-CR model provided better discriminative capacity for prediction of OS compared with the cytogenetic risk group, DRI-R and HCT-CI/Age models. The HCT-CR model had a C-index of 0.62 while C-index for the cytogenetic risk group was 0.55, for DRI-R was 0.60, and for HCT-CI/Age was 0.54 (Table 5). The cytogenetic risk, DRI-R and HCT-CI/Age model were each compared to the HCT-CR model for goodness of fit. In each instance, the HCT-CR model fit the data significantly better than the other models (P<0.001).

The second validation was done by applying the HCT-CR model to a validation cohort. Compare with the low risk group (N=96), patients with intermediate (N=53), high (N=95) and very high-risk group (N=64) had significantly lower OS with HR of 1.73 (95%CI 1.15-2.08, P=0.04), 2.02 (95%CI 1.68-2.34, P<0.001) and 2.46 (95%CI 1.86-3.89, P<0.001), respectively, confirming the accuracy and stability of the model.

DISCUSSION

Over the past decade, several advances have been developed in the field of AHSCT, which have helped overcome major limitations and expanded this type of treatment to more patients in need; such as the development of several reduced-intensity conditioning regimens, extending transplantation for older age groups, improvements in supportive care and the use of alternative donors, including haploidentical donors for transplantation.(3, 4, 23, 24) Even with these advances, not all patients will benefit from AHSCT since many will experience treatment failure related to disease relapse and procedure-related mortality.

One of the most challenging decisions for most transplant physicians is to accurately assess the risks and benefits of transplantation, to better select patients for this procedure in order to provide the best survival outcome. Even though several prognostic schemes have been developed (8–10), their usefulness in predicting transplant outcomes remains limited

because not all factors important to predict survival have been accounted for in a model. To account for the heterogeneity of disease and disease status before transplant, the Disease Risk Index (DRI) was developed as a tool to predict post-transplant survival in patients with various hematologic malignancies based on disease type, disease-specific characteristics and stage before transplant.(15) Its power in post-transplant survival prediction has been validated in some studies.(25, 26) Later on, a refined DRI (DRI-R) was developed by the same group to include broader disease types and create a regimen-independent risk scheme by using data from the Center for International Blood and Marrow Transplant Research (CIBMTR).(16) Results from the internal validation have shown that the DRI-R can stratify patients into 3 or 4 groups with very different survival post-transplant regardless of conditioning intensity.(16) For AML and MDS, the DRI and DRI-R stratify patients base on disease type (AML/MDS), cytogenetics (low/intermediate/adverse) and stage (remission/advanced). Even though the DRI and DRI-R have proven their ability in post-transplant survival prediction, their benefit can be seen only in patients who are already eligible for AHSCT, while DRI and DRI-R were not developed for helping in the process of transplant patient selection, since several patient characteristics such as age or comorbidities are not accounted for in a model.

Our group has previously shown that accounting for both disease risk factors (cytogenetics and remission status) and comorbidities can provide valuable information that helps predict post-transplant survival in patients with AML and MDS receiving haploidentical transplantation.(27) Correspondingly, in the current study, we propose a novel hematopoietic cell transplant - composite risk (HCT-CR) model of the commonly used disease risk factor (DRI-R) and HCT-CI/Age to predict post-transplant survival in a large and homogeneous group of patients with AML/MDS transplanted with different donors. Results from this study showed that patients with low, intermediate, high and very high HCT-CR had significantly different post-transplant outcomes with median OS rates ranging from 9 months (very high-risk group) to more than 10 years (low-risk group). In addition, we have demonstrated that the new HCT-CR model performs better in predicting post-transplant survival than models using the cytogenetic risk group, DRI-R or HCT-CI/Age individually.

Moreover, using the bootstrap method for internal validation of model, we were able to confirm that the HCT-CR model accurately predicted post-transplant survival when applied to the data set similar to the training set. The bootstrapping has been accepted as one of the internal validation methods of which the new data sets used for the validation will be recreated multiple times by resampling and replacement, provides accurate analysis result without the need to split the whole data set which might lead to an over or underestimation of the result.(21, 22) Additionally, the reproducibility and stability of the HCT-CR model were also confirmed by using the traditional split sample method for model development and validation, which showed that the model could be used to stratify patients into 4 risk groups with significantly different survival.

We consider the important strengths of our HCT-CR model are the incorporation of disease biology assessed by cytogenetic risk, disease status before transplant (which are included in the DRI-R model) and the HCT-CI/Age, an important patient-related factor. Most importantly, this HCT-CR model can be applied not only to HLA-matched but also for HLA

mismatched transplants, including haploidentical transplants, which would increase the generalizability of our results, and include now the great majority of patients receiving allogeneic transplantation. Moreover, this is a simple model, which can be used in clinical practice for evaluation of patients with AML and MDS undergoing transplantation.

Even though our study was conducted with a larger cohort of AML and MDS patients, its limitations may still be related to the relatively small number of patients evaluated, the retrospective nature of the study, which could potentially lead to failure to capture important information that might not have been recorded. However, missing data on all measures included in this study were less than 5%, therefore we have no reason to believe that missing data would have altered the results.

In conclusion, our study shows that the integration of both disease and patient characteristics in a new HCT-CR model is possible and can help better predict outcomes after AHSCT. This could have important implications as it can help better identify patients who will benefit the most from transplantation, provide a useful tool to compare transplant outcomes among different studies, provide important prognostic information for patients before transplant, and may impact the choice of intensity of preparative regimens for transplantation as well as post-transplant maintenance therapy. Additional studies (i.e., larger and/or prospective) are needed to externally validate these findings in different settings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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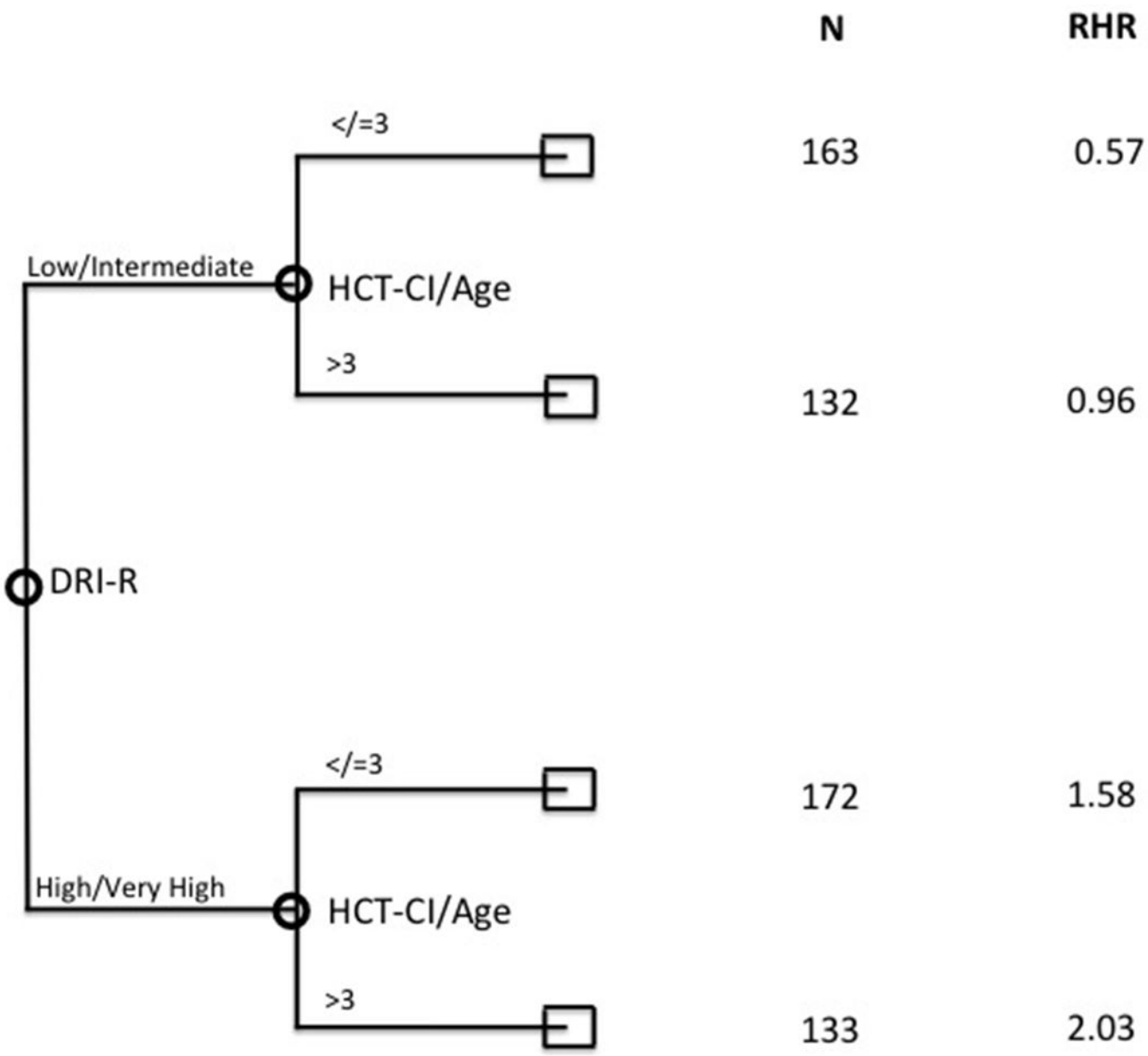
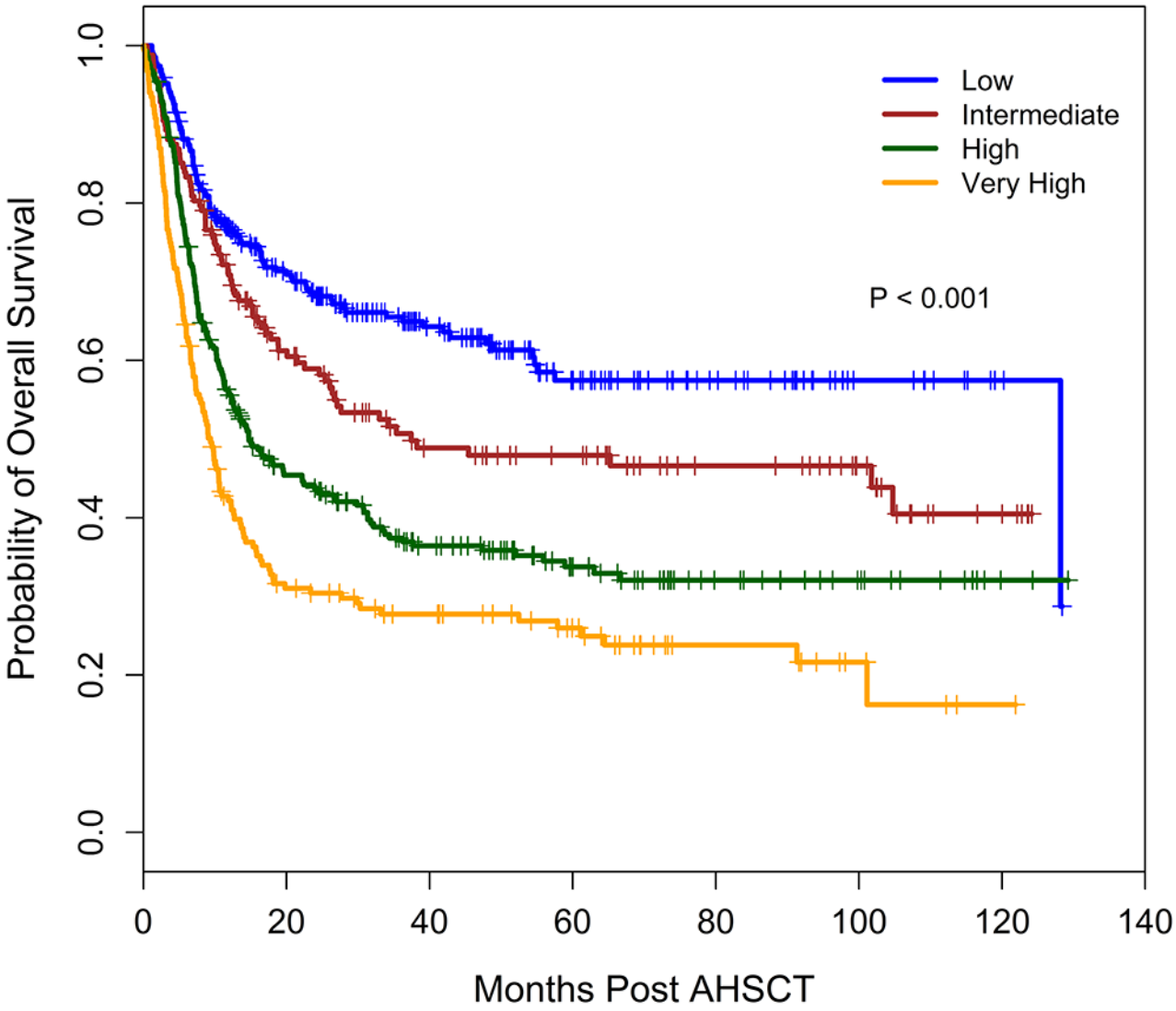
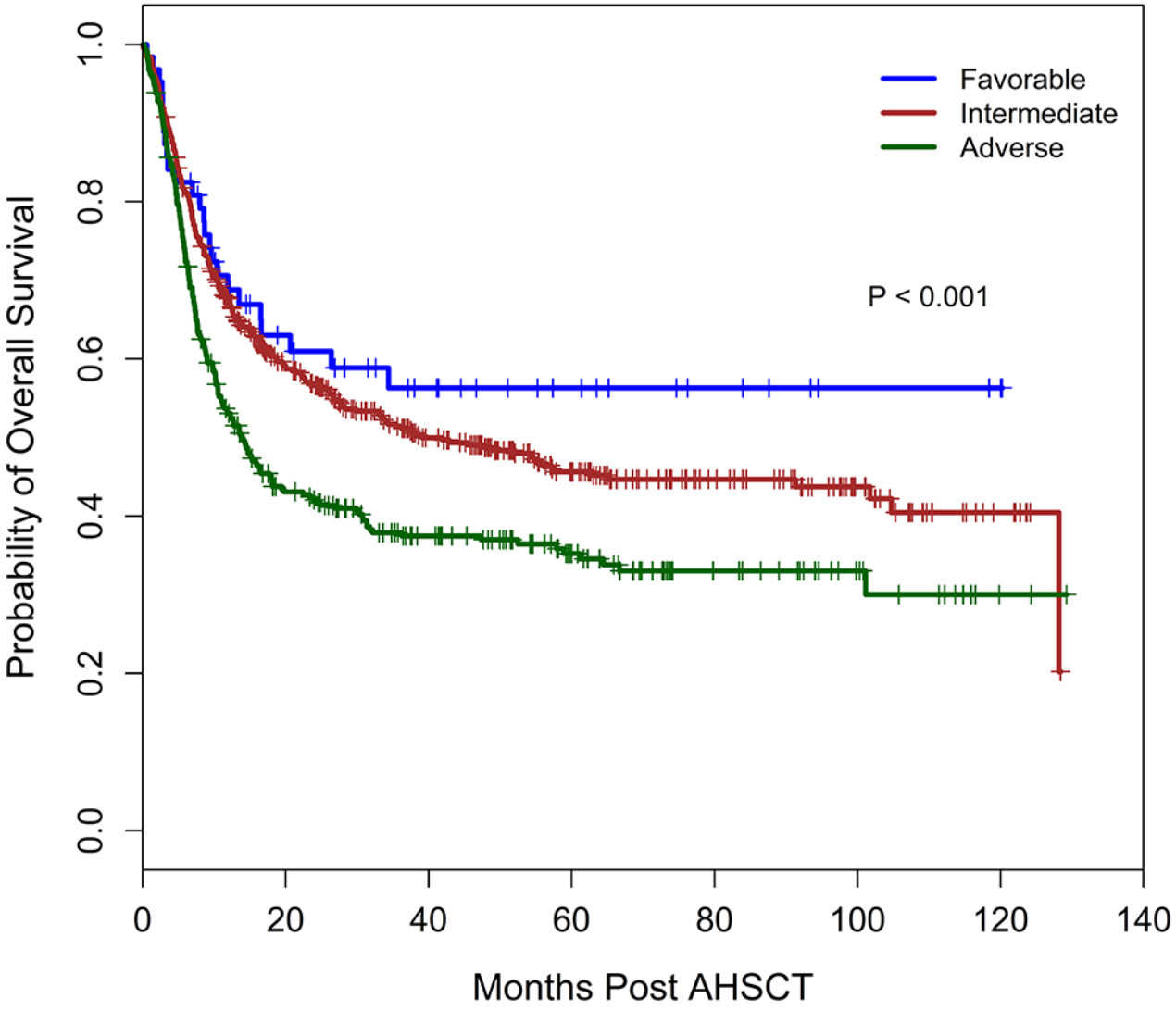


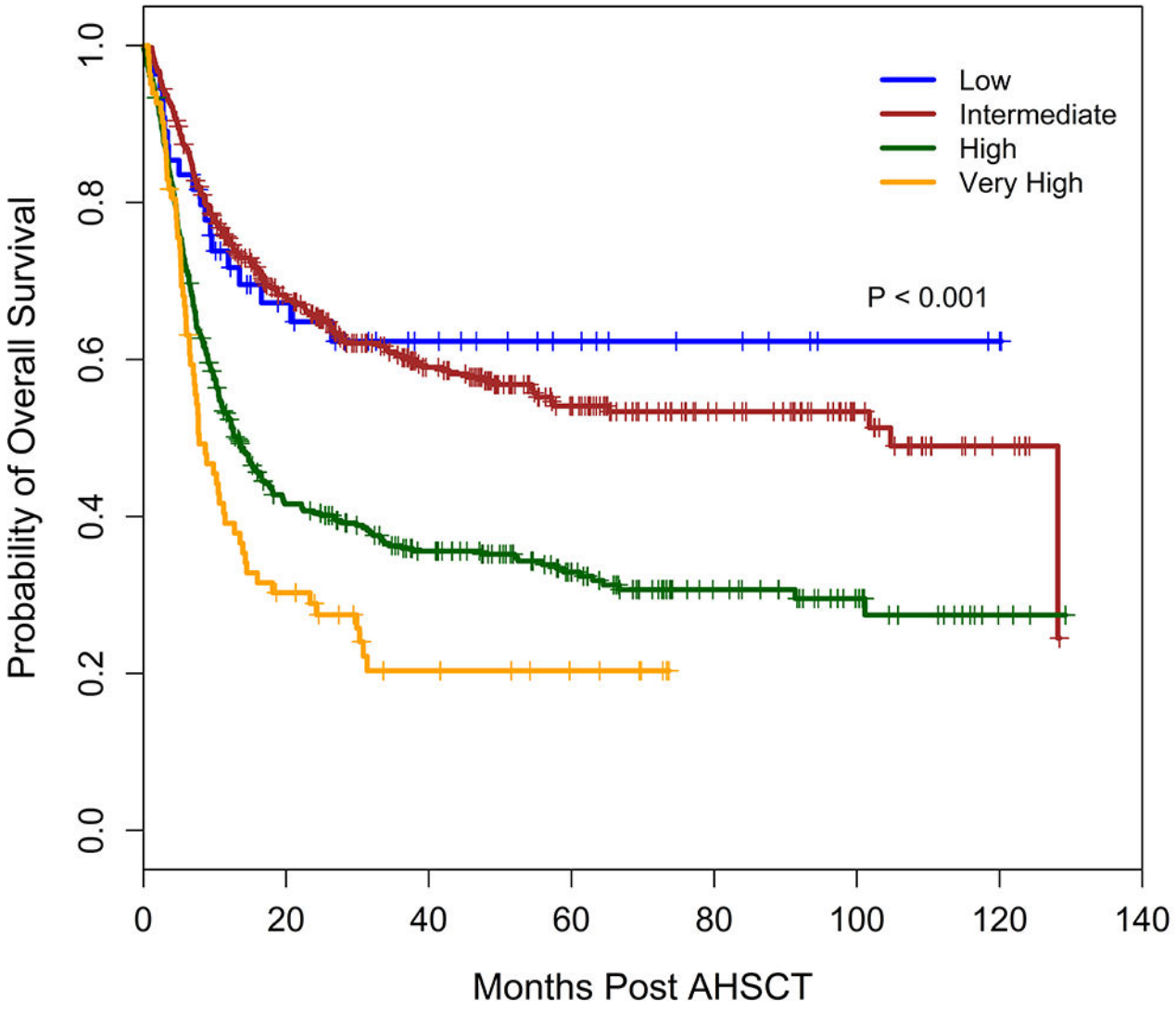
Figure 1.
The classification and regression trees (CART) analysis in a training cohort



Low	272	157	96	54	30	12	3	0
Intermediate	168	82	52	43	27	18	6	0
High	284	110	71	44	21	12	2	0
Very High	184	52	38	26	11	5	1	0



Favorable	63	31	20	13	7	3	2	0
Intermediate	523	257	165	109	58	31	8	0
Adverse	342	127	86	54	25	13	2	0



Low	55	28	18	12	7	3	2	0
Intermediate	399	223	142	93	50	27	7	0
High	392	141	101	65	33	17	3	0
Very High	82	23	10	6	0	0	0	0

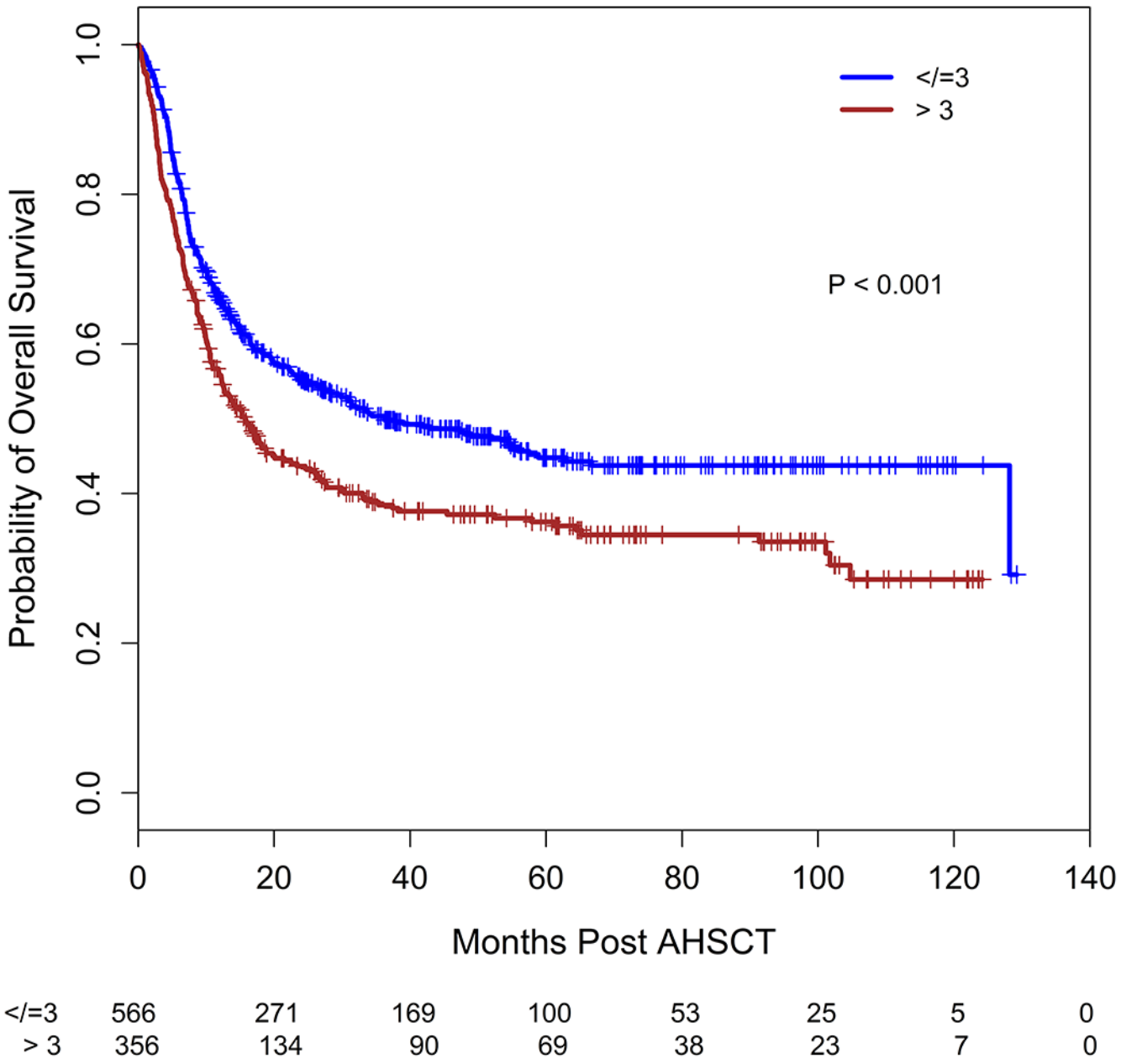


Figure 2.
Overall survival by the hematopoietic cell transplant - composite risk groups **(A)**, cytogenetic risk groups **(B)**, DRI-R **(C)** and HCT-CI/Age **(D)**

Table 1.

Patient and clinical characteristics

Characteristics	Total (N=942)	Hematopoietic cell transplant - composite risk group*			
		Low (N=272)	Intermediate (N=168)	High (N=284)	Very high (N=184)
Gender, n (%)					
Male	492 (52)	151 (56)	74 (44)	173 (61)	74 (40)
Female	450 (48)	121 (44)	94 (56)	111 (39)	110 (60)
Age in years					
Median (range)	53 (18 - 65)	51 (18 - 65)	57 (19 - 65)	47 (18 - 65)	57 (19 - 65)
Disease status at transplant, n (%)					
CR1	432 (46)	159 (58)	90 (54)	112 (39)	61 (33)
CR2	114 (12)	59 (22)	35 (21)	6 (2)	3 (2)
>CR2	6 (1)	2 (1)	3 (2)	1 (0.4)	0
Marrow CR	95 (10)	29 (11)	23 (14)	20 (7)	18 (10)
No response	176 (19)	0	0	96 (34)	75 (41)
Hypo-plastic marrow	57 (6)	21 (8)	12 (7)	14 (5)	9 (5)
Progressive disease	1 (0.1)	1 (0.4)	0	0	0
Untreated	61 (6)	1 (0.4)	5 (3)	35 (12)	18 (10)
Donor type, n (%)					
MRD	377 (40)	115 (42)	61 (36)	105 (37)	73 (40)
MUD	416 (44)	110 (40)	81 (48)	133 (47)	87 (47)
MMUD	68 (7)	19 (7)	12 (7)	20 (7)	16 (9)
MMRD	8 (1)	2 (1)	3 (2)	2 (1)	1 (1)
HAPLO	73 (8)	26 (10)	11 (7)	24 (8)	7 (4)
Cytogenetic risk, n (%)					
Favorable	63 (7)	30 (11)	23 (14)	4 (1)	4 (2)
Intermediate	523 (56)	242 (89)	145 (86)	79 (28)	42 (23)
Unfavorable	342 (37)	0	0	201 (71)	138 (75)
Missing	14	0	0	0	0
Stem cell source, n (%)					
Peripheral blood	589 (63)	173 (64)	103 (61)	168 (59)	118 (64)
Bone marrow	353 (37)	99 (36)	65 (39)	116 (41)	66 (36)
DRI-R, n (%)					
Low	55 (6)	30 (11)	23 (14)	0	0
Intermediate	399 (43)	242 (89)	145 (86)	0	0
High	392 (42)	0	0	238 (84)	149 (81)
Very high	82 (9)	0	0	46 (16)	35 (19)
Missing	14	0	0	0	0
HCT-CI/Age					

Characteristics	Total (N=942)	Hematopoietic cell transplant - composite risk group*			
		Low (N=272)	Intermediate (N=168)	High (N=284)	Very high (N=184)
Number of patients	922	272	168	284	184
Median (range)	3.0 (0.0 – 18.0)	2.0 (0.0 – 3.0)	5.0 (4.0 – 12.0)	1.0 (0.0 – 3.0)	5.0 (4.0 – 18.0)
HCT-CI/Age >3, n (%)	356 (39)	0	168 (100)	0	184 (100)
CMV reactivation, n (%)					
Yes	425 (45)	104 (38)	83 (49)	135 (48)	86 (47)
No	517 (55)	168 (62)	85 (51)	149 (52)	98 (53)
ATG use, n (%)					
Yes	428 (45)	112 (41)	81 (48)	144 (51)	85 (46)
No	514 (55)	160 (59)	87 (52)	140 (49)	99 (54)
Conditioning regimen intensity, n (%)					
MAC	787 (84)	241 (89)	139 (83)	243 (86)	134 (73)
RIC	155 (16)	31 (11)	29 (17)	41 (14)	50 (27)
Protocol status, n (%)					
On clinical trial	665 (71)	201 (74)	132 (79)	198 (70)	121 (66)
Standard of care	277 (29)	71 (26)	36 (21)	86 (30)	63 (34)

Legend: CR1: first complete remission, CR2: second complete remission, MRD: matched related donor, MUD: matched unrelated donor, MMUD: mismatched unrelated donor, MMRD: mismatched related donor, HAPO: haploidentical donor, DRI-R: refined disease risk index, HCT-CI/Age: hematopoietic stem cell transplant comorbidity-age index, ATG: antithymocyte globulin, MAC: myeloablative conditioning, RIC: reduced intensity conditioning.

Note: Percentages may not add to 100 because of rounding.

*Hematopoietic cell transplant-composite risk (HCT-CR) low: patients with low or intermediate DRI-R and HCT-CI/Age </=3, intermediate: patients with low or intermediate DRI-R and HCT-CI/Age >3, High: patients with high or very high DRI-R and HCT-CI/Age </=3; Very high: patients with high or very high DRI-R and HCT-CI/Age >3

Table 2.

Post-transplant outcomes by the hematopoietic cell transplant - composite risk groups

Hematopoietic cell transplant - composite risk (HCT-CR) group	N	5-year OS (%)	5-year PFS (%)	1-year NRM (%)	5-year relapse incidence (%)
Low: patients with low or intermediate DRI-R and HCT-CI/Age </=3	272	57	55	10	29
Intermediate: patients with low or intermediate DRI-R and HCT-CI/Age > 3	168	48	46	20	27
High: patients with high or very high DRI-R and HCT-CI/Age </=3	284	34	30	12	54
Very high: patients with high or very high DRI-R and HCT-CI/Age > 3	184	26	23	33	41
P value		<0.001	<0.001	<0.001	<0.001

Legend: OS: overall survival, PFS: progression free survival, NRM: non-relapse mortality, DRI-R: refined disease risk index, HCT-CI/Age hematopoietic stem cell transplant comorbidity-age index

Table 3.

Univariable analysis for overall survival

	N	Median OS (month)	HR	95% CI	P value
Cytogenetic risk					
Favorable	63	NR	Reference		
Intermediate	523	39	1.24	0.82-1.87	0.30
Adverse	342	14	1.78	1.18-2.70	0.006
DRI-R					
Low	55	NR	Reference		
Intermediate	399	105	1.10	0.68-1.76	0.71
High	392	13	2.20	1.38-3.50	<0.001
Very high	82	8	3.08	1.84-5.16	<0.001
HCT-CI/Age					
</=3	566	36	Reference		
>3	356	16	1.40	1.17-1.67	<0.001
HCT-CR risk *					
Low	272	128	Reference		
Intermediate	168	37	1.42	1.06-1.91	0.02
High	284	15	2.11	1.65-2.70	<0.001
Very high	184	9	3.02	2.32-3.92	<0.001

Legend: NR: not reach, HR: hazard ratio, CI: confidence interval, DRI-R: refined disease risk index, HCT-CI/Age: hematopoietic stem cell transplant comorbidity-age index

* Hematopoietic cell transplant-composite risk (HCT-CR) low: patients with low or intermediate DRI-R and HCT-CI/Age </=3, intermediate: patients with low or intermediate DRI-R and HCT-CI/Age >3, High: patients with high or very high DRI-R and HCT-CI/Age </=3; Very high: patients with high or very high DRI-R and HCT-CI/Age >3

Table 4.

Multivariable analysis for overall survival and validation of the hematopoietic cell transplant - composite risk model using bootstrap method

	N	Multivariable analysis			Model validation by bootstrap method		
		Adjusted HR	95% CI	P value	Mean HR	95%CI	Proportion of p value <0.05**
Hematopoietic cell transplant - composite risk group *							
Low	272	Reference			Reference		
Intermediate	168	1.37	1.02-1.85	0.04	1.39	0.98-1.87	0.51
High	284	2.08	1.62-2.67	<0.001	2.11	1.63-2.65	1.00
Very high	184	2.92	2.23-3.82	<0.001	2.98	2.25-3.92	1.00
Age							
≤ 60 years	747	Reference			Reference		
> 60 years	161	1.36	1.08-1.70	0.008	1.37	1.10-1.68	0.76
Gender							
Female	436	Reference			Reference		
Male	472	1.24	1.03-1.48	0.02	1.25	1.02-1.50	0.64
Donor type							
MRD	354	Reference			Reference		
MUD	411	1.17	0.94-1.46	0.17	1.19	0.96-1.47	0.33
MMD	75	1.40	0.96-2.05	0.08	1.45	0.96-2.18	0.44
TCR-Haplo	68	1.21	0.77-1.90	0.42	1.25	0.75-1.85	0.14
Stem cell source							
BM	346	Reference			Reference		
PB	562	1.12	0.89-1.42	0.34	1.13	0.88-1.47	0.17
Transplant protocol							
On protocol	652	Reference			Reference		
Standard of care	256	1.17	0.96-1.42	0.13	1.18	0.94-1.45	0.34
Conditioning regimen intensity							
MAC	757	Reference			Reference		
RIC	151	1.06	0.83-1.34	0.64	1.07	0.85-1.35	0.08

Legend: HR: hazard ratio, MRD: matched-related donor, MUD: matched-unrelated donor, MMD: HLA-mismatched related and unrelated donors, TCR-haplo: T-cell replete haploidentical donor, PB: peripheral blood, BM: bone marrow, RIC: reduced-intensity conditioning, MAC: myeloablative conditioning

* Hematopoietic cell transplant-composite risk (HCT-CR) low: patients with low or intermediate DRI-R and HCT-CI/Age </=3, intermediate: patients with low or intermediate DRI-R and HCT-CI/Age >3, high: patients with high or very high DRI-R and HCT-CI/Age </=3; very high: patients with high or very high DRI-R and HCT-CI/Age >3

** Represents the power of the bootstrapped models, where a value equal to 1.00 means the p-value for the group comparison was < 0.05 in each of the 500 models.

Table 5.

Comparisons of performance of the hematopoietic cell transplant - composite risk model, cytogenetic risk group, DRI-R and HCT-CI/Age

	Overall Survival			
	C-index*	**95% CI**	**−2 Log L****	**P value*****
HCT-CR model****	0.62	0.59-0.64	6120.1	Reference
Cytogenetic risk group	0.55	0.53-0.57	6297.5	<0.001
DRI-R	0.60	0.58-0.63	6240.7	<0.001
HCT-CI/Age	0.54	0.52-0.57	6326.6	<0.001

Legend: DRI-R: refined disease risk index, HCT-CI/Age: hematopoietic stem cell transplant comorbidity-age index

* C-index were computed for overall survival as time to event outcome

** Log likelihood

*** Likelihood ratio test

**** Hematopoietic cell transplant-composite risk (HCT-CR) low: patients with low or intermediate DRI-R and HCT-CI/Age </=3, intermediate: patients with low or intermediate DRI-R and HCT-CI/Age >3, high: patients with high or very high DRI-R and HCT-CI/Age </=3; very high: patients with high or very high DRI-R and HCT-CI/Age >3