HemaSphere

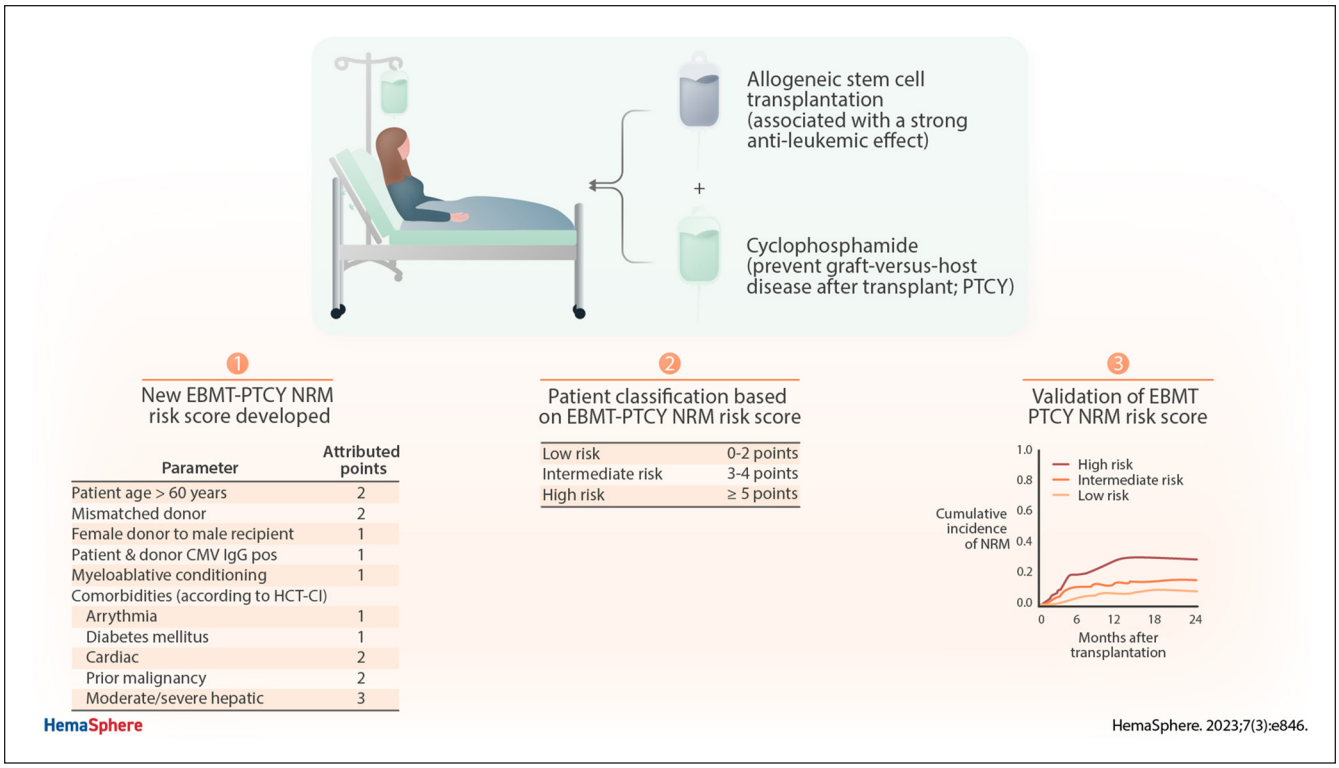
EHA EUROPEAN HEMATOLOGY ASSOCIATION

Article
Open Access

Prediction of Nonrelapse Mortality in Patients With Acute Myeloid Leukemia and Acute Lymphoblastic Leukemia Receiving Allogeneic Stem Cell Transplantation With Posttransplantation Cyclophosphamide-based Graft Versus Host Disease Prophylaxis

Sjoerd J. F. Hermans[1,*], Jurjen Versluis[1,*], Myriam Labopin[2], Sebastian Giebel[3], Yvette van Norden[1], Ivan Moiseev[4], Didier Blaise[5], Jose L. Díez Martín[6], Ellen Meijer[7], Montserrat Rovira[8], Goda Choi[9], Anna Maria Raiola[10], Yener Koc[11], Péter Reményi[12], Jan Vydra[13], Nicolaus Kröger[14], Simona Sica[15,16], Massimo Martino[17], Gwendolyn van Gorkom[18], Patrice Chevallier[19], Alessandro Busca[20], Concepcion Herrera Arroyo[21], Eolia Brissot[2], Zinaida Peric[22], Arnon Nagler[23], Roni Shouval[24], Fabio Ciceri[25], Jan J. Cornelissen[1], Mohamad Mohty[2]

GRAPHICAL ABSTRACT



HemaSphere

EHA EUROPEAN HEMATOLOGY ASSOCIATION

Article
Open Access

Prediction of Nonrelapse Mortality in Patients With Acute Myeloid Leukemia and Acute Lymphoblastic Leukemia Receiving Allogeneic Stem Cell Transplantation With Posttransplantation Cyclophosphamide-based Graft Versus Host Disease Prophylaxis

Sjoerd J. F. Hermans[1,*], Jurjen Versluis[1,*], Myriam Labopin[2], Sebastian Giebel[3], Yvette van Norden[1], Ivan Moiseev[4], Didier Blaise[5], Jose L. Díez Martín[6], Ellen Meijer[7], Montserrat Rovira[8], Goda Choi[9], Anna Maria Raiola[10], Yener Koc[11], Péter Reményi[12], Jan Vydra[13], Nicolaus Kröger[14], Simona Sica[15,16], Massimo Martino[17], Gwendolyn van Gorkom[18], Patrice Chevallier[19], Alessandro Busca[20], Concepcion Herrera Arroyo[21], Eolia Brissot[2], Zinaida Peric[22], Arnon Nagler[23], Roni Shouval[24], Fabio Ciceri[25], Jan J. Cornelissen[1], Mohamad Mohty[2]

Correspondence: Jurjen Versluis (j.versluis.1@erasmusmc.nl).

ABSTRACT

Graft versus host disease (GVHD) prophylaxis with posttransplantation cyclophosphamide (PTCY) has been established to reduce severe GVHD, and thereby potentially reducing nonrelapse mortality (NRM) after allogeneic stem cell transplantation (alloSCT). We evaluated the predictive capacity of established NRM-risk scores in patients receiving PTCY-based GVHD prophylaxis, and subsequently developed and validated a novel PTCY-specific NRM-risk model. Adult patients (n = 1861) with AML or ALL in first complete remission who received alloSCT with PTCY-based GVHD prophylaxis were included. The PTCY-risk score was developed using multivariable Fine and Gray regression, selecting parameters from the hematopoietic cell transplantation-comorbidity index (HCT-CI) and European Group

[1]Erasmus MC Cancer Institute, University Medical Center Rotterdam, The Netherlands
[2]Department of Hematology, Hôpital Saint Antoine, Paris, France
[3]Department of Bone Marrow and Onco-Hematology, Maria Sklodowska-Curie National Research Institute of Oncology, Gliwice Branch, Gliwice, Poland
[4]RM Gorbacheva Research Institute, Pavlov University, St. Petersburg, Russia
[5]Programme de Transplantation & Therapie Cellulaire, Centre de Recherche en Cancérologie de Marseille, Institut Paoli Calmettes, Marseille, France
[6]Hematology, Hospital GU Gregorio Marañón, Instituto de Investigación Sanitaria Gregorio Marañon, Departamento de Medicina, UCM, Madrid, Spain
[7]Department of Hematology, VU University Medical Center, Amsterdam, The Netherlands
[8]Department of Hematology, Hospital Clinic, Institute of Hematology & Oncology, Barcelona, Spain
[9]University Medical Center Groningen, University of Groningen, The Netherlands
[10]IRCCS Policlinico San Martino Hospital, Genova, Italy
[11]Medicana International, Bone Marrow Transplant Unit, Istanbul, Turkey
[12]Department of Haematology and Stem Cell Transplant, St. István and St. László Hospital of Budapest, Hungary
[13]Institute of Hematology and Blood Transfusion, Prague, Czech Republic
[14]University Hospital Eppendorf, Bone Marrow Transplantation Centre, Hamburg, Germany
[15]Dipartimento di Diagnostica per Immagini, Radioterapia Oncologica ed Ematologia, Fondazione Policlinico Universitario A, Gemelli IRCCS, Roma, Italy
[16]Sezione di Ematologia, Dipartimento di Scienze Radiologiche ed Ematologiche, Università Cattolica del Sacro Cuore, Roma, Italy
[17]Stem Cell Transplantation and Cellular Therapies Unit (CTMO), Grande Ospedale Metropolitano "Bianchi-Melacrino-Morelli," Reggio Calabria, Italy
[18]Department of Internal Medicine, Division of Hematology, GROW School for Oncology and Developmental Biology, Maastricht University Medical Center, Maastricht, The Netherlands
[19]CHU Nantes Department of D'Hematologie, Nantes, France
[20]S.S.C.V.D Trapianto di Cellule Staminali, A.O.U Citta della Salute e della Scienza di Torino, Italy
[21]Department of Hematology, Reina Sofía University Hospital, IMIBIC, University of Cordoba, Spain
[22]University Hospital Center Zagreb, School of Medicine, University of Zagreb, Croatia
[23]Hematology and Bone Marrow Transplant Department, Chaim Sheba Medical Center, Tel Hashomer, Israel
[24]Adult Bone Marrow Transplant Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, USA
[25]University Vita-Salute San Raffaele, Milan, Italy
*SJFH and JV contributed equally to this work.

Previous Presentation: Presented in abstract form at the 48th Annual Meeting of the European Society for Blood and Marrow Transplantation, March 19–23, 2022.
Supplemental digital content is available for this article.

HemaSphere (2023) 7:3(e846).
http://dx.doi.org/10.1097/HS9.0000000000000846.
Received: September 7, 2022 / Accepted: January 9, 2023

for Blood and Marrow Transplantation (EBMT) score with a subdistribution hazard ratio (SHR) of ≥1.2 for 2-year NRM in the training set (70% split), which was validated in the test set (30%). The performance of the EBMT score, HCT-CI, and integrated EBMT score was relatively poor for discriminating 2-year NRM (c-statistic 51.7%, 56.6%, and 59.2%, respectively). The PTCY-risk score included 10 variables which were collapsed in 3 risk groups estimating 2-year NRM of 11% ± 2%, 19% ± 2%, and 36% ± 3% (training set, c-statistic 64%), and 11% ± 2%, 18% ± 3%, and 31% ± 5% (test set, c-statistic 63%), which also translated into different overall survival. Collectively, we developed an NRM-risk score for acute leukemia patients receiving PTCY that better predicted 2-year NRM compared with existing models, which might be applicable to the specific toxicities of high-dose cyclophosphamide.

INTRODUCTION

Postremission treatment with allogeneic stem cell transplantation (alloSCT) for patients with acute myeloid leukemia (AML) or acute lymphoblastic leukemia (ALL) provides a potent graft versus leukemia (GVL) effect that significantly contributes to cure in acute leukemia.[1,2] Transplantation-related morbidity and mortality, considered as nonrelapse mortality (NRM) might compromise outcome after alloSCT. Therefore, a personalized approach weighing both the benefit (ie, GVL) and the risk of the transplant-procedure (ie, NRM) has been advocated for all patients before proceeding to alloSCT.[1,2]

To support decision-making for alloSCT, prediction models have been developed to assess the risk of NRM of which the European Group for Blood and Marrow Transplantation (EBMT) score and the hematopoietic cell transplantation-comorbidity index (HCT-CI) are widely used. The EBMT score consists of patient- and transplant-related factors, and was originally constructed in a cohort of chronic myeloid leukemia (CML) patients to predict overall survival (OS),[3] and subsequently validated for the prediction of NRM.[4] The HCT-CI was developed by Sorror et al[5] and consists of 17 comorbidities predictive of NRM and OS after alloSCT. Over the past decades, these NRM-risk models have been used for informing transplant decisions. Since then, the implementation of reduced-intensity conditioning (RIC) has allowed elderly, and younger patients with comorbidities to become increasingly eligible for alloSCT.[6] A previous study demonstrated poor predictive performance of the EBMT score and HCT-CI in a large EBMT cohort of AML patients receiving RIC alloSCT, emphasizing the need to continually reassess and refine existing risk scores.[7] That study proposed a different score for AML patients receiving RIC alloSCT, which integrated risk factors of the EBMT score and HCT-CI, which was validated by others.[8]

Recently, posttransplant cyclophosphamide (PTCY) has emerged as an alternative for GVHD prophylaxis after alloSCT. PTCY was developed by the Baltimore group in the context of haploidentical donor alloSCT,[9,10] but has successfully been extended to other donor types.[11,12] PTCY has been associated with in vivo depletion of alloreactive T cells while preserving the GVL-effect, which results in decreased incidence of severe GVHD and subsequent NRM.[11,13,14] Consequently, NRM-risk scores should be re-evaluated and refined in the setting of PTCY-based alloSCT. Therefore, we evaluated the discriminatory capacity of the EBMT score, HCT-CI, and integrated EBMT score for 2-year NRM in a cohort of AML and ALL patients receiving alloSCT, all followed by PTCY. We then set out to construct a novel risk score to better predict 2-year NRM, which was validated internally.

PATIENTS AND METHODS

Patients

A total of 1861 adult patients diagnosed with AML or ALL who received alloSCT in first complete remission (CR1) using PTCY-based GVHD prophylaxis between 2010 and 2018 were identified in the EBMT registry. Patients were included if comorbidities were scored according to the HCT-CI, both patient and donor CMV serology were available, alloSCT was administered within 2 years after diagnosis, and outcome measures were available.

A total of 76.4% (n = 1421) AML patients were included with a median age at alloSCT of 53 years (Suppl. Table S1). ALL patients (23.6%, n = 440) were significantly younger compared with AML patients with a median age of 39 years ($P < 0.001$) at alloSCT. The median time from diagnosis to alloSCT for patients with AML and ALL was significantly different (153 and 188 days, respectively, $P < 0.001$). Haploidentical donors were used in 55.8% of transplants, whereas matched-related, matched-unrelated, and mismatched-unrelated donors were used in 13.6%, 29.8%, and 0.8%, respectively. Conditioning was considered myeloablative (MAC) if it included either total body irradiation (TBI) ≥ 8.0 Gray, >9.6 mg/kg busulfan, or >42 g/m^2 treosulfan. Regimens were also considered MAC if these were associated with high scores according to the Transplant Conditioning Intensity score.[15] MAC regimens were used in 54.5% of ALL patients, which was significantly higher compared with AML patients (22.6%; $P < 0.001$). Antithymocyte globulin was added to the conditioning regimen in 13.5% (n = 252) of patients. The majority (68.9%) of patients received additional GVHD prophylaxis with a calcineurin inhibitor and mycophenolic acid/methotrexate (Table 1).

At least one comorbidity (defined by the HCT-CI[5]) was present in 38.5% (n = 717) of patients (Figure 1). Pulmonary disease (moderate 12.2%; severe 7.0%), infection requiring treatment at transplantation (6.9%), and prior solid tumors (6.3%) were most frequently reported.

Endpoints

The primary endpoint was the cumulative incidence of NRM at 2 years, for which relapse was considered a competing event. Secondary endpoints were OS, relapse-free survival (RFS), and cumulative incidence of relapse. The event for OS was death from any cause, and patients were censored at the last day of follow-up if alive. The events for RFS were NRM and relapse of leukemia. All time-to-event outcomes were analyzed from the date of transplantation until the first event or date of last contact.

Statistical analysis

Cumulative incidence curves were used to estimate the probabilities of NRM and relapse. These events are considered as competing events, which means that the occurrence of relapse excludes patients to be at risk for NRM and vice versa. The Kaplan–Meier method was used to determine OS and RFS. The inverse Kaplan–Meier method was used to calculate the median follow-up time with being alive at the end of follow-up considered as the event of interest.

Prediction of NRM using existing NRM-risk scores

The EBMT score,[3] HCT-CI,[5] and integrated EBMT score[7] were calculated for all patients using the previously defined criteria. The predictive performance of these NRM-risk scores was assessed using competing risks analysis and calculation of the area under the receiver operating characteristic (ROC) curve (AUC). The AUC is summarized with the concordance statistic (c-statistic) reflecting the probability of predicting the outcome

Table 1
Patient Characteristics

Parameter	Overall
No. patients	1861 (100)
Age at transplant, median (range)	51 (18–79)
Sex, n (%)	
Male	1051 (56.5)
Female	807 (43.4)
Unknown	3 (0.1)
Days from diagnosis to alloSCT, median (IQR)	162 (124–218)
Year of alloSCT, median (range)	2017 (2010–2018)
Conditioning regimen intensity	
MAC	561 (30.1)
Non-MAC	1300 (69.9)
Donor type	
Matched related	254 (13.6)
Matched unrelated	554 (29.8)
MMUD	14 (0.8)
Haplo	1039 (55.8)
Stem cell source	
Bone marrow	504 (27.1)
Peripheral blood	1354 (72.7)
Bone marrow and peripheral blood	3 (0.2)
Donor-recipient sex match	
Female donor to male recipient	358 (19.2)
Other	1496 (80.4)
Donor or patient sex not known	7 (0.4)
Patient/donor CMV match	
–/–	319 (17.1)
+/–	404 (21.7)
–/+	143 (7.7)
+/+	995 (53.5)
Graft versus host disease prophylaxis	
PTCY + CNI + MMF/MTX	1283 (68.9)
PTCY + CNI	292 (15.7)
PTCY + MMF/MTX	96 (5.2)
Other	190 (10.2)
Antithymocyte globulin	
Yes	252 (13.5)
No	1609 (86.5)

alloSCT = allogeneic stem cell transplantation; CMV = cytomegalovirus; CNI = calcineurin inhibitor; haplo = haploidentical donor; MAC = myeloablative conditioning regimen; MMF = mycophenolic acid; MMUD = mismatched unrelated donor; MTX = methotrexate; PTCY = posttransplant cyclophosphamide.

better than chance (c-statistic = 0.5). A c-statistic of 1.0 indicates no false positives, which means that no patients experiencing NRM were missed by the model.

Development of a novel NRM-risk score

We then reassessed the individual parameters of the EBMT score, HCT-CI, and integrated EBMT score to develop a new risk model. The dataset was randomly split into a training set (n = 1303; 70%) and a test set (n = 558, 30%). Multivariable regression using the Fine and Gray subdistribution hazards model was used to determine the predictive capacity of individual variables for the prediction of NRM in the training data. The subdistribution hazards model estimates the effect of covariates on the subdistribution hazard function and on the cumulative incidence of NRM. The multivariable model contained variables of the HCT-CI, EBMT, and integrated EBMT score, including comorbidities (yes versus no) if present in ≥15 patients, CMV serology (patient and donor positive versus patient or donor positive versus patient and donor negative), time from diagnosis to alloSCT (<6 months versus ≥6 months), and conditioning (MAC versus non-MAC). Age at alloSCT was included as previously defined in the integrated EBMT score.[7] Disease stage was not included because all patients were transplanted in CR1. Next, covariates with a subdistribution hazard ratio (SHR) ≥1.2 were selected for the final model, similar to the approach used in the development of the HCT-CI and integrated EBMT score.[5,7] Patients were then assigned points based on the rounded SHRs of the selected covariates. We defined a 3-tiered risk score based on the aggregate of cumulative incidence of NRM for each score.

Using these 3 risk groups, the predictive performance was assessed in the training and test sets by competing risks analysis and estimation of AUC for 2-year NRM, and the Kaplan–Meier method for OS.

Statistical software

All analyses were performed using R (version 4.0.0 or higher) by the R Core Team. The *survival* and *cmprsk* packages were used for the time-to-event, competing risks, and competing risks regression analyses, whereas packages *haven*, *magrittr*, *ggplot2*, *survminer*, *caret*, and *timeROC* were used for data management, data visualization, data splitting, and AUC calculation.

RESULTS

Cohort outcomes

Overall, 608 (32.7%) patients died and 1253 (67.3%) patients were alive at the end of follow-up. The median follow-up was 28 ± 1 months in the full cohort, which was similar between the training and the test set. The 2-year OS and RFS were 66% ± 1% and 59% ± 1%, respectively. The cumulative incidence of NRM at 2 years was estimated as 18% ± 1%, which was similar among the training and test cohorts. It was also similar between AML and ALL patients (18% ± 1% versus 18% ± 2%, $P = 0.90$).

Prediction of NRM using existing NRM-risk scores

Validation of the established risk scores in the full cohort showed relatively poor predictive performance. Using the EBMT score, the majority of patients were assigned to the intermediate-risk group (n = 1182, 63.5%), whereas 1.8% (n = 33) and 34.7% (n = 646) of patients were in the low- or high-risk subgroups, respectively. The cumulative incidence estimates of NRM at 2 years were 13% ± 6%, 18% ± 1%, and 20% ± 2% in the low-, intermediate-, and high-risk subgroups, respectively (Figure 2A). Most patients in the HCT-CI were assigned to the low-risk subgroup (n = 1144, 61.5%). The low- and intermediate-risk subgroups of the HCT-CI were found to have a similar cumulative incidence of 2-year NRM, which was higher in the high-risk group (16% ± 1%, 18% ± 2%, and 27% ± 3%, respectively, Figure 2B). The integrated EBMT score classified 45.5% and 48.0% of patients in the low- and intermediate-risk group, respectively, whereas only 6.5% of patients were assigned to the high-risk group. The cumulative incidence of NRM in the integrated EBMT score estimated 13% ± 1%, 23% ± 2%, and 25% ± 4% in the low-, intermediate- and high-risk groups, respectively (Figure 2C).

These existing NRM-risk scores were found to have relatively poor discrimination of 2-year NRM (AUC of 51.7%, 56.6%, and 59.2% for the EBMT, HCT-CI, and integrated EBMT score, respectively). Consequently, we sought to develop a novel NRM-risk score specifically for patients receiving PTCY-based alloSCT.

Development of a novel NRM-risk score

Using a Fine and Gray multivariable regression model, we selected covariates with an SHR ≥1.2. A total of 22 covariates

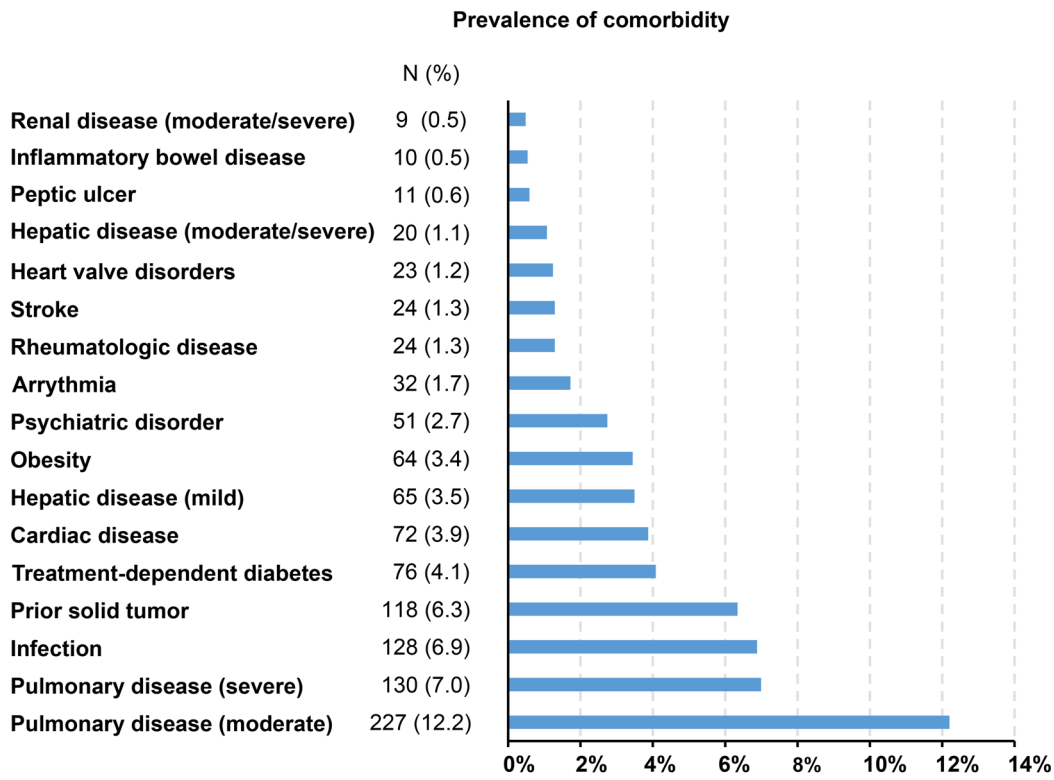


Figure 1. Prevalence of comorbidities according to HCT-CI. The proportion of patients (relative to total number of patients in the EBMT-PTCY cohort) are tabulated for each comorbidity identified by HCT-CI. EBMT = European Group for Blood and Marrow Transplantation; HCT-CI = hematopoietic cell transplantation-comorbidity index; PTCY = posttransplantation cyclophosphamide.

were considered of which 12 did not meet the cutoff and were thus not selected for the final model (Suppl. Table S2). Interactions were tested between variables (ie, age and conditioning, diagnosis and conditioning, and donor type and diagnosis), which were not statistically significant. The final model consisted of ten covariates, including age at alloSCT >60 years, patient and donor CMV positivity, female donor to male recipient, MAC, haploidentical donor, arrhythmia, diabetes mellitus, prior solid tumor, cardiac disease, and hepatic disease (Table 2). Moderate/severe hepatic disease, age at transplantation >60 years, and prior solid tumor were associated with the highest SHRs for 2-year NRM after alloSCT. The SHRs of these 10 covariates were rounded to the nearest integer and patients were attributed points for each covariate. The sum of these points resulted in the final score which ranged from 0 to 10 points, with a median of 3 points in the development cohort. These scores were collapsed into a 3-tiered risk model based on the 2-year NRM estimates for each point level (Suppl. Figure S1). Patients were considered low-, intermediate-, or high-risk if they scored between 0 and 2 points, 3–4 points, or ≥5 points, respectively.

This 3-tier EBMT-PTCY-risk score captured most patients in the low-risk (n = 518; 39.8%) and intermediate-risk group (n = 556; 42.7%). A smaller proportion of patients (n = 229, 17.5%) were allocated to the high-risk group.

The predictive performance of this novel EBMT-PTCY-risk score in the training data was assessed using competing risks analysis for 2-year NRM, and AUC. The cumulative incidence of NRM was 11% ± 2%, 19% ± 2%, and 36% ± 3% for each risk group, respectively (Figure 3A). The novel risk score demonstrated a relatively better predictive capacity of 2-year NRM, as measured by AUC (64.2%). The score also predicted 100-day NRM with an AUC of 66.6%. Furthermore, the risk score discriminated for 2-year OS, with survival estimates of 72±2%, 68±2%, and 51±4% associated with the low-, intermediate-, and high-risk group, respectively (AUC 57.3%) (Figure 3B). The cumulative incidence of relapse was not different across the 3 risk strata (Suppl. Figure S2).

Model validation

The novel risk score was evaluated using the test data (n = 558) in which a median score of 3 points (range 0–11) was observed. The distribution of patients in the different risk strata was similar compared with the training set (Figure 4). The EBMT-PTCY-risk score yielded a cumulative incidence of 2-year NRM of 11% ± 2%, 18% ± 3%, and 31% ± 5% in the low-, intermediate-, and high-risk group, respectively (Figure 4A). In addition, the AUC for 2-year NRM in the novel risk score was 63.3% in the test data indicating relatively reasonable performance in an unseen dataset. An AUC of 64.7% for 100-day NRM was observed in the test data. Comparable to the training data, the novel risk score also discriminated for 2-year OS (low-risk: 72% ± 3%; intermediate-risk: 63% ± 3%; high-risk: 50% ± 6%) with an AUC of 59.3% (Figure 4B). The cumulative incidence of relapse in the different risk groups was similar in the test set (Suppl. Figure S3).

DISCUSSION

Weighing the risks of NRM and relapse is considered essential for risk-adapted strategies in the application of alloSCT in patients with acute leukemia.[2] Clinical care of transplant recipients is continuously evolving with strategies aiming to reduce relapse on the one hand, and reduce transplant-related toxicity and mortality on the other. With respect to the latter, GVHD prophylaxis with PTCY has been associated with lower rates of chronic GVHD and NRM after alloSCT and is increasingly being administered.[16,17] Given the reduced

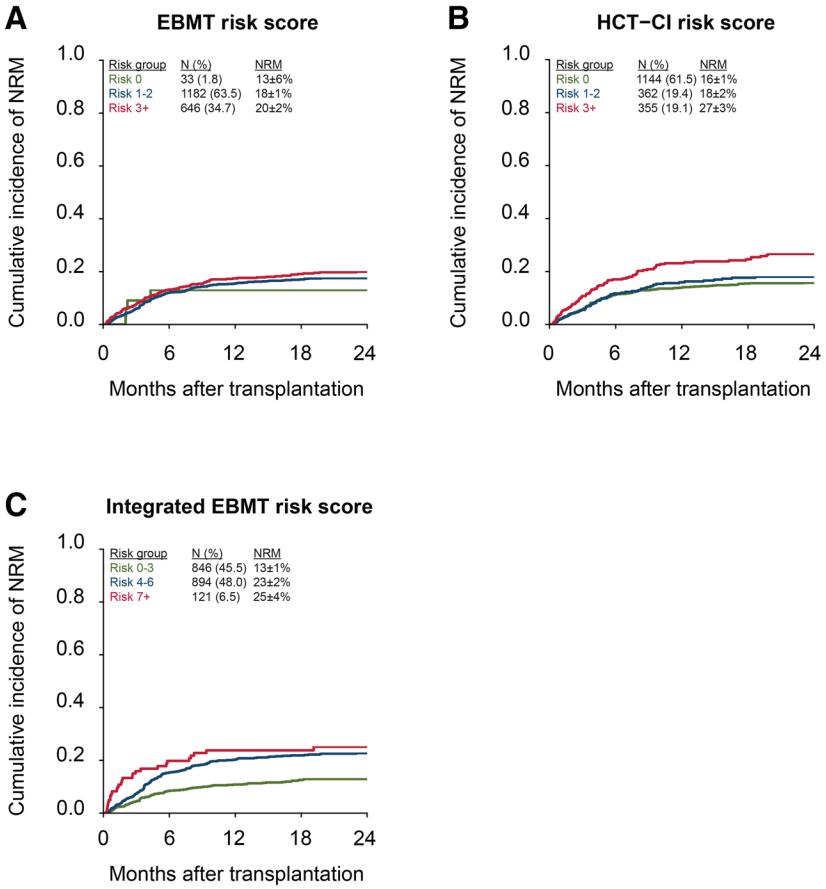


Figure 2. NRM by the EBMT score, HCT-CI and integrated EBMT score. Cumulative incidence of NRM by (A) the EBMT score, (B) the HCT-CI, and (C) the integrated EBMT-score. EBMT = European Group for Blood and Marrow Transplantation; HCT-CI = hematopoietic cell transplantation-comorbidity index; NRM = nonrelapse mortality.

Table 2

Parameters Included in the EBMT-PTCY NRM-risk Score

Parameter	SHR	Attributed Points
Patient and donor CMV serology positive	1.22	1
Myeloablative conditioning	1.26	1
Female donor to male recipient	1.28	1
Arrythmia[a]	1.31	1
Treatment-dependent diabetes mellitus[a]	1.43	1
Donor type: MMUD/Haplo	1.65	2
Cardiac disease[a]	2.10	2
Prior solid tumor[a]	2.14	2
Age at alloSCT > 60 years	2.17	2
Hepatic disease (moderate/severe)[a]	2.54	3

[a]According to HCT-CI.

alloSCT = allogeneic stem cell transplantation; CMV = cytomegalovirus; haplo = haploidentical donor; HCT-CI = hematopoietic cell transplantation-comorbidity index; MMUD = mismatched unrelated donor; NRM = nonrelapse mortality; PTCY = posttransplant cyclophosphamide.

incidence of NRM and the specific risk–benefit ratio of cyclophosphamide, established NRM-risk scores need to be re-evaluated.

In this study, we found a relatively poor predictive value for 2-year NRM in 3 previously developed NRM-risk models, including the HCT-CI, EBMT score and integrated EBMT score.[3,5,7] Using the individual parameters of these models, we developed a novel NRM-risk score in patients with AML and ALL in CR1 receiving alloSCT with PTCY-based GVHD-prophylaxis. The risk model consisted of 10 variables which were assigned points and then used in a 3-tiered risk score. The EBMT-PTCY-risk score captures patients in risk groups that are associated with distinct estimates for NRM. The associated distinct outcome and discriminatory capacity of the novel risk score were preserved in an independent test set, indicating a robust prediction model. We observed higher performance of the novel NRM-risk score in both development and test sets for the prediction of 2-year NRM compared with the HCT-CI, EBMT score, and integrated EBMT score. Finally, the new risk score was also associated with differential 2-year OS.

NRM is predominantly caused by severe GVHD and its related complications, which has encouraged the development of strategies that reduce GVHD. Intensified GVHD-prophylaxis with PTCY to deplete proliferating alloreactive T cells has been developed in the setting of haploidentical donor alloSCT by the Baltimore group.[9] Effective GVHD prevention after haploidentical donor alloSCT was shown with relatively low rates of severe acute and chronic GVHD, which resulted in promising NRM and overall outcome.[9,12] PTCY has been subsequently administered as GVHD prophylaxis for matched donor alloSCT with substantially reduced rates of chronic GVHD and low NRM.[14,18–21] Recently, the prospective randomized phase III HOVON-96 trial demonstrated improved GRFS for patients receiving HLA-matched alloSCT with PTCY+cyclosporine versus cyclosporine+mycophenolic acid, and confirmed a low NRM after PTCY-based GVHD prophylaxis.[14] Among other improvements in transplant care, the increasing application of PTCY and its favorable association with NRM warrants an evaluation of existing NRM-risk scores in that patient group for whom PTCY is considered as GVHD prophylaxis.

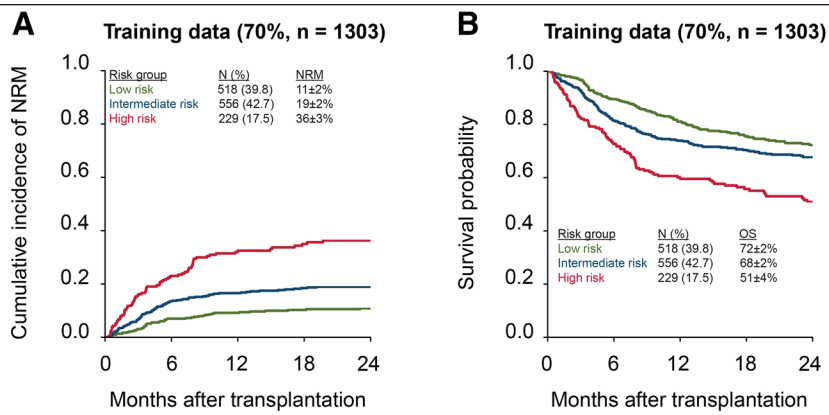


Figure 3. Training: non-relapse mortality and overall survival by the novel EBMT-PTCY risk score. (A) Cumulative incidence of NRM by the novel three-tiered EBMT-PTCY risk score in the training set. (B) Overall survival by the novel EBMT-PTCY risk score in the training set. EBMT = European Group for Blood and Marrow Transplantation; NRM = nonrelapse mortality; PTCY = posttransplantation cyclophosphamide.

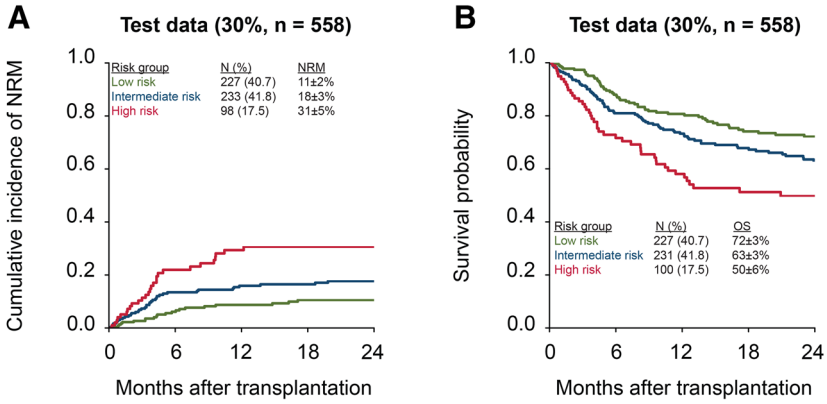


Figure 4. Test: NRM and overall survival by the novel EBMT-PTCY risk score. (A) Cumulative incidence of NRM by the novel three-tiered EBMT-PTCY risk score in the test set. (B) Overall survival by the novel EBMT-PTCY risk score in the test set. EBMT = European Group for Blood and Marrow Transplantation; NRM = nonrelapse mortality; PTCY = posttransplantation cyclophosphamide.

The EBMT score and HCT-CI are commonly used to assess transplant-related morbidity and mortality.[3,5] These risk models have limitations including reproducibility in other cohorts of patients over time with different transplant strategies or disease types.[22–25] As a result, the integrated EBMT score, combining elements from both EBMT score and HCT-CI, has been developed for patients with AML in CR1 who received RIC alloSCT.[7] That risk model was associated with better predictive capacity of 2-year NRM compared with the EBMT score and HCT-CI in a specific subgroup of older RIC alloSCT recipients. Similarly, several studies to further improve existing risk scores or to develop novel models have been performed.[22,24,26,27] These studies have shown that validation of prediction tools in different, more recent cohorts results in less predictive power, possibly explained by the continuous improvement in transplant strategies. Here, we were also not able to validate the EBMT score, HCT-CI, and integrated EBMT score for the prediction of 2-year NRM in AML and ALL recipients of alloSCT with PTCY-based GVHD-prophylaxis, emphasizing the need for continuous re-assessment of existing scores in changing patient populations and in new treatment modalities. This should be ideally performed regularly allowing clinicians for the most updated and accurately informed transplant decision.

In this study, we have developed a novel risk model for the prediction of 2-year NRM in patients receiving PTCY-based GVHD prophylaxis. Patient- and transplantation-related variables were included in the risk model, with different weighing compared with previous studies which included various hematological diseases.[3,5] Acute leukemia patients in CR1 constitute a specific patient population receiving intensified induction chemotherapy with attributable toxicity including cardiac morbidity, pulmonary function decline, and infection requiring prolonged treatment.

Pretransplant cardiac comorbidity might be of concern as PTCY could induce cardiac toxicity in a cumulative-/dose-related fashion,[28–30] further worsening cardiac function after alloSCT. In our PTCY cohort, pretransplant cardiac comorbidity was indeed associated with a two-fold increased risk for NRM. Data are not available to assess whether patients with cardiac comorbidity experienced cardiac-related mortality induced by PTCY. Recently, pretransplant cardiac toxicity was investigated in a single-center study of 585 patients receiving HLA-matched alloSCT combined with both PTCY and non-PTCY-based GVHD prophylaxis. Pretransplant cardiac toxicity was reported to be associated with age >55 years, history of hypertension, arrhythmia, and diabetes, but this association was independent of GVHD prophylaxis used, contradicting earlier reported PTCY-based cardiac toxicity.[31] These findings are in contrast to the retrospective observation that patients treated with PTCY developed more cardiac events during the first 100 days posttransplant than patients in the non-PTCY group.[32] Using a composite risk model of cardiovascular comorbidities might further improve prediction of NRM, which has been reported recently.[27]

We found no association of pretransplant pulmonary comorbidity with 2-year NRM, although the frequency of moderate and severe pulmonary disease was 12% and 7%, respectively. Since PTCY predominantly reduces chronic GVHD, we hypothesize that patients with pulmonary comorbidities receiving PTCY harbor no apparent increased risk of NRM because of reduced severe pulmonary GVHD.

Similarly, infections requiring treatment at time of alloSCT were not associated with NRM in our PTCY-specific risk score. The overall reduction of higher grades of GVHD using PTCY might again prevent NRM due to pre-existing infections.

Current risk-adapted strategies are weighting risk factors for NRM, as assessed by predictive scores, with the risk of disease relapse.[1,2] Acute leukemia relapse is primarily determined by genetic characteristics of the underlying leukemia, age of the patient, and response to treatment, especially whether or not residual disease has been eradicated before proceeding to transplant.[33–36] In personalized transplant approaches, patients at low risk of relapse have limited absolute benefit of a GVL-effect, and are therefore not considered for alloSCT because of the counterbalancing risk of NRM. We found a cumulative incidence of NRM of 11% in the low-risk group, in which the estimate was only 3% in patients with 0 points. These very low 2-year NRM estimates might identify subgroups of patients with favorable disease characteristics for whom the GVL effects of alloSCT might still be beneficial with respect to overall outcome. For these subgroups, alloSCT might be considered as consolidation treatment instead of additional chemotherapy.

The development of predictive models is influenced by the modeling approach applied. In general, clinical prediction research has been hampered by the selection of predictors based on statistical significance, categorization of predictors, and inadequate sample sizes,[37] along with selective evaluation of model performance.[38] The TRIPOD statement[39,40] is a framework for clinical prediction modeling to address these analytic difficulties. Here, we present the results of a novel prediction tool that was developed with predefined primary and secondary outcomes and did not rely on statistical significance for model development. Furthermore, the risk score was developed in a training cohort, and validated in a dedicated, independent test set. All of these decisions are consistent with the TRIPOD statement.[39,40] Some comorbidities were relatively infrequent, which limits predictive capacity. However, this statistical limitation reflects the current transplantation practice and highlights the need for external validation. Additionally, the score may be improved by evaluating composite predictors, such as composite cardiac comorbidity (valvular disease, arrhythmia, and congestive/ischemic heart disease), or by investigating the additive effect of previously identified biomarkers, such as lactate dehydrogenase,[41] serum ferritin,[42] albumin,[43] or circulating endothelial cells.[44] The EBMT database does not routinely report these factors, precluding their validation into EBMT-based risk scores.

In conclusion, ongoing improvements in transplant care require continuous reassessments of NRM prediction scores. GVHD-prophylaxis with PTCY has demonstrated a substantial reduction of GVHD and subsequent NRM, which encourages the need to reassess and refine existing NRM-risk scores. Here, we have presented a novel risk score for NRM prediction in patients with AML or ALL in CR1 receiving PTCY, that better predicted 2-year NRM compared with existing models, and which might be preferential in the setting of specific toxicities of high-dose cyclophosphamide. The risk score was validated in an independent EBMT test set with preserved predictive capacity. External validation of this EBMT-PTCY risk score is needed to further establish the clinical applicability.

ACKNOWLEDGMENTS

Following EBMT publication rules, co-authorship was offered to centers contributing the highest number of patients. Nevertheless, the authors highly appreciate the contribution by many physicians and data managers throughout the EBMT, who made this analysis possible.

AUTHOR CONTRIBUTIONS

SJFH and JV designed the study, analyzed the data, and wrote the article; YN and ML provided statistical oversight and guidance. JV, JJC, and MM supervised the study. All other authors provided clinical data and carefully reviewed and approved the final version of this article.

DISCLOSURES

RS served as a consultant to MyBiotics and Medexus. All the other authors have no conflicts of interest to disclose.

REFERENCES

1. Versluis J, Cornelissen JJ. Risks and benefits in a personalized application of allogeneic transplantation in patients with AML in first CR. *Semin Hematol*. 2019;56:164–170.
2. Cornelissen JJ, Gratwohl A, Schlenk RF, et al. The European LeukemiaNet AML Working Party consensus statement on allogeneic HSCT for patients with AML in remission: an integrated-risk adapted approach. *Nat Rev Clin Oncol*. 2012;9:579–590.
3. Gratwohl A, Hermans J, Goldman JM, et al. Risk assessment for patients with chronic myeloid leukaemia before allogeneic blood or marrow transplantation. Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation. *Lancet*. 1998;352:1087–1092.
4. Gratwohl A, Stern M, Brand R, et al. Risk score for outcome after allogeneic hematopoietic stem cell transplantation: a retrospective analysis. *Cancer*. 2009;115:4715–4726.
5. Sorror ML, Maris MB, Storb R, et al. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. *Blood*. 2005;106:2912–2919.
6. Passweg JR, Baldomero H, Bregni M, et al. Hematopoietic SCT in Europe: data and trends in 2011. *Bone Marrow Transplant*. 2013;48:1161–1167.
7. Versluis J, Labopin M, Niederwieser D, et al. Prediction of non-relapse mortality in recipients of reduced intensity conditioning allogeneic stem cell transplantation with AML in first complete remission. *Leukemia*. 2015;29:51–57.
8. Barba P, Martino R, Orti G, et al. Validation of a new integrated prognostic score to predict non-relapse mortality in patients undergoing reduced-intensity conditioning allogeneic hematopoietic cell transplantation. *Bone Marrow Transplant*. 2015;50:1371–1374.
9. Luznik L, O'Donnell PV, Symons HJ, et al. HLA-haploidentical bone marrow transplantation for hematologic malignancies using nonmyeloablative conditioning and high-dose, posttransplantation cyclophosphamide. *Biol Blood Marrow Transplant*. 2008;14:641–650.
10. O'Donnell PV, Luznik L, Jones RJ, et al. Nonmyeloablative bone marrow transplantation from partially HLA-mismatched related donors using posttransplantation cyclophosphamide. *Biol Blood Marrow Transplant*. 2002;8:377–386.
11. Pasic I, Lipton JH, Kim DD, et al. Post-transplant cyclophosphamide combined with anti-thymocyte globulin for graft-vs-host disease prophylaxis improves survival and lowers non-relapse mortality in older patients undergoing allogeneic hematopoietic cell transplantation. *Ann Hematol*. 2020;99:1377–1387.
12. Bashey A, Zhang X, Sizemore CA, et al. T-cell-replete HLA-haploidentical hematopoietic transplantation for hematologic malignancies using post-transplantation cyclophosphamide results in outcomes equivalent to those of contemporaneous HLA-matched related and unrelated donor transplantation. *J Clin Oncol*. 2013;31:1310–1316.
13. Ruggeri A, Sun Y, Labopin M, et al. Post-transplant cyclophosphamide versus anti-thymocyte globulin as graft- versus-host disease prophylaxis in haploidentical transplant. *Haematologica*. 2017;102:401–410.
14. Broers AEC, de Jong CN, Bakunina K, et al. Posttransplant cyclophosphamide for prevention of graft-versus-host disease: the prospective randomized HOVON-96 trial. *Blood Adv*. 2022;6:3378–3385.
15. Spyridonidis A, Labopin M, Savani BN, et al. Redefining and measuring transplant conditioning intensity in current era: a study in acute myeloid leukemia patients. *Bone Marrow Transplant*. 2020;55:1114–1125.

16. Battipaglia G, Labopin M, Kröger N, et al. Posttransplant cyclophosphamide vs antithymocyte globulin in HLA-mismatched unrelated donor transplantation. *Blood*. 2019;134:892–899.
17. Gagelmann N, Bacigalupo A, Rambaldi A, et al. Haploidentical stem cell transplantation with posttransplant cyclophosphamide therapy vs other donor transplantations in adults with hematologic cancers: a systematic review and meta-analysis. *JAMA Oncol*. 2019;5:1739–1748.
18. Luznik L, Bolaños-Meade J, Zahurak M, et al. High-dose cyclophosphamide as single-agent, short-course prophylaxis of graft-versus-host disease. *Blood*. 2010;115:3224–3230.
19. Kanakry CG, O'Donnell PV, Furlong T, et al. Multi-institutional study of post-transplantation cyclophosphamide as single-agent graft-versus-host disease prophylaxis after allogeneic bone marrow transplantation using myeloablative busulfan and fludarabine conditioning. *J Clin Oncol*. 2014;32:3497–3505.
20. Mielcarek M, Furlong T, O'Donnell PV, et al. Posttransplantation cyclophosphamide for prevention of graft-versus-host disease after HLA-matched mobilized blood cell transplantation. *Blood*. 2016;127:1502–1508.
21. Bolaños-Meade J, Reshef R, Fraser R, et al. Three prophylaxis regimens (tacrolimus, mycophenolate mofetil, and cyclophosphamide; tacrolimus, methotrexate, and bortezomib; or tacrolimus, methotrexate, and maraviroc) versus tacrolimus and methotrexate for prevention of graft-versus-host disease with haemopoietic cell transplantation with reduced-intensity conditioning: a randomised phase 2 trial with a non-randomised contemporaneous control group (BMT CTN 1203). *Lancet Haematol*. 2019;6:e132–e143.
22. Barba P, Piñana JL, Martino R, et al. Comparison of two pretransplant predictive models and a flexible HCT-CI using different cut off points to determine low-, intermediate-, and high-risk groups: the flexible HCT-CI Is the best predictor of NRM and OS in a population of patients undergoing allo-RIC. *Biol Blood Marrow Transplant*. 2010;16:413–420.
23. Barba P, Martino R, Pérez-Simón JA, et al. Combination of the hematopoietic cell transplantation comorbidity index and the European Group for Blood and Marrow Transplantation score allows a better stratification of high-risk patients undergoing reduced-toxicity allogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2014;20:66–72.
24. Shouval R, Fein JA, Shouval A, et al. External validation and comparison of multiple prognostic scores in allogeneic hematopoietic stem cell transplantation. *Blood Adv*. 2019;3:1881–1890.
25. Castagna L, Fürst S, Marchetti N, et al. Retrospective analysis of common scoring systems and outcome in patients older than 60 years treated with reduced-intensity conditioning regimen and alloSCT. *Bone Marrow Transplant*. 2010;46:1000–1005.
26. Sorror ML, Storer B, Storb RF. Validation of the hematopoietic cell transplantation-specific comorbidity index (HCT-CI) in single and multiple institutions: limitations and inferences. *Biol Blood Marrow Transplant*. 2009;15:757–758.
27. Shouval R, Fein JA, Cho C, et al. The Simplified Comorbidity Index (SCI) - a new tool for prediction of non-relapse mortality in allogeneic HCT. *Blood Adv*. 2022;6:1525–1535.
28. Goldberg MA, Antin JH, Guinan EC, et al. Cyclophosphamide cardiotoxicity: an analysis of dosing as a risk factor. *Blood*. 1986;68:1114–1118.
29. de Jonge ME, Huitema ADR, Rodenhuis S, et al. Clinical pharmacokinetics of cyclophosphamide. *Clin Pharmacokinet*. 2005;44:1135–1164.
30. Iqubal A, Iqubal MK, Sharma S, et al. Molecular mechanism involved in cyclophosphamide-induced cardiotoxicity: Old drug with a new vision. *Life Sci*. 2019;218:112–131.
31. Yeh J, Whited L, Saliba RM, et al. Cardiac toxicity after matched allogeneic hematopoietic cell transplant in the posttransplant cyclophosphamide era. *Blood Adv*. 2021;5:5599–5607.
32. Duléry R, Mohty R, Labopin M, et al. Early cardiac toxicity associated with post-transplant cyclophosphamide in allogeneic stem cell transplantation. *JACC Cardio Oncol*. 2021;3:250–259.
33. Hunger SP, Mullighan CG. Redefining ALL classification: toward detecting high-risk ALL and implementing precision medicine. *Blood*. 2015;125:3977–3987.
34. Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood*. 2017;129:424–447.
35. Dillon R, Hills R, Freeman S, et al. Molecular MRD status and outcome after transplantation in NPM1-mutated AML. *Blood*. 2020;135:680–688.
36. Venditti A, Piciocchi A, Candoni A, et al. GIMEMA AML1310 trial of risk-adapted, MRD-directed therapy for young adults with newly diagnosed acute myeloid leukemia. *Blood*. 2019;134:935–945.
37. Steyerberg EW, Uno H, Ioannidis JPA, et al. Poor performance of clinical prediction models: the harm of commonly applied methods. *J Clin Epidemiol*. 2018;98:133–143.
38. Potdar R, Varadi G, Fein J, et al. Prognostic scoring systems in allogeneic hematopoietic stem cell transplantation: where do we stand? *Biol Blood Marrow Transplant*. 2017;23:1839–1846.
39. Moons KGM, Altman DG, Reitsma JB, et al. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): explanation and elaboration. *Ann Intern Med*. 2015;162:W1–W73.
40. Collins GS, Reitsma JB, Altman DG, et al. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. *BMJ*. 2015;350:g7594.
41. Geva M, Pryce A, Shouval R, et al. High lactate dehydrogenase at time of admission for allogeneic hematopoietic transplantation associates to poor survival in acute myeloid leukemia and non-Hodgkin lymphoma. *Bone Marrow Transplant*. 2021;56:2690–2696.
42. Kataoka K, Nannya Y, Hangaishi A, et al. Influence of pretransplantation serum ferritin on nonrelapse mortality after myeloablative and nonmyeloablative allogeneic hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant*. 2009;15:195–204.
43. Shouval R, de Jong CN, Fein J, et al. Baseline renal function and albumin are powerful predictors for allogeneic transplantation-related mortality. *Biol Blood Marrow Transplant*. 2018;24:1685–1691.
44. Beije N, Versluis J, Kraan J, et al. Circulating endothelial cell enumeration demonstrates prolonged endothelial damage in recipients of myeloablative allogeneic stem cell transplantation. *Haematologica*. 2015;100:e246–e249.