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Utility of Treatment-Related Mortality (TRM) Score to Predict Outcomes of Adults with Acute Myeloid Leukemia Undergoing Allogeneic Hematopoietic Cell Transplantation

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Abstract

There is long-standing interest in estimating non-relapse mortality (NRM) after allogeneic hematopoietic cell transplantation (HCT) for AML, but existing tools have limited discriminative capacity. Using single institution data from 861 adults with AML, we retrospectively examined the treatment-related mortality (TRM) score, originally developed to predict early mortality following induction chemotherapy, as a predictor of post-HCT outcome. NRM risks increased stepwise across the 4 TRM score quartiles (at 3 years: 9% [95% confidence interval: 5–13%] in Q1 vs. 28% [22–34%] in Q4). The 3-year risk of relapse was lower in patients with lower TRM score (26% [20–32%] in Q1 vs. 37% [30–43%] in Q4). Consequently, relapse-free survival (RFS) and overall survival (OS) estimates progressively decreased (RFS at 3 years: 66% [59–72%] in Q1 vs. 36%

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AUTHORSHIP CONTRIBUTIONS

L.C.Z. contributed to the collection and assembly of data and drafting of the manuscript. M.O. conducted all statistical analyses and participated in data interpretation and drafting of the manuscript. B.M.S., F.M., M.B., H.J.D., F.R.A., and R.S. contributed to the provision of study material, patient recruitment, and acquisition of data. G.S. and C.D. contributed to the collection and assembly of data. R.B.W. conceptualized and designed this study and participated in data analysis and interpretation and drafting of the manuscript. All authors revised the manuscript critically and gave final approval to submit for publication.

CONFLICT OF INTEREST

The authors declare no competing financial interests.

[29–42%] in Q4; OS at 3 years: 72% [66–78%] in Q1 vs. 39% [33–46%] in Q4). With a C-statistic of 0.661 (continuous variable) or 0.642 (categorized by quartile), the TRM score predicted NRM better than the Pretransplantation Assessment of Mortality (PAM) score (0.603) or the HCT-CI/age composite score (0.576). While post-HCT outcome prediction remains challenging, these findings suggest that the TRM score may be useful for risk stratification for adults with AML undergoing allogeneic HCT.

INTRODUCTION

Allogeneic hematopoietic cell transplantation (HCT) is often considered for adults with acute myeloid leukemia (AML) in morphologic remission.[1–3] Still, post-HCT relapse remains common, and a higher risk of non-relapse mortality (NRM) relative to chemotherapy-only post-remission therapy can curtail or negate any benefits associated with allografting. Since the likelihood of post-HCT morbidity and mortality varies greatly across patients, there has long been interest in tools to estimate adverse event risks and survival for individual patients. Many patient- and disease-specific characteristics have individually been associated with increased mortality after allogeneic HCT, and varying combinations thereof have been integrated into validated prognostic scores. These include, for example, the HCT-specific Comorbidity Index (HCT-CI),[4–7] which was designed to capture patient co-morbidities and predict NRM and overall survival (OS) post-HCT, the Pretransplantation Assessment of Mortality (PAM) score,[8,9] the (modified) European Society for Blood and Marrow Transplantation (EBMT) risk score,[10,11] the Comorbidity-EBMT index,[12] the revised Disease Risk Index (rDRI),[13] the NRM-J index,[14] and the Simplified Comorbidity Index (SCI),[15] among others. While frequently used, existing tools are useful for risk stratification but, at the individual patient level, have relatively limited discriminative capacity.[14,16,17] Hence, there is an ongoing need for new or refined tools to predict NRM and other outcomes following allogeneic HCT.

Here, we used data from a large cohort of adults with AML undergoing allogeneic HCT in first or second morphologic remission to examine the simplified treatment-related mortality (TRM) score as a predictor of post-HCT outcome. This score is composed of weighted information from 8 covariates (age, performance status, white blood cell [WBC] count, peripheral blood blast percentage, type of AML [de novo *vs.* secondary], platelet count, albumin, and creatinine).[18] It was initially developed in a non-HCT cohort of 2,238 adults with previously untreated AML who received intensive induction chemotherapy and predicted the probability of death within 28 days with good accuracy, as indicated by an area under the receiver operator characteristic curve (AUC) of 0.83.[18] So far, the TRM score's ability to predict outcomes in the setting of allogeneic HCT after myeloablative or non-myeloablative conditioning (MAC and non-MAC) has not been studied.

PATIENTS AND METHODS

Study cohort

All patients ≥18 years of age with AML (2016 WHO criteria[19]) who underwent a first allogeneic HCT while in first or second remission (i.e. <5% blasts in bone marrow) at

our institution between 4/2006 and 12/2019 were included in this analysis. Partial data from all but 7 patients in the study cohort were previously reported.[20–30] High-resolution HLA-typing was used for donor selection. Post-transplant outcomes were maintained via the Long-Term Follow-Up Program and chart review of those on research studies. All patients were treated with standard of care protocols or on Institutional Review Board (IRB)-approved research protocols (all registered with ClinicalTrials.gov) and gave consent in accordance with the Declaration of Helsinki. Outcomes are updated as of March 30, 2021. This retrospective analysis was approved by the Fred Hutchinson Cancer Research Center IRB (#2562).

AML risk classification and treatment response

Cytogenetic risk at diagnosis was assigned using MRC/NCRI[31] criteria. Patients were considered cytogenetically normal when a normal karyotype was present, irrespective of the number of metaphases.[29,32] Secondary AML was defined as disease following an antecedent hematologic disorder or treatment with systemic chemotherapy and/or radiotherapy for a different disorder.[22,24,29] Treatment responses were defined according to the European LeukemiaNet criteria[3] with exception of post-HCT relapse, which was defined as >5% blasts by morphology or multiparameter flow cytometry in blood or bone marrow, re-emergence of previously seen cytogenetic abnormalities, or any level of disease leading to a therapeutic intervention.

Classification of pre-transplant comorbidity scores

The TRM score (online calculator: https://trmcalculator.fredhutch.org) was computed using clinical and laboratory data from the first day of conditioning therapy as described before, and corresponds to the predicted probability of death within 28 days of beginning intensive AML chemotherapy.[18] Performance status was designated according to documented physician assessment (more commonly used for later part of study period) or estimated by chart review (more commonly used for earlier part of study period) by one of the authors (L.C.Z.) according to criteria proposed by the Eastern Cooperative Oncology Group (ECOG).[33] A composite score between the HCT-specific comorbidity index (HCT-CI) and age (HCT-CI/age composite score) was calculated as described.[34] The PAM score, which integrates information on age, donor type, HLA matching, disease risk, forced expiratory volume in the first second (FEV1), and patient/donor CMV status, was calculated, and patients were categorized into 4 groups (<17 *vs.* 17–23 *vs.* 24–30 *vs.* >30), as described.[8,9] The modified EBMT risk score, which includes data on age, disease stage, donor type, and gender match, was calculated for all patients except those receiving cord blood or HLA-haploidentical grafts as described.[11,35]

Types and intensity of conditioning regimens

Regimens including high-dose fractionated total body irradiation (TBI; ≥12 Gy) with or without cyclophosphamide (CY) or fludarabine (FLU), high-dose TBI/thiotepa/FLU, busulfan (4 days) with CY or FLU, treosulfan/FLU with or without low-dose TBI, or any regimen containing a radiolabeled antibody, all of which targeting CD45, were considered MAC. Regimens with 2–3 Gy TBI with or without fludarabine and those with cyclophosphamide as part of conditioning in HLA-haploidentical and cord blood HCT

were considered nonmyeloablative (NMA). All others were considered reduced intensity conditioning (RIC) regimens.[36,37]

Detection of MRD by multiparameter flow cytometry

All patients underwent bone marrow aspirate analysis with ten-color flow cytometry as part of the pre-HCT work-up as described.[20–22,24,25,29,30,38] As done before, any detectable MRD was considered positive.[20–30] Next-generation sequencing-based MRD testing was not routinely done at our institution, and such data could therefore not be considered in our analyses.

Statistical analysis

Unadjusted probabilities of relapse-free survival (RFS; events = relapse and death) and OS (event = death) were estimated using the Kaplan-Meier method, and probabilities of relapse and NRM were summarized using cumulative incidence estimates. NRM was defined as death without prior relapse and was considered a competing risk for relapse, while relapse was a competing risk for NRM. Categorical patient characteristics were compared using Fisher's exact test and quantitative characteristics were compared with the Wilcoxon rank sum test. Associations with RFS and OS were assessed using Cox regression; cause-specific regression models were used for relapse and NRM. Besides the TRM score (both continuous and categorized), covariates evaluated were: age at HCT, gender, HCT-CI/age composite score (0 *vs.* 1–2 *vs.* 3–4 *vs.* ≥5), PAM score (<17 *vs.* 17–23 *vs.* 24–30 *vs.* >30), modified EBMT score (0–2 *vs.* 3 *vs.* ≥4), conditioning intensity (MAC *vs.* non-MAC), first *vs.* second remission at time of HCT, karyotype/cytogenetic risk group at AML diagnosis (favorable/intermediate *vs.* adverse), type of AML at diagnosis (secondary *vs.* de novo), cytogenetics at time of HCT (normalized *vs.* not normalized for patients presenting with abnormal karyotypes), peripheral blood counts at the time of HCT (recovered [i.e. absolute neutrophil count >1,000/μL and platelet count >100,000/μL] *vs.* not recovered), donor type (related *vs.* unrelated) and stem cell source. Missing cytogenetic risk at diagnosis, karyotype at HCT, and PAM score were accounted for as separate categories. C-statistics were calculated for regression models to quantify their ability to predict outcomes,[39] with values of 0.6–0.7, 0.7–0.8, and 0.8–0.9 commonly considered as poor, fair, and good, respectively. The relative importance of predictors in the regression models was evaluated by the value of the partial Wald Chi-squared statistic minus the predictor's degrees of freedom. Complete-case analyses were performed for each analysis reported. Two-sided *P*-values are reported. Statistical analyses were performed using STATA 16.1 (StataCorp LP, College Station, TX) and R (R Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org).

RESULTS

Characteristics of study cohort

Eight hundred and ninety-two adults met the inclusion criteria for our retrospective study. Of these, 19 did not agree to their data being used for research purposes, 1 did not have sufficient data available to calculate a pre-HCT TRM score, and 11 did not undergo pre-HCT MRD testing at our institution during the pre-HCT work-up, leaving 861 patients for analysis: 544 underwent MAC HCT and 317 underwent non-MAC HCT (RIC HCT:

n=98; NMA HCT: n=219), respectively. Table 1 provides a summary of the characteristics of the study cohort, donors, and HCTs, stratified by conditioning intensity (MAC *vs.* non-MAC). Since we routinely prioritize MAC unless significant comorbidities are present at our institution, there were expected differences between MAC and non-MAC HCT, including age at time of HCT, proportion of secondary AML, and various risk scores. These 2 patient cohorts indeed differed significantly regarding TRM scores, HCT-CI/Age composite scores, PAM scores, and modified EBMT scores (all $P<0.001$).

Relationship between TRM score and post-HCT outcome

Four hundred and twenty-one deaths, 282 relapses, and 179 NRM events contributed to the probability estimates for NRM, relapse, RFS, and OS in our dataset. At the time of data cut, the median follow-up time after HCT among survivors was 64 (12–175) months: 72 (12–171) months for MAC and 53 (13–175) months for non-MAC HCT patients, respectively. TRM scores were relatively low across the study cohort overall (median: 1.73, 95% confidence interval [CI]: 0.29–7.85). Unsurprisingly, they were lower in the MAC subset (1.16 [95% CI: 0.21–5.54) than the non-MAC subset (2.85 [95% CI: 0.59–11.15; $P<0.001$). In a first analysis, we assessed the relationship between TRM score and post-HCT outcome, stratifying patients by quartile of TRM score: 1st quartile, TRM score ≤0.790; 2nd quartile, TRM score >0.790 but ≤1.723; 3rd quartile, TRM score >1.723 but ≤3.311; and 4th quartile, TRM score >3.311. Consistent with the TRM score being affected, among other factors, by age and proportion of secondary AML, many of patient characteristics and HCTs differed across these quartiles (Supplementary Table 1). In the entire cohort, the cumulative incidence of NRM increased in a stepwise fashion across the 4 TRM score quartiles (Figure 1 and Table 2). Relative to the increase in NRM, the relapse risk was only modestly increased in patients with higher TRM scores. Consistent with these increases in NRM and, to a lesser degree, relapse risks, RFS and OS estimates stepwise decreased with increasing quartile of TRM score. Qualitatively similar results to these overall findings were obtained in the MAC and non-MAC patient subsets (Supplementary Figure 1 and Table 2). Like the TRM score, a higher PAM score identified patients with higher risk of NRM and relapse and lower OS and RFS (Supplementary Figure 2). However, unlike the TRM score, only a small proportion of patients (72/812 [9%] and 17/812 [2%]) fell into the higher 2 categories of PAM scores (24–30 and >30, respectively). Compared to TRM and PAM scores, outcomes of patients were much more similar across the HCT-CI/age composite score categories (Supplementary Figure 3).

TRM score as independent prognostic factor for post-HCT outcomes

To study the relationship between pre-HCT TRM score and post-HCT outcomes in more detail, we evaluated univariate and multivariable regression models for the endpoints of NRM, relapse, RFS, and OS, accounting for the covariates noted in *Patients and Methods*. In these models, we used the TRM score both as a continuous as well as a categorical variable. As summarized in Table 3, as a continuous variable, the TRM score was associated with higher risk of NRM and relapse as well as lower RFS and OS (all $P<0.001$), with a C-statistic value of 0.661 (standard error=0.0227) for the prediction of NRM (univariate associations between individual components of the TRM score and NRM, relapse, RFS, and OS are summarized in Table 4). When categorizing patients based on quartiles of TRM

score, consistently higher risks for NRM and relapse and lower RFS and OS were found in patients with TRM scores above the median (i.e. 3rd and 4th quartile) relative to patients within the lowest quartile of TRM scores (all $P<0.005$). Compared to the use of TRM as a continuous variable, the prediction accuracy was slightly lower for the categorical TRM score (e.g. C-statistic of 0.642 (0.0216) for NRM). As shown in Figure 2, performance status and age were the 2 most important components of the TRM score for prediction of NRM, relapse, RFS, and OS, with the relative importance of other components varying for the different endpoints. In our cohort, outcomes also worsened with increasing PAM score for all 4 endpoints of interest, although the C-statistic was slightly lower compared to the TRM score (e.g. 0.603 [0.0206] for NRM). Likewise, estimates for NRM, RFS, and OS worsened with higher HCT-CI/age composite index although differences only reached statistical significance for the subset of 280 (33%) of patients with HCT-CI/age composite score ≥5 (*vs.* 0–1) and the magnitude of effect and C-statistic were lower (e.g. 0.576 [0.0215] for NRM).

We then built multivariable models to examine the contribution of risk scores to NRM prediction further. For a basic model that included gender, cytogenetic risk at diagnosis, remission number, pre-HCT MRD status, pre-HCT karyotype, pre-HCT ANC, pre-HCT platelet count, conditioning intensity, donor type/source, and year of HCT, a C-statistic of 0.670 (0.0210) was obtained. With addition of the TRM score as a categorical variable, the C-statistic increased to 0.695 (0.0213). Basic models with inclusion of either PAM score or HCT-CI/age composite score yielded C-statistics of 0.673 (0.0213) and 0.675 (0.0211), respectively. Models that included basic variables and 2 of the 3 risk scores resulted in C-statistics of 0.680 (0.0210) for PAM score together with HCT-CI/age composite score, 0.697 (0.0205) for HCT-CI/age composite score together with TRM score, and 0.693 (0.0211) for PAM score together with TRM score. A full model that included basic covariates and all 3 risk scores yielded a C-statistic of 0.699 (0.0205). For the other endpoints of relapse, RFS, and OS, C-statistics of the full model were 0.715 (0.0155), 0.692 (0.0125), and 0.685 (0.0135; Table 5). After this multivariable adjustment, increasing quartiles of the TRM scores remained statistically significantly associated with higher risks for NRM and relapse and shorter RFS and OS as did the PAM score but not the HCT-CI/age composite score (Table 5). Likewise, after adjustment for the same covariates, the TRM score as continuous variable remained statistically significantly associated with higher risks for NRM (hazard ratio [HR]: 1.10, 95% confidence interval [95% CI]: 1.06–1.13, $P<0.001$; C-statistic: 0.704 [0.0209]), lower RFS (HR=1.05 [95% CI: 1.02–1.08], $P<0.001$; C-statistic: 0.692 [0.0125]), and lower OS (HR=1.07 [95% CI: 1.04–1.10], $P<0.001$, C-statistic: 0.685 [0.0135]) but not higher risk for relapse (HR=1.01 [95% CI: 0.97–1.06], $P=0.55$; C-statistic: 0.715 [0.0155]).

Pre-HCT TRM score as independent prognostic factor for post-HCT outcomes in specific patient subsets

Finally, we examined the relationship between TRM score and post-HCT outcomes in several discrete patient subsets, specifically the 544 patients who underwent allogeneic HCT after MAC, the 317 patients who underwent allogeneic HCT after non-MAC, and the subset of 620 patients who underwent allogeneic HCT with 10/10 HLA-matched unrelated donor or 10/10 HLA-identical sibling donor allografts; in the latter, we included the modified

EBMT score as additional covariate of interest. In multivariable analyses, overall findings in these patient subsets were like those obtained in the entire study cohort for the outcome of NRM. For RFS and OS, the magnitude of effect of the TRM score on outcome appeared greater for non-MAC HCT as compared to MAC HCT (Table 6).

DISCUSSION

For AML in remission, allogeneic HCT provides greater anti-AML efficacy than chemotherapy, making it an attractive post-remission strategy for many patients. However, even though HCT outcomes have gradually improved over the years,[40–42] the benefit of reduced relapse rates seen after HCT must still be balanced against HCT-related non-relapse morbidity and mortality. Here, we evaluated the value of the TRM score as a predictor of NRM and other outcomes after allogeneic HCT for adults with AML in morphologic remission. Our findings support three main conclusions. First, this score – used without recalibration as originally developed for adults undergoing intensive AML chemotherapy – was indeed associated with NRM as well as RFS and OS in our cohort, with qualitatively similar results seen in patients receiving myeloablative and non-myeloablative conditioning. Second, while the prediction accuracy of individual tools was overall limited, the TRM score predicted NRM better than the PAM score and the HCT-CI. And third, the accuracy of multicomponent models to predict NRM, RFS, and OS was better than for models using the TRM score alone, indicating the potential to develop refined prediction tools in future research.

The TRM score was originally developed to overcome, at least partially, the limitations of single factors such as PS or age to predict early death after intensive AML chemotherapy in the non-HCT setting.[18] With the exception of PS, this score was purposefully built to include objective covariates, obtained mostly from routine laboratory testing of a peripheral blood sample. At our institution, the TRM score is now routinely used to assess medical fitness of adults with AML or other high-grade myeloid neoplasm to inform the treatment decision-making process and to serve as a central eligibility criterion in investigator-initiated AML chemotherapy trials.[43–47]

Our current data indicate that the TRM score could similarly serve to inform on outcomes of AML patients undergoing allogeneic HCT, with higher scores predicting higher NRM, lower RFS, and lower OS compared to lower scores. Among the factors included in the TRM score, PS (not contained in PAM score or HCT-CI/age composite score) and age (contained in the HCT-CI/age composite score but not the original HCT-CI score) were the most important ones for the early mortality prediction accuracy in the non-HCT setting.[18] The studies described herein identify PS and age again as the most important individual predictors in the setting of allogeneic HCT when assessing NRM, RFS, and OS outcomes with the TRM score. While the predictive accuracy of the TRM score for NRM compared favorably relative to that of the PAM score and of the HCT-CI/age composite score in our cohort, the prediction accuracy of all examined instruments was limited, with C-statistics for NRM not exceeding 0.66 (for the TRM score) when used in isolation. With this, albeit helpful to some degree, our data caution against over-reliance on the TRM score (or any other of the assessed prediction tools) to guide decision-making and prognostication in

individual patients. This limitation also highlights a need for better predictive tools for outcomes after HCT.

It is plausible that the performance of the TRM score could be improved by recalibrating individual covariates using data from contemporary patients undergoing allogeneic HCT rather than using the TRM score as built with data from patients treated with AML chemotherapy between 1995 and 2008.[18] Moreover, the observation that multivariable models that included the TRM score plus additional covariates yielded higher C-statistics than models encompassing the TRM score alone suggests the possibility that a more accurate prediction tool could be developed by combining some or all of the TRM score factors with additional covariates.

Several limitations must be acknowledged. First, while based on many patients, our analyses were retrospective in nature. Validation (ideally, prospectively) of our findings in an independent cohort of patients will be important. Such future analyses should include comparisons with other scoring system not tested in the current study, e.g. the rDRI,[13] the NRM-J index,[14] and/or the SCI.[15] Second, our work was restricted to adults undergoing allogeneic HCT for AML in remission. We purposefully limited our studies to people with AML because the TRM score was developed using data exclusively from adults with AML receiving induction chemotherapy.[18] To what degree our findings are generalizable and could be extrapolated to other patient populations (e.g. different disease or disease stage) is unknown. Third, no uniform HCT strategy was pursued in our patients. Rather, patients were assigned to various conditioning regimens of differing intensities in a (largely) non-randomized fashion based primarily on age, comorbidities, and protocol eligibility. Fourth, as an intrinsic limitation of all retrospective analyses, emerging changes in medical practice (e.g. changes in immune suppressive therapies such as the increasing use of post-HCT cyclophosphamide) may not be captured. And fifth, our multivariable models include several scores measuring similar things, thus are colinear, which could partly explain differences in results (hazard ratios, etc.) between univariate and multivariable analyses. Acknowledging these limitations, our data suggest that the TRM score may be useful for risk stratification for adults with AML undergoing allogeneic HCT and, with this, possibly aid in the decision to pursue or not pursue allografting as post-remission therapy. To unify the approach in our retrospective analysis, we calculated the TRM score using data from the first day of conditioning therapy. An earlier time point would need to be chosen for TRM score calculation to provide guidance in decision making. Considering that many patients have relatively stable laboratory findings during the pre-HCT work-up, the TRM score is expected to be relatively stable during this time. However, our findings also highlight the limited accuracy of current tools, including the original TRM score, to predict NRM and other outcomes after allografting. Thus, other factors should be considered in the decision-making process. Efforts to recalibrate the TRM score for use in the setting of allogeneic HCT, and its potential augmentation with additional factors, are ongoing.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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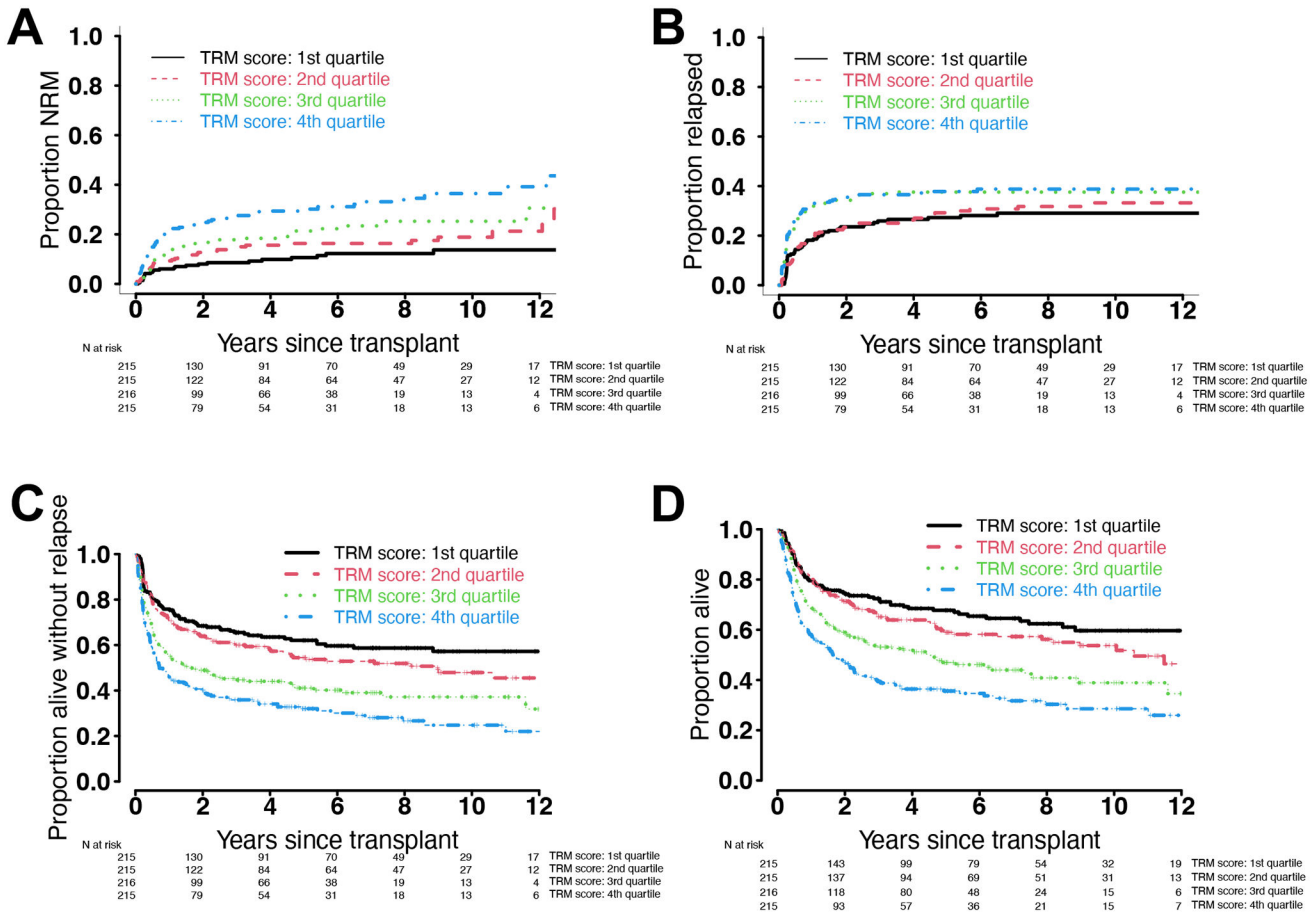

Figure 1. Post-HCT outcomes for 861 adults with AML undergoing allogeneic HCT while in first or second morphologic remission, stratified by quartile of TRM score.

(**A**) Risk of non-relapse mortality, (**B**) time to relapse, (**C**) relapse-free survival, and (**D**) overall survival, shown for the entire study cohort.

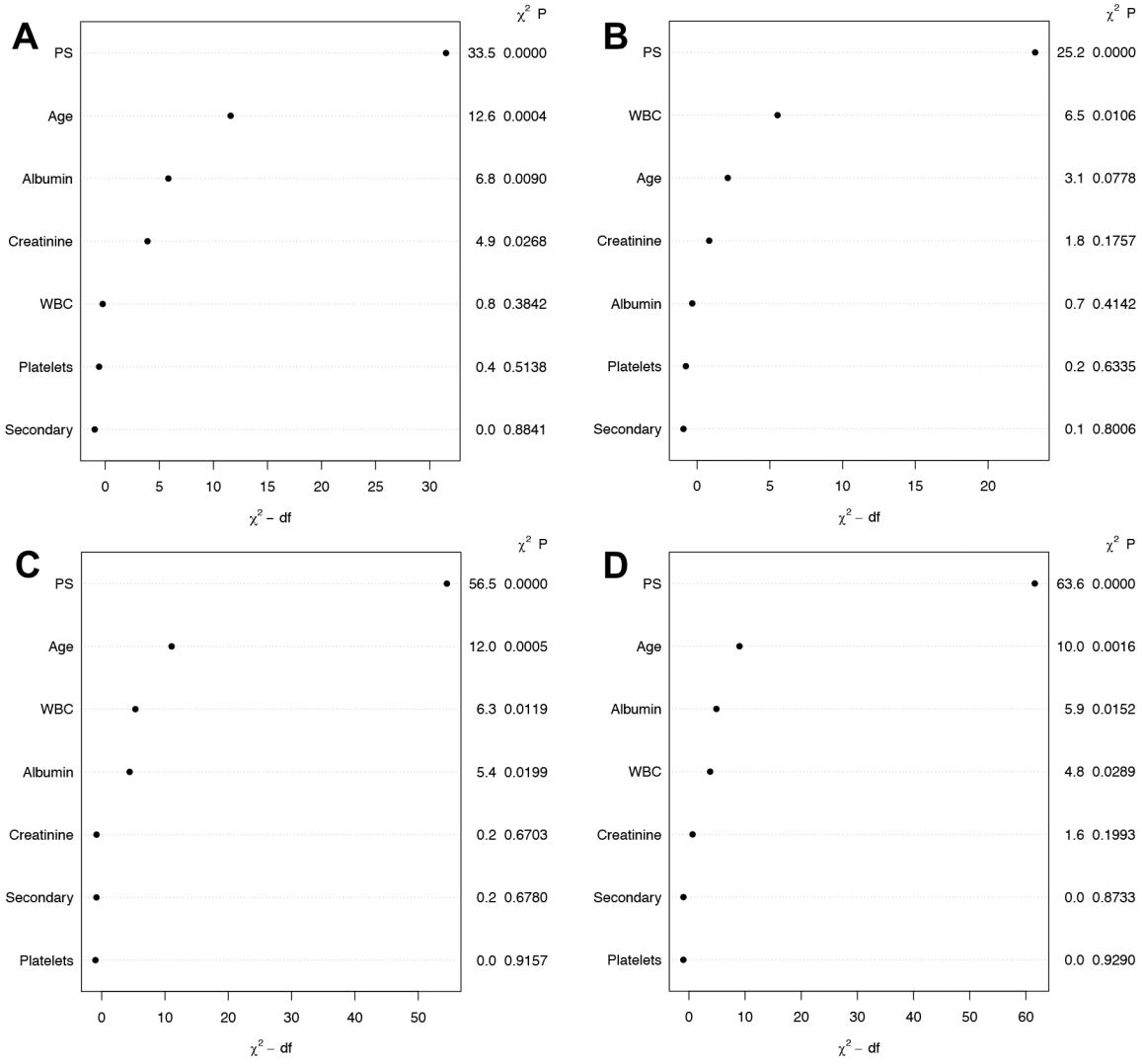

Figure 2. Prediction of post-HCT outcomes with TRM score.

Importance of individual covariates to predict (**A**) non-relapse mortality, (**B**) relapse, (**C**) relapse-free survival, and (**D**) overall survival with TRM score using Chi-squared (χ^2) values. "Importance" is evaluated with the Wald χ^2 statistic minus the predictor's degrees of freedom (df). Covariates with larger χ^2 values are considered more "important" in predicting the outcome of interest. Covariates are listed on the y-axis in order of their χ^2 values, with highest values at the top and lowest values at the bottom.

TABLE 1.

Pre-transplantation demographic and clinical characteristics of study cohort, stratified by conditioning intensity

	MAC (n=544)	Non-MAC (n=317)	All patients (n=861)	*P*-value
Median age at HCT (range), years	48.5 (18.1–72.6)	65.1 (20.0–79.5)	54.4 (18.1–79.5)	<0.001
Male gender, n (%)	282 (52)	182 (57)	464 (54)	0.12
Cytogenetic risk, n (%)				0.64
Favorable/intermediate	392 (72)	221 (70)	613 (71)	
Adverse	129 (24)	84 (27)	213 (25)	
Missing	23 (4)	12 (4)	35 (4)	
Secondary AML, n (%)	116 (21)	117 (37)	233 (27)	<0.001
Remission status at HCT, n (%)				0.37
First remission	407 (75)	246 (78)	653 (76)	
Second remission	137 (25)	71 (22)	208 (24)	
Pre-HCT MRD status by flow cytometry, n (%)				0.93
MRD^{neg}	435 (80)	255 (80)	690 (80)	
MRD^{pos}	109 (20)	62 (20)	171 (20)	
Cytogenetics before HCT, n (%)				0.39
Normalized karyotype	228 (42)	115 (36)	343 (40)	
Abnormal karyotype	82 (15)	53 (17)	135 (16)	
Non-informative karyotype *	214 (39)	134 (42)	348 (40)	
Missing	20 (4)	15 (5)	35 (4)	
Recovered ANC before HCT, n (%)**	512 (94)	289 (91)	801 (93)	0.13
Recovered platelet count before HCT, n (%)**	415 (76)	209 (66)	624 (72)	0.0012
Recovered peripheral blood counts before HCT, n (%)**	412 (76)	206 (65)	618 (72)	<0.001
ECOG performance status, n (%)				<0.001
0	113 (21)	39 (12)	152 (18)	
1	405 (74)	241 (76)	646 (75)	
2–3	26 (5)	37 (12)	63 (7)	
Median TRM score (range)	1.16 (0.03–25.88)	2.86 (0.09–50.36)	1.73 (0.03–50.36)	<0.001
1^{st} quartile (≤0.790), n (%)	183 (34)	32 (10)	215 (25)	<0.001

	MAC (n=544)	Non-MAC (n=317)	All patients (n=861)	*P*-value
2nd quartile (>0.790–1.723), n (%)	158 (29)	57 (18)	215 (25)	
3rd quartile (>1.723–3.311), n (%)	123 (23)	93 (29)	216 (25)	
4th quartile (>3.311), n (%)	80 (15)	135 (43)	215 (25)	
HCT-CI/Age Composite score, n (%)				<0.001
0	25 (5)	2 (1)	27 (3)	
1–2	201 (37)	62 (20)	263 (31)	
3–4	200 (37)	113 (36)	313 (36)	
≥5	118 (22)	140 (44)	258 (30)	
Median PAM score (range)	14.6 (0.9–96.0)	19.3 (5.4–37.3)	16.4 (0.9–96.0)	<0.001
<17, n (%)	342 (63)	107 (34)	449 (52)	<0.001
17–23, n (%)	141 (26)	133 (42)	274 (32)	
24–30, n (%)	24 (4)	48 (15)	72 (8)	
>30, n (%)	3 (1)	14 (4)	17 (2)	
Missing	34 (6)	15 (5)	49 (6)	
Modified EBMT score, n (%)				<0.001
0–1	27 (5)	3 (1)	30 (3)	
2	132 (24)	34 (11)	166 (19)	
3	208 (38)	133 (42)	341 (40)	
>4	78 (14)	95 (30)	173 (20)	
Not applicable	99 (18)	52 (16)	151 (18)	
Pre-HCT laboratory studies				
WBC (range), $x10^3/\mu L$	3.8 (0.0–24.8)	3.9 (0.1–11.5)	3.8 (0.0–24.8)	0.74
Platelet count (range), $x10^3/\mu L$	126 (10–670)	110 (5–721)	121 (5–721)	0.045
Creatinine (mg/dL)	0.82 (0.40–1.80)	0.96 (0.45–2.08)	0.87 (0.40–2.08)	<0.001
Albumin (g/L)	3.9 (2.3–5.1)	3.8 (1.9–4.7)	3.9 (1.9–5.1)	0.019
Unrelated donor, n (%)	371 (68)	247 (78)	618 (72)	0.0022
HLA matching, n (%)				<0.001
10/10 HLA-identical related donor	160 (29)	51 (16)	211 (25)	
10/10 HLA-matched unrelated donor	233 (43)	176 (56)	409 (48)	
1–2 allele/antigen HLA-mismatched unrelated donor	52 (10)	38 (12)	90 (10)	
HLA-haploidentical donor	9 (2)	17 (5)	26 (3)	

	MAC (n=544)	Non-MAC (n=317)	All patients (n=861)	*P*-value
UCB	90 (17)	35 (11)	125 (15)	
Source of stem cells, n (%)				<0.001
PB	389 (72)	273 (86)	662 (77)	
BM	65 (12)	9 (3)	74 (9)	
UCB	90 (17)	35 (11)	125 (15)	
GVHD prophylaxis, n (%)				<0.001
CNI + MMF ± sirolimus	166 (31)	262 (83)	428 (50)	
CNI + MTX ± other	308 (57)	23 (7)	331 (38)	
PTCy	58 (11)	31 (10)	89 (10)	
Other	12 (2)	1 (0)	13 (2)	
Transplant year, n (%)				0.016
2006–2012	268 (49)	129 (41)	397 (46)	
2013–2019	276 (51)	188 (59)	464 (54)	

*Normal cytogenetics in patient with cytogenetically normal AML or missing cytogenetics at diagnosis.

**ANC ≥1,000/μL and platelets ≥100,000/μL.

Abbreviations: BM, bone marrow; CNI, calcineurin inhibitor; EBMT, European Bone and Marrow Transplantation; ECOG, Eastern Cooperative Oncology Group; HCT, hematopoietic cell transplantation; MAC, myeloablative conditioning; MMF, mycophenolate mofetil; MTX, methotrexate; PB, peripheral blood; PTCy, post transplantation cyclophosphamide; TBI, total body irradiation; UCB, umbilical cord blood; WBC, total white blood cell count.

TABLE 2.

Outcome probabilities (with 95% confidence interval) stratified by conditioning intensity and TRM score

	CI of NRM at 100 days	CI of NRM at 3 years	CI of relapse at 3 years	RFS at 3 years	OS at 3 years
All patients (n=861)	5% (4–7%)	17% (15–20%)	31% (28–34%)	51% (48–55%)	57% (54–61%)
TRM score					
1st quartile (n=215)	4% (2–7%)	9% (5–13%)	26% (20–32%)	66% (59–72%)	72% (66–78%)
2nd quartile (n=215)	4% (2–7%)	15% (10–20%)	25% (19–31%)	60% (53–66%)	65% (58–71%)
3rd quartile (n=216)	3% (1–6%)	18% (13–24%)	37% (30–43%)	45% (38–51%)	53% (46–60%)
4th quartile (n=215)	9% (6–13%)	28% (22–34%)	37% (30–43%)	36% (29–42%)	39% (33–46%)
MAC HCT (n=544)	5% (3–7%)	13% (10–16%)	28% (24–32%)	59% (55–63%)	64% (59–68%)
TRM score					
1st quartile (n=183)	3% (2–7%)	8% (4–12%)	26% (20–33%)	66% (58–72%)	71% (64–77%)
2nd quartile (n=158)	5% (2–9%)	14% (9–20%)	22% (16–29%)	65% (56–72%)	68% (60–75%)
3rd quartile (n=123)	2% (0–5%)	13% (8–20%)	32% (24–40%)	55% (45–63%)	61% (52–69%)
4th quartile (n=80)	11% (6–19%)	25% (16–35%)	37% (26–47%)	39% (28–50%)	43% (32–54%)
Non-MAC HCT (n=317)	5% (3–8%)	25% (20–30%)	37% (31–42%)	39% (33–44%)	47% (41–52%)
TRM score					
1st quartile (n=32)	6% (1–18%)	13% (4–27%)	23% (10–39%)	64% (45–79%)	81% (62–91%)
2nd quartile (n=57)	2% (0–8%)	19% (10–31%)	34% (22–47%)	47% (33–60%)	56% (42–69%)
3rd quartile (n=93)	4% (1–10%)	25% (17–35%)	43% (33–53%)	31% (22–41%)	43% (32–53%)
4th quartile (n=135)	7% (4–13%)	29% (22–37%)	36% (28–45%)	34% (26–42%)	37% (29–45%)

Abbreviations: CI, cumulative incidence; HCT, hematopoietic cell transplantation; MAC, myeloablative conditioning; MRD, measurable residual disease; NRM, non-relapse mortality; OS, overall survival; RFS, relapse-free survival.

TABLE 3.

Univariate regression models of entire study cohort

	Non-relapse mortality	Relapse	Relapse-free survival	Overall survival
TRM score (continuous)	1.12 (1.10–1.15), *P*<0.001	1.07 (1.04–1.10), *P*<0.001	1.09 (1.08–1.11), *P*<0.001	1.11 (1.09–1.14), *P*<0.001
TRM score (by quartiles)				
1st quartile (n=215)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
2nd quartile (n=215)	1.71 (1.03–2.84), *P*=0.040	1.12 (0.78–1.60), *P*=0.54	1.29 (0.96–1.72), *P*=0.087	1.29 (0.95–1.75), *P*=0.10
3rd quartile (n=216)	2.59 (1.58–4.25), *P*<0.001	1.64 (1.17–2.30), *P*=0.004	1.92 (1.46–2.54), *P*<0.001	1.85 (1.38–2.48), *P*<0.001
4th quartile (n=215)	4.33 (2.71–6.90), *P*<0.001	1.87 (1.34–2.62), *P*<0.001	2.56 (1.96–3.36), *P*<0.001	2.66 (2.00–3.53), *P*<0.001
PAM score				
<17 (n=449)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
17–23 (n=274)	2.00 (1.45–2.76), *P*<0.001	1.62 (1.24–2.12), *P*<0.001	1.77 (1.44–2.17), *P*<0.001	1.82 (1.47–2.26), *P*<0.001
24–30 (n=72)	2.34 (1.38–3.96), *P*=0.0016	2.87 (1.99–4.13), *P*<0.001	2.68 (1.99–3.62), *P*<0.001	2.55 (1.85–3.50), *P*<0.001
>30 (n=17)	3.38 (1.36–8.37), *P*=0.0086	2.84 (1.39–5.82), *P*=0.0043	3.03 (1.73–5.32), *P*<0.001	3.42 (1.94–6.02), *P*<0.001
HCT-CI/Age Composite score				
0 (n=27)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
1–2 (n=263)	1.76 (0.55–5.66), *P*=0.34	0.96 (0.50–1.86), *P*=0.91	1.15 (0.65–2.03), *P*=0.63	1.09 (0.60–1.97), *P*=0.78
3–4 (n=313)	2.19 (0.69–6.99), *P*=0.16	1.02 (0.53–1.95), *P*=0.96	1.29 (0.73–2.27), *P*=0.38	1.23 (0.68–2.21), *P*=0.49
≥5 (n=258)	3.26 (1.02–10.36), *P*=0.045	1.02 (0.57–2.10), *P*=0.79	1.58 (0.90–2.78), *P*=0.11	1.55 (0.86–2.79), *P*=0.15
Age at HCT	1.03 (1.02–1.04), *P*<0.001	1.01 (1.00–1.02), *P*=0.038	1.02 (1.01–1.02), *P*<0.001	1.02 (1.01–1.02), *P*<0.001
Gender				
Female (n=387)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Male (n=464)	1.47 (1.09–1.98), *P*=0.012	1.14 (0.90–1.44), *P*=0.29	1.25 (1.04–1.51), *P*=0.017	1.23 (1.01–1.49), *P*=0.038
Cytogenetic risk				
Favorable/intermediate (n=613)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Adverse (n=213)	0.70 (0.47–1.04), *P*=0.075	1.99 (1.56–2.56), *P*<0.001	1.40 (1.14–1.72), *P*=0.0012	1.27 (1.02–1.57), *P*=0.032
Type of AML				
De novo (n=628)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Secondary (n=233)	1.40 (1.03–1.91), *P*=0.033	1.13 (0.88–1.47), *P*=0.34	1.23 (1.01–1.50), *P*=0.037	1.22 (0.99–1.51), *P*=0.056
Disease status				
First remission (n=653)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)

	Non-relapse mortality	Relapse	Relapse-free survival	Overall survival
Second remission (n=208)	1.35 (0.97–1.88), *P*=0.074	1.44 (1.11–1.87), *P*=0.0055	1.41 (1.15–1.72), *P*=0.001	1.48 (1.20–1.83), *P*<0.001
Pre-HCT MRD status				
MRD^{neg} (n=690)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
MRD^{pos} (n=171)	1.48 (1.00–2.20), *P*=0.051	4.18 (3.28–5.32), *P*<0.001	2.99 (2.44–3.65), *P*<0.001	2.44 (1.98–3.01), *P*<0.001
Pre-HCT karyotype				
Normalized (n=343)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Not normalized (n=135	1.62 (1.03–2.55), *P*=0.035	2.29 (1.69–3.11), *P*<0.001	2.06 (1.60–2.65), *P*<0.001	1.92 (1.48–2.51), *P*<0.001
Pre-HCT ANC *				
Recovered (n=801)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Not recovered (n=60)	1.76 (1.04–2.99), *P*=0.037	1.90 (1.29–2.81), *P*=0.0013	1.85 (1.35–2.54), *P*<0.001	1.90 (1.37–2.64), *P*<0.001
Pre-HCT platelet count *				
Recovered (n=624)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Not recovered (n=237)	1.74 (1.28–2.36), *P*<0.001	1.08 (0.83–1.41), *P*=0.54	1.31 (1.07–1.60), *P*=0.0077	1.37 (1.12–1.69), *P*=0.0026
Pre-HCT blood counts *				
Recovered (n=618)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Not recovered (n=243)	1.72 (1.27–2.34), *P*<0.001	1.10 (0.85–1.43), *P*=0.46	1.32 (1.08–1.60), *P*=0.0061	1.39 (1.13–1.71), *P*=0.0015
Donor				
Related (n=243)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Unrelated (n=618)	1.36 (0.97–1.88), *P*=0.074	0.92 (0.72–1.19), *P*=0.53	1.07 (0.87–1.31), *P*=0.53	1.14 (0.92–1.41), *P*=0.24
Stem cell source				
PB (n=662)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
BM (n=74)	0.54 (0.28–1.06), *P*=0.074	1.31 (0.90–1.89), *P*=0.16	1.00 (0.72–1.38), *P*=0.99	0.95 (0.68–1.34), *P*=0.79
UCB (n=125)	1.09 (0.73–1.64), *P*=0.67	0.83 (0.58–1.20), *P*=0.32	0.93 (0.71–1.22), *P*=0.61	1.02 (0.77–1.35), *P*=0.90
HLA matching				
10/10 HLA-identical related donor (n=211)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
10/10 HLA-matched unrelated donor (n=409)	1.15 (0.77–1.70), *P*=0.49	1.03 (0.77–1.37), *P*=0.85	1.07 (0.85–1.35), *P*=0.55	1.08 (0.85–1.38), *P*=0.53
9/10 HLA-matched unrelated donor (n=90)	2.63 (1.66–4.19), *P*<0.001	1.22 (0.81–1.86), *P*=0.34	1.70 (1.25–2.30), *P*<0.001	1.88 (1.37–2.59), *P*<0.001
HLA-haploidentical donor (n=26)	2.05 (0.86–4.86), *P*=0.10	2.08 (1.17–3.70), *P*=0.012	2.10 (1.30–3.38), *P*=0.0024	2.00 (1.19–3.34), *P*=0.0086
UCB (n=125)	1.47 (0.90–2.40), *P*=0.10	0.86 (0.57–1.31), *P*=0.49	1.07 (0.78–1.47), *P*=0.67	1.19 (0.86–1.65), *P*=0.29
Year of HCT				

	Non-relapse mortality	Relapse	Relapse-free survival	Overall survival
2006–2012 (n=397)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
2013–2019 (n=464)	1.06 (0.78–1.45), *P*=0.70	0.75 (0.59–0.95), *P*=0.017	0.88 (0.72–1.07), *P*=0.20	0.85 (0.71–1.03), *P*=0.095

Results are presented as hazard radio (95% confidence interval), and *P*-value;

*Recovered: ANC ≥1,000/μL and platelets ≥100,000/μL; not recovered: ANC <1,000/μL and/or platelets <100,000/μL.

Abbreviations: ANC, absolute neutrophil count; BM, bone marrow; HCT, hematopoietic cell transplantation; MAC, myeloablative conditioning; MRD, measurable residual disease; PB, peripheral blood; UBC, umbilical cord blood; WBC, total white blood cell count.

TABLE 4.

Univariate regression models for individual components of TRM score (entire study cohort)

	Non-relapse mortality	Relapse	Relapse-free survival	Overall survival
Age at HCT	1.03 (1.02–1.04), *P*<0.001	1.01 (1.00–1.02), *P*=0.038	1.02 (1.01–1.02), *P*<0.001	1.02 (1.01–1.02), *P*<0.001
ECOG performance status				
0 (n=152)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
1 (n=646)	2.36 (1.44–3.87), *P*<0.001	1.48 (1.06–2.08), *P*=0.022	1.76 (1.33–2.32), *P*<0.001	1.84 (1.37–2.47), *P*<0.001
2–3 (n=63)	8.79 (4.78–16.18), *P*<0.001	3.80 (2.36–6.12), *P*<0.001	5.24 (3.62–7.60), *P*<0.001	5.85 (3.98–8.60), *P*<0.001
Type of AML				
De novo (n=628)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Secondary (n=233)	1.40 (1.03–1.91), *P*=0.033	1.13 (0.88–1.47), *P*=0.34	1.23 (1.01–1.50), *P*=0.037	1.22 (0.99–1.51), *P*=0.056
WBC at HCT	0.94 (0.88–1.01), *P*=0.10	0.92 (0.87–0.97), *P*=0.0026	0.93 (0.89–0.97), *P*<0.001	0.93 (0.89–0.98), *P*=0.0025
Platelet count at HCT	1.00 (0.99–1.00), *P*=0.01	1.00 (1.00–1.00), *P*=0.08	1.00 (1.00–1.00), *P*=0.0031	1.00 (1.00–1.00), *P*=0.0037
Serum creatinine at HCT	2.71 (1.63–4.51), *P*<0.001	0.81 (0.50–1.32), *P*=0.40	1.37 (0.96–1.95), *P*=0.08	1.57 (1.09–2.26), *P*=0.016
Serum albumin at HCT	0.39 (0.26–0.58), *P*<0.001	0.71 (0.51–0.98), *P*=0.035	0.56 (0.43–0.72), *P*<0.001	0.55 (0.42–0.71), *P*<0.001

Results are presented as hazard radio (95% confidence interval), and *P*-value; Abbreviations: ECOG, Eastern Cooperative Oncology Group; HCT, hematopoietic cell transplantation; WBC, total white blood cell count.

TABLE 5.

Multivariable regression models of entire study cohort for quartiles of TRM score

	Non-relapse mortality c=0.699 (0.0205)	Relapse c=0.719 (0.0154)	Relapse-free survival c=0.694 (0.0124)	Overall survival c=0.682 (0.0133)
TRM score (ref: 1st quartile)				
2nd quartile	1.50 (0.89–2.54), *P*=0.13	1.00 (0.69–1.47), *P*=0.99	1.16 (0.85–1.57), *P*=0.29	1.16 (0.84–1.61), *P*=0.36
3rd quartile	2.17 (1.28–3.68), *P*=0.0039	1.45 (1.00–2.11), *P*=0.05	1.67 (1.23–2.26), *P*<0.001	1.61 (1.17–2.23), *P*=0.0035
4th quartile	2.96 (1.69–5.21), *P*<0.001	1.21 (0.79–1.86), *P*=0.38	1.72 (1.23–2.40), *P*=0.0016	1.89 (1.33–2.68), *P*<0.001
PAM score (ref: <17)				
17–23	1.30 (0.89–1.89), *P*=0.17	1.21 (0.89–1.66), *P*=0.22	1.28 (1.01–1.62), *P*=0.042	1.35 (1.05–1.73), *P*=0.019
24–30	1.31 (0.70–2.44), *P*=0.39	2.20 (1.43–3.41), *P*<0.001	1.83 (1.28–2.60), *P*<0.001	1.67 (1.15–2.43), *P*=0.0074
>30	1.90 (0.69–5.24), *P*=0.22	1.19 (0.54–2.63), P=0.67	1.36 (0.73–2.53), *P*=0.33	1.70 (0.90–3.19), *P*=0.10
HCT-CI/Age Composite score (ref: 0)				
1–2	1.17 (0.35–3.89), *P*=0.80	0.83 (0.41–1.66), *P*=0.60	0.91 (0.50–1.65), *P*=0.75	0.77 (0.42–1.44), *P*=0.42
3–4	1.17 (0.36–3.87), *P*=0.79	0.68 (0.34–1.37), *P*=0.29	0.81 (0.45–1.47), *P*=0.49	0.72 (0.39–1.34), *P*=0.30
≥5	1.47 (0.44–4.90), *P*=0.53	0.74 (0.36–1.50), *P*=0.40	0.92 (0.51–1.69), *P*=0.80	0.86 (0.46–1.61), *P*=0.63
Male gender (ref: female)	1.37 (1.00–1.88), *P*=0.053	0.97 (0.76–1.25), *P*=0.83	1.10 (0.91–1.34), *P*=0.33	1.12 (0.92–1.37), *P*=0.26
Cytogenetic risk (ref: favorable/intermediate)				
Adverse	0.59 (0.37–0.95), *P*=0.03	1.59 (1.14–2.21), *P*=0.0059	1.14 (0.88–1.48), *P*=0.34	1.08 (0.82–1.43), *P*=0.58
Second remission (ref: first remission)	1.27 (0.89–1.82), *P*=0.18	1.60 (1.20–2.15), *P*=0.0015	1.42 (1.13–1.78), *P*=0.0022	1.41 (1.12–1.78), *P*=0.0036
MRD status (ref: MRD neg)				
MRDpos	1.20 (0.79–1.84), *P*=0.39	3.53 (2.69–4.64), *P*<0.001	2.45 (1.96–3.06), *P*<0.001	1.94 (1.54–2.44), *P*<0.001
Pre-HCT karyotype (ref: normalized)				
Not normalized	1.07 (0.66–1.73), *P*=0.79	1.54 (1.10–2.15), *P*=0.012	1.37 (1.05–1.81), *P*=0.022	1.23 (0.92–1.65), *P*=0.15
Pre-HCT ANC * (ref: recovered)				
Not recovered	1.17 (0.65–2.09), *P*=0.60	1.89 (1.20–2.97), *P*=0.0061	1.49 (1.05–2.12), *P*=0.027	1.37 (0.94–1.98), *P*=0.10
Pre-HCT platelet count * (ref: recovered)				
Not recovered	0.96 (0.66–1.40), *P*=0.82	0.67 (0.48–0.93), *P*=0.017	0.78 (0.61–0.99), *P*=0.045	0.81 (0.62–1.04), *P*=0.099
MAC HCT (ref: non-MAC HCT)	1.56 (1.10–2.20), *P*=0.012	1.42 (1.09–1.85), *P*=0.01	1.47 (1.19–1.81), *P*<0.001	1.32 (1.06–1.65), *P*=0.012
Donor type/source (ref: HLA-identical related donor)				

	Non-relapse mortality c=0.699 (0.0205)	Relapse c=0.719 (0.0154)	Relapse-free survival c=0.694 (0.0124)	Overall survival c=0.682 (0.0133)
HLA-identical unrelated donor	0.97 (0.64–1.46), *P*=0.88	0.97 (0.72–1.32), *P*=0.86	0.97 (0.76–1.24), *P*=0.83	0.98 (0.76–1.26), *P*=0.86
1–2 allele/antigen mismatched donor	1.74 (1.02–2.96), *P*=0.041	0.76 (0.48–1.21), *P*=0.25	1.11 (0.79–1.56), *P*=0.56	1.35 (0.95–1.93), *P*=0.095
HLA-haploidentical donor	1.37 (0.54–3.46), *P*=0.51	1.17 (0.63–2.17), *P*=0.62	1.28 (0.77–2.14), *P*=0.34	1.46 (0.84–2.53), *P*=0.17
Umbilical cord blood	1.40 (0.83–2.38), *P*=0.21	0.76 (0.49–1.19), *P*=0.23	0.98 (0.70–1.37), *P*=0.89	1.10 (0.77–1.57), *P*=0.59
Years 2013–2019 of HCT (ref: 2006–2012)	0.94 (0.68–1.30), *P*=0.71	0.80 (0.62–1.03), *P*=0.08	0.85 (0.70–1.04), *P*=0.11	0.85 (0.69–1.05), *P*=0.14

C-statistic values (standard error) are provided.

* Recovered: ANC ≥1,000/μL and platelets ≥100,000/μL; not recovered: ANC <1,000/μL and/or platelets <100,000/μL.

Abbreviations: ANC, absolute neutrophil count; BM, bone marrow; HCT, hematopoietic cell transplantation; MAC, myeloablative conditioning; MRD, measurable residual disease; PB, peripheral blood; UBC, umbilical cord blood; WBC, total white blood cell count.

TABLE 6.

Results from multivariable regression models for TRM score in discrete patient subsets

	Non-relapse mortality	Relapse	Relapse-free survival	Overall survival
Subset of MAC HCT patients *				
TRM score (cont. variable)	1.15 (1.08–1.22), *P*<0.001	1.05 (0.99–1.11), *P*=0.11	1.07 (1.02–1.12), *P*=0.002	1.07 (1.02–1.12), *P*=0.0022
TRM score (quartiles)				
1st quartile	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
2nd quartile	1.65 (0.91–2.98), *P*=0.099	0.81 (0.54–1.23), *P*=0.32	1.03 (0.74–1.45), *P*=0.84	1.03 (0.72–1.46), *P*=0.89
3rd quartile	2.08 (1.12–3.85), *P*=0.02	1.01 (0.66–1.54), *P*=0.96	1.28 (0.90–1.81), *P*=0.16	1.26 (0.88–1.82), *P*=0.21
4th quartile	3.58 (1.90–6.75), *P*<0.001	1.06 (0.66–1.68), *P*=0.82	1.50 (1.02–2.18), *P*=0.037	1.50 (1.01–2.24), *P*=0.046
Subset of non-MAC HCT patients *				
TRM score (cont. variable)	1.10 (1.07–1.14), *P*<0.001	1.10 (0.96–1.05), *P*=0.87	1.05 (1.03–1.08), *P*<0.001	1.09 (1.06–1.12), *P*<0.001
TRM score (quartiles)				
1st quartile	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
2nd quartile	1.71 (0.60–4.86), *P*=0.32	1.45 (0.64–3.31), *P*=0.38	1.59 (0.83–3.04), *P*=0.16	1.77 (0.88–3.54), *P*=0.11
3rd quartile	2.88 (1.10–7.56), *P*=0.031	2.55 (1.19–5.45), *P*=0.016	2.76 (1.52–5.02), *P*<0.001	2.57 (1.35–4.90), *P*=0.0043
4th quartile	3.69 (1.47–9.28), *P*=0.0056	1.71 (0.81–3.64), *P*=0.16	2.44 (1.36–4.36), *P*=0.0027	2.86 (1.52–5.36), *P*=0.0011
Subset of 10/10 HLA-matched HCT patients **				
TRM score (cont. variable)	1.15 (1.09–1.22), *P*<0.001	1.02 (0.97–1.08), *P*=0.41	1.07 (1.03–1.11), *P*=0.0012	1.10 (1.05.−1.14), *P*<0.001
TRM score (quartiles)				
1st quartile	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
2nd quartile	1.40 (0.72–2.75), *P*=0.32	1.06 (0.66–1.70), *P*=0.81	1.17 (0.79–1.72), *P*=0.43	1.33 (0.88–2.01), *P*=0.17
3rd quartile	1.78 (0.90–3.51), *P*=0.096	1.44 (0.90–2.29), *P*=0.13	1.54 (1.05–2.26), *P*=0.026	1.53 (1.01–2.32), *P*=0.042
4th quartile	2.75 (1.33–5.70), *P*=0.0064	1.40 (0.82–2.39), *P*=0.21	1.74 (1.13–2.68), *P*=0.012	2.07 (1.31–3.27), *P*=0.0018

* Besides TRM score, models included karyotype/cytogenetic risk group at AML diagnosis, first *vs.* second remission at time of HCT, and pre-HCT MRD status.

** Besides TRM score, models included gender, karyotype/cytogenetic risk group at AML diagnosis, first *vs.* second remission at time of HCT, pre-HCT MRD status, cytogenetics at time of HCT, HCT-CI/age composite score, PAM score, revised EBMT score, ANC recovery before HCT, platelet count recovery before HCT, donor type (related *vs.* unrelated), and conditioning intensity.

Abbreviations: ANC, absolute neutrophil count; HCT, hematopoietic cell transplantation; MAC, myeloablative conditioning; TRM, treatment-related mortality.