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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

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A B S T R A C T

This study was conducted to determine whether the integration of the Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI) and the European Group for Blood and Marrow Transplantation (EBMT) score would improve individual capacity for stratification of high-risk HCT candidates. A total of 442 consecutive patients receiving an allogeneic HCT after reduced-toxicity conditioning was included. Final HCT-CI and EBMT scores were calculated and validated. Then, patients were grouped into a 6-category new combination model according to the HCT-CI (0, 1 to 2, ≥3) and EBMT scores (0 to 3, 4 to 7), and the model's predictive capacity was also evaluated. Median HCT-CI and EBMT scores were 3 and 4, respectively. Increased HCT-CI was associated with higher 4-year nonrelapse mortality (NRM) and lower 4-year overall survival (OS), whereas a high EBMT score was associated with higher 4-year NRM. The HCT-CI showed a trend for a better predictive capacity than the EBMT score (*c*-statistic .6 versus .54, $P = .1$). According to the new model, patients within HCT-CI of 0 and HCT-CI of 1 to 2 groups had similar risk of NRM independently of their EBMT score. Within the HCT-CI ≥ 3 group, patients with low EBMT score showed lower NRM (25% versus 40%, $P = .04$) and a trend to higher OS (52% versus 36%, $P = .06$) than patients with a high EBMT score. Moreover, patients with HCT-CI ≥ 3 and EBMT score 0 to 3 had similar outcomes than those with HCT-CI of 1 to 2. In conclusion, the combination of HCT-CI and the EBMT score is feasible and might contribute to a better identification of high-risk patients, improving selection of best allogeneic HCT candidates.

INTRODUCTION

Allogeneic hematopoietic cell transplantation (allo-HCT) is inherently associated with a risk of nonrelapse mortality (NRM) that varies greatly depending on transplant and patient characteristics. The assessment of the risk of complications and mortality before the procedure is extremely important when facing the decision of transplant indication, conditioning regimen, and patient counseling.

With the advent of reduced-toxicity conditionings (including reduced-intensity and nonmyeloablative conditionings), the indication of allo-HCT has been expanded. In this setting, a careful assessment of the risk of complications after the procedure is of utmost importance because reduced-toxicity conditioned allo-HCT recipients are older and have more and severer comorbidities than patients receiving conventional myeloablative allo-HCT [1].

Several pretransplant models [2-5] have been developed to predict the outcome after allo-HCT through the selection of the best candidates and conditioning regimens. Two models have emerged as the most popular, 1 on each side of the Atlantic: the HCT Comorbidity Index (HCT-CI) and the European Group for Blood and Marrow Transplantation (EBMT) score. The former summarizes 17 comorbid conditions of the patients before transplantation, whereas the latter is a global prognostic model including several transplant-related variables. These models have been validated by several groups in several transplant and diseases settings [6-10]. However, their predictive capacity for a particular patient is limited, suggesting that further improvement is still needed in this setting.

Considering that these 2 models are focused on different pre-HCT characteristics (HCT-CI on comorbidities and the EBMT score on more classical risk factors), we hypothesized that the combination of the 2 could improve their individual predictive capacity. To that end, we conducted a study in a large and homogeneous population of patients receiving reduced-toxicity allo-HCT. Each model was individually evaluated, and then a full integration of both models was conducted to explore the possible role in the identification of high-risk patients.

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METHODS

The study included all consecutive adult patients who received an allo-HCT with reduced-toxicity conditioning in the Hospital Vall d'Hebrón (Barcelona), Hospital de Sant Pau (Barcelona), Hospital Universitario (Salamanca), and Hospital Clínic (Barcelona) between February 1998 and November 2008. The transplant protocol was approved by local and national ethics committees, and patients gave written informed consent for their inclusion in the protocol.

Transplant Procedure

The transplant protocol was published elsewhere in detail [11]. In brief, conditioning regimen for all patients included fludarabine (150 mg/m^2) in combination with melphalan (70 to 140 mg/m^2; lymphoid malignancies and multiple myeloma), busulfan (8 to 10 mg/kg; myeloid malignancies, except for chronic myeloid leukemia), cyclophosphamide (120 mg/kg; solid malignancies), or low-dose total body irradiation (2 Gy; chronic myeloid leukemia). Although the above combinations may not be strictly considered as reduced-intensity conditioning regimens (ie, fludarabine and busulfan 10 mg/kg) [12], the aim of this protocol was to expand transplant indication to older and unfit patients. Thus, in line with other investigators [13], these regimens are referred to as reduced-toxicity conditionings throughout the article.

Reduced-toxicity conditioning was preferred over myeloablative conditioning in patients ≥50 years of age and with previous HCT and severe comorbidities. Graft-versus-host disease (GVHD) prophylaxis included a calcineurin inhibitor (mainly cyclosporine A) and short-course methotrexate (day +1 at 15 mg/m^2 and days +3,+6, +11 at 10 mg/m^2, with folinic acid rescue) or cyclosporine A plus mycophenolate mofetil. In vivo T cell depletion was used in patients receiving a transplant from HLA mismatched related or unrelated donors (antithymocyte globulin or alemtuzumab). Advanced risk for baseline disease was defined following the EBMT criteria [3] and is summarized in Table 1.

Acyclovir, fluconazole, and quinolones were administered as infectious prophylaxis. Cytomegalovirus infection screening (using antigenemia pp65 before 2003 and RT-PCR after that year) for guiding preemptive therapy and Galactomannan Platelia assay (Bio-Rad Laboratories, Hercules, CA, since 2003) determinations in blood and serum samples were performed as described [14,15].

Regarding HLA typing, family donors were tested for HLA-A, -B (low resolution), and -DRB1 (high resolution). Unrelated donors were tested for HLA-A, -B, -C, -DRB1, and -DQB1 (high resolution).

Predictive Models

The HCT-CI and the EBMT score were calculated as originally defined [2,3]. All patients underwent laboratory studies, pulmonary function tests, and echocardiography performed in each center within day −30 and day −10 of HCT.

Calculation of the HCT-CI and EBMT scores was retrospectively performed based on medical records and results of pretransplant studies. According to the HCT-CI, patients were grouped by low risk (HCT-CI = 0), intermediate risk (HCT-CI = 1 to 2), or high risk (HCT-CI ≥ 3) per Sorror et al. [2]. Regarding the EBMT score, patients were classified as 0 to 2, 3, 4, 5, or 6 to 7 to ensure at least 5% of patients in each group.

The individual predictive capacity of the HCT-CI and the EBMT score for NRM and overall survival (OS) was evaluated. Thereafter, a new combination model was built based on the risk group of both models. To limit the number of categories of the new model, the EBMT score was categorized into high- and low-risk groups according to the median score (low risk for EBMT scores from 0 to 3 and high risk for EBMT scores from 4 to 7). The final 6-category combination model classified patients as follows: group 1, HCT-CI = 0 and EBMT score = 0 to 3; group 2, HCT-CI = 0 and EBMT score = 4 to 7; group 3, HCT-CI = 1 to 2 and EBMT score = 0 to 3; group 4, HCT-CI = 1 to 2 and EBMT score = 4 to 7; group 5, HCT-CI ≥ 3 and EBMT score = 0 to 3; and group 6, HCT-CI ≥ 3 and EBMT score 4 to 7.

Endpoints, Definitions, and Statistical Analysis

The primary endpoint of the study was NRM defined as the time from day 0 of the transplant to death from any cause but relapse/progressive disease. Secondary outcomes were OS defined as the time from day 0 of the transplant to death from any cause and description of the patient distribution according to both models.

Neutrophil and platelet engraftment were defined as the first of 3 consecutive days with neutrophil count >.5 × 10^9/L (without granulocyte colony-stimulating factor support) and transfusion-independent platelet count >50 × 10^9/L, respectively. Patients dying before day +100 were not considered for chronic GVHD analysis.

The incidence of NRM, GVHD, and relapse were calculated using cumulative incidence estimates, taking into account the competing risk model, considering relapse as a competitive event [16]. The probability of OS was estimated using Kaplan-Meier curves and compared using log rank tests [17]. Univariate Cox regression analysis was used to estimate risk factors of 4-year NRM and OS. The possible risk factors for early (100-day) NRM were analyzed by using logistic regression. Variables tested in the univariate Cox regression analysis for transplant outcomes are listed in Table 2. Multivariate analysis (MVA) was performed taking into account the competing risk structure. The HCT-CI and the EBMT score were forced into the MVA model. Other pretransplant variables were included in the MVA model when a significance level of $P \leq .1$ was detected in the univariate Cox regression analysis. A significance level of $P \leq .05$ (2 sided) was required in the MVA. In the risk factor analysis of the EBMT score, variables already included in the score were not included in the MVA. The *c*-statistic was calculated to estimate the predictive capacity of the HCT-CI and EBMT score for NRM, as previously described [18]. All statistical analyses were performed using SPSS version 17.0 (SPSS, Chicago, IL) and NCSS 2004 (Number Cruncher Statistical System, Kaysville, UT).

Table 1
Patient Characteristics (N = 442)

Characteristic	Value
Median age, yr (range)	53 (16-71)
Gender, male, n (%)	268 (61)
Female donor to male recipient	115 (26)
Underlying disease, n (%)	
Acute leukemia and MDS	156 (35)
Hodgkin lymphoma	56 (13)
NHL and CLL	125 (28)
Multiple myeloma	72 (16)
Others	33 (7)
Advanced disease status at HCT,* n (%)	209 (47)
Recipient–donor CMV serology, n (%)	
Recipient and donor negative	49 (11)
Other	393 (89)
Donor type, n (%)	
HLA identical sibling	353 (80)
Alternative (VUD or MsM related)	89 (20)
Conditioning regimen, n (%)	
Fludarabine-melphalan	270 (61)
Fludarabine-busulfan	146 (33)
Other	26 (6)
Peripheral blood stem cells, n (%)	422 (95)
Alemtuzumab or ATG-based conditioning, n (%)	60 (14)
GVHD prophylaxis, n (%)	
CsA-MTX	288 (65)
CsA-MMF	128 (29)
Other	26 (6)
Year of HCT, median (range)	2003 (1999-2008)
Median follow-up for survivors, mo (range)	53 (3-123)

MDS indicates myelodysplastic syndrome; NHL, non-Hodgkin lymphoma; CLL, chronic lymphocytic leukemia; CMV, cytomegalovirus; VUD, volunteer unrelated donor; MsM, HLA mismatch; ATG, antithymocyte globulin; CsA, cyclosporine A; MTX, methotrexate; MMF, micophenolate mophetil.

* Advanced disease status: acute leukemia in >2nd complete remission, chronic myeloid leukemia in blastic phase, Hodgkin disease, lymphomas and multiple myeloma in ≥3rd remission. Other patients with partial remission or persistent disease at transplantation (except for myeloma and Hodgkin disease) were also considered as advanced disease.

RESULTS

Patient Characteristics

Of the 468 transplanted patients, 442 had enough data for HCT-CI and EBMT score calculation and were included in the study. Pretransplant characteristics of the patients in the study are listed in Table 1. In brief, median age at transplantation was 53 years (range, 16 to 71). Most patients received allo-HCT from HLA identical sibling donors (n = 353, 80%) mainly for acute leukemia and myelodysplastic syndromes (n = 156, 35%). Median follow-up for survivors was 53 months (range, 3 to 123).

HCT-CI and EBMT Score

The median HCT-CI and EBMT scores were 3 (range, 0 to 13) and 4 (range, 1 to 7), respectively. Patient distribution

Table 2
Univariate and Multivariate Analysis of Pretransplant Variables on Transplant Outcomes

Variables	100-Day NRM	*P*	4-Year NRM	*P*	4-Year OS	*P*
Univariate analysis						
Male vs. female	1.2 (.7-2.1)	.5	1 (.7-1.5)	.7	1.1 (.9-1.5)	.4
Age > 60	.9 (.5-1.8)	.8	1.7 (1.2-2.5)	.007	1.5 (1.1-2)	.01
HLA alternative	2 (1.1-3.8)	.02	1.7 (1.2-2.5)	.006	1.3 (1.1-1.9)	.03
Female to male	.8 (.4-1.5)	.5	1.5 (1-2.1)	.04	1.3 (1-1.8)	.04
CMV status neg-neg	.4 (1-1.5)	.2	.6 (.3-1.2)	.2	.6 (.4-1)	.04
High-risk disease	2.5 (1.2-5)	.01	1.2 (.8-1.8)	.4	1 (.7-1.2)	.6
PBSC vs. other	1.8 (.6-5.7)	.3	.9 (.4-1.8)	.7	.7 (.4-1.2)	.2
Lymphoid vs. myeloid	.5 (.3-1)	.05	1 (.7-1.4)	1	.9 (.7-1.1)	.3
Flu-bu vs. other	1.8 (.9-3.5)	.1	.9 (.6-1.3)	.5	1 (.8-1.4)	.8
Time to HCT >12 mo	.4 (1-1.8)	.2	1.2 (.6-2.4)	.7	1.1 (.6-1.8)	.8
Year of HCT (1999-2003)						
TCD	.9 (.4-2)	.8	1.4 (.9-2.3)	.13	1.2 (.8-1.8)	.3
EBMT score						
1-3	1.0		1.0		1.0	
4-7	2 (1-4.1)	.06	1.4 (.9-2.2)	.09	1.3 (.9-1.7)	.1
HCT-CI						
0	1.0		1.0		1.0	
1-2	2 (.6-6.2)	.2	1.6 (.9-3)	.09	1.4 (.8-2)	.17
≥3	3.9 (1.4-10.9)	.01	2.2 (1.3-3.8)	.004	1.8 (1.3-2.7)	.002
Multivariate analysis						
Age > 60	—		2 (1.3-3)	.002	1.6 (1.2-2.2)	.005
HLA alternative	2.5 (1.3-4.8)	.007	2.4 (1.6-3.7)	<.001	1.8 (1.3-2.5)	.001
Female to male	—		1.5 (1.1-2.2)	.02	1.3 (1-1.8)	.05
High-risk disease	2.6 (1.3-2.5)	.01	—		—	
HCT-CI						
0	1.0		1.0		1.0	
1-2	1.9 (.7-6)	.3	1.6 (.9-3)	.09	1.3 (.8-2)	.2
≥3	4.4 (1.5-13)	.007	2.3 (1.3-3.8)	.003	1.9 (1.3-2.8)	.002
EBMT score						
1-3	1.0		1.0		1.0	
4-7	1.2 (.5-3.1)	.7	1.4 (.9-2.1)	.1	1.2 (.9-1.7)	.2

CMV indicates cytomegalovirus; PBSC, peripheral blood stem cells; Flu-bu, fludarabine and busulfan; TCD, T cell depletion.

according to the HCT-CI was as follows: HCT-CI = 0, n = 87 (19%); HCT-CI = 1 to 2, n = 130 (29%); and HCT-CI ≥ 3, n = 225 (51%). According to the EBMT score, 62 (14%), 64 (14%), 130 (29%), 128 (29%), and 61 (14%) patients had a score of 0 to 2, 3, 4, 5, and 6 to 7, respectively.

Patients with higher HCT-CI showed higher risk of NRM at 100 days (HCT-CI = 0, reference [ref]; HCT-CI = 1 to 2, hazard ratio [HR], 1.9 [95% confidence interval {CI}, .7 to 6], $P = .2$; and HCT-CI ≥ 3, HR, 4.4 [95% CI, 1.5 to 13], $P = .007$) and at 4 years (HCT-CI = 0, ref; HCT-CI = 1 to 2, HR, 1.6 [95% CI, .9 to 3], $P = .09$; and HCT-CI ≥ 3, HR, 2.3 [95% CI, 1.3 to 3.8], $P = .003$) and a lower probability of OS (HCT-CI = 0, ref; HCT-CI = 1 to 2, HR, 1.3 [95% CI, .8 to 2], $P = .2$; and HCT-CI ≥ 3, HR, 1.9 [95% CI, 1.3 to 2.8], $P = .002$) in the MVA (Table 2). The *c*-statistic for the HCT-CI for NRM was .601 (c-95% CI, .55 to .64).

Patients with higher EBMT scores showed a trend to an increased risk of 4-year NRM (EBMT score = 0 to 3, ref; EBMT score = 4 to 7, HR, 1.4 [95% CI, .9 to 2.1], $P = .1$) and similar risk of 100-day NRM (EBMT score = 0 to 3, ref; EBMT score = 4 to 7, HR, 1.2 [95% CI, .5 to 3.1], $P = .7$) and 4-year OS (EBMT score = 0 to 3, ref; EBMT score = 4 to 7, HR, 1.2 [95% CI, .9 to 1.7], $P = .2$) than patients with low EBMT scores. Regarding individual scores, an increased risk of 100-day NRM (HRs of 1.0 (ref), .8, 1.2, 1.6, and 3.9 for EBMT scores of 0 to 2, 3, 4, 5, and 6 to 7, respectively [global $P = .003$]) and 4-year NRM (HRs of 1.0, .8, 1.1, 1.2, and 2.4 for EBMT scores of 0 to 2, 3, 4, 5, and 6 to 7, respectively [global $P = .007$]) were observed in higher EBMT scores. There was a nonsignificant trend for worse OS in patients with higher EBMT scores (HRs 1.0, .8, 1.1, 1.1, and 1.6 for EBMT scores of 0 to 2, 3, 4, 5, and 6 to 7, respectively [global $P = .08$]). The *c*-statistic for the EBMT score for NRM was .542 (c-95% CI, .51 to .58), and a trend to a lower predictive capacity than the HCT-CI was observed ($P = .1$). More detailed information on the impact of all EBMT scores on NRM and OS is summarized in Supplementary Table 1.

Combination Model

After integrating the HCT-CI and the EBMT score as detailed in Methods, a new combination model was built. The distribution of patients according to the 6 categories of the new combination model is summarized in Table 3 and ranged from 32 patients (7%) in group 1 (HCT-CI = 0 and EBMT score <4) to 168 patients (38%) in group 6 (HCT-CI ≥ 3 and EBMT score ≥4).

Risks of NRM and OS according to the 6-category model combining HCT-CI and EBMT score are summarized in Table 3, Figure 1, and Supplementary Figure 1. In the group of HCT-CI = 0, patients with EBMT score <4 (group 1) and EBMT score 4 to 7 (group 2) had similar NRM (20% [95% CI, 10% to 42%] versus 19% [95% CI, 11% to 33%], $P = .9$) and OS (54% [95% CI, 44% to 64%] versus 63% [95% CI, 56% to 70%], $P = .5$). Also, in the group of HCT-CI = 1 to 2, patients with EBMT score <4 (group 3) and EBMT score 4 to 7 (group 4) had similar NRM (28% [95% CI, 17% to 48%] versus 28% [95% CI, 20% to 39%], $P = .8$) and OS (58% [95% CI, 50% to 66%] versus 53% [95% CI, 48% to 58%], $P = .4$). Regarding the group of HCT-CI ≥ 3, patients with EBMT score <4 (group 5) had lower NRM (25% [95% CI, 16% to 39%] versus 40% [95% CI, 33% to 48%], $P = .04$) and a trend to higher OS (52% [95% CI, 45% to 59%] versus 36% [95% CI, 32% to 40%], $P = .06$) than patients with EBMT score 4 to 7 (group 6). Additionally, patients in group 5 (HCT-CI ≥ 3 and EBMT score <4) had similar NRM (25% [95% CI, 16% to 39%] versus 28% [95% CI, 20% to 37%], $P = .5$) and OS (52% [95% CI, 45% to 59%] versus 54% [95% CI, 50% to 58%], $P = .9$) than patients in groups 3 and 4 (HCT-CI = 0 to 2).

Table 3
Patient Distribution and Transplant Outcomes According to the New 6-Category Model

	N (%)	4-Year NRM			4-Year OS		
		Events (%)	HR (95% CI)	Percent	Alive (%)	HR (95% CI)	Percent (95%CI)
Group 1: HCT-CI = 0 and EBMT score <4	32 (7)	6 (19)	1 (ref)	20	19 (59)	1 (ref)	54 (44-64)
Group 2: HCT-CI = 0 and EBMT score ≥4	55 (12)	10 (18)	1 (.4-2.7)	19	36 (66)	.8 (.4-1.6)	63 (56-70)
Group 3: HCT-CI = 1-2 and EBMT score <4	37 (8)	10 (27)	1.4 (.5-3.9)	28	22 (60)	.9 (.5-2)	58 (50-66)
Group 4: HCT-CI = 1-2 and EBMT score ≥4	93 (21)	25 (27)	1.6 (.7-4)	28	51 (55)	1.2 (.7-2.3)	53 (48-58)
Group 5: HCT-CI ≥3 and EBMT score <4	57 (13)	14 (25)	1.4 (.5-3.6)	25	32 (54)	1.2 (.6-2.3)	52 (45-59)
Group 6: HCT-CI ≥3 and EBMT score ≥4	168 (38)	63 (38)	2.5 (1.1-5.8)	40	67 (39)	1.8 (1-3.2)	36 (32-40)
Total	442 (100)	128 (29)	—	30	227 (51)	—	48 (46-51)

NRM and OS according to the new 6-category model integrating the HCT-CI and EBMT score. *P* value for transplant outcomes between group 6 and group 5: 4-year NRM, $P = .04$; 4-year OS, $P = .06$. *P* value for transplant outcomes between group 5 and groups 3 and 4 (together): 4-year NRM, $P = .5$; 4-year OS, $P = .9$.

General Outcomes

Nonrelapse mortality

Overall, 56 (13%) and 131 patients (30%) experienced NRM at 100 days and at 4 years, respectively. Cumulative incidence of 4-year NRM was 30% (95% CI, 26% to 35%). The most common causes of NRM were GVHD and infections (51 patients died from GVHD with infection, 45 from infection without GVHD, and 27 from GVHD without infection).

Risk factors for NRM in the MVA are summarized in Table 2. The impacts of HCT-CI and EBMT score and the combination model have been shown. Other variables associated with a higher risk of 100-day NRM were donor type (non-HLA identical sibling donors: HR, 2.5 [95% CI, 1.3 to 4.8], $P = .007$) and high-risk diseases (HR, 2.6 [95% CI, 1.3 to 2.5], $P = .01$). Other variables associated with a higher risk of 4-year NRM were donor type (non-HLA identical siblings: HR, 2.4 [95% CI, 1.6 to 3.7], $P < .001$), age at HCT (age > 60 years: HR, 2 [95% CI, 1.3 to 3], $P = .002$), and donor–recipient gender combination (female-to-male: HR, 1.5 [95% CI, 1.1 to 2.2], $P = .02$). For the subset of patients with HCT-CI = 0 (groups 1 and 2) and HCT-CI = 1 to 2 (groups 3 and 4), no risk factors for NRM could be identified (Supplementary Table 2).

Relapse and OS

Globally, 145 patients (33%) experienced relapse of baseline disease, for a cumulative incidence of 32% (95% CI, 28% to 37%) at 4 years. A total of 227 patients (51%) remained alive at median follow-up for a probability of 4-year OS of 48% (95% CI, 46% to 51%). The impact of HCT-CI and EBMT score and the combination model on OS has been shown. Other variables associated with worse OS in the MVA were donor type (non-HLA identical siblings: HR, 1.8 [95% CI, 1.3 to 2.5], $P = .001$), age at HCT (age > 60 years: HR, 1.6 [95% CI, 1.2 to 2.2], $P = .005$), and donor–recipient gender combination (female-to-male: HR, 1.3 [95% CI, 1 to 1.8], $P = .05$).

Other transplant outcomes

Neutrophil ($>.5 \times 10^9$/L) and platelet ($>50 \times 10^9$/L) recovery occurred at a median of 15 days (range, 9 to 68) and 19 days (range, 8 to 203), respectively. Globally, 436 and 380 patients were assessable for acute and chronic GVHD, respectively. Cumulative incidence of grades II to IV acute GVHD and any grade of chronic GVHD were 26% (95% CI, 22% to 30%) and 51% (95% CI, 46% to 56%), respectively.

DISCUSSION

This is the first published study integrating 2 commonly used predictive models in the HCT setting (the HCT-CI and the EBMT score) in a large population of allo-HCT recipients, showing that the consideration of the EBMT score in patients with HCT-CI ≥ 3 results in a better discrimination of high-risk patients. This information is especially relevant in patients undergoing reduced-toxicity allo-HCT because these patients are more likely to have advanced comorbidities.

The HCT-CI and EBMT score were developed in very large cohorts of HCT patients and have been studied in other settings, including different diseases, stem cell sources, and conditioning regimens. Whereas the HCT-CI summarizes 17 comorbid conditions of the patients under 1 score, the EBMT score is a global prognostic model including several transplant-related variables. Many studies have confirmed their predictive capacity for several transplant outcomes [6-10], although some others have not [19,20]. Furthermore, each of these models looks at a particular group of risk factors but neglects some others. For instance, the HCT-CI includes a high number of carefully selected comorbid conditions but does not consider other patient- and transplant-related variables such as age, disease status, and donor type, which have been associated with an adverse outcome after the procedure. In addition, the EBMT score does not consider comorbidities and assigns the same theoretical risk to a fit patient as it does to a recipient with renal, hepatic, and pulmonary impairment with similar transplant-related characteristics.

In clinical practice, variables included in both models are considered daily when facing decisions on the intensity of conditioning and even transplant indication for a particular patient. Moreover, the final score of these models is usually taken into account, although data on how to integrate this information are lacking. For instance, it is not clear how to proceed with a patient with high risk of mortality according to 1 model (ie, HCT-CI = 5) but with low risk according to another model (ie, EBMT score = 1). A few studies have separately applied each of these 2 models to the same cohort of patients [20,21] with disparity of results between them. Others have evaluated the addition of some variables included in the EBMT score to the HCT-CI. Hence, Sorror et al. [22] combined the HCT-CI with disease status, showing that this combination allowed a better stratification of patients at high risk of NRM after the procedure. Nonetheless, these models have not been fully integrated before.

Our results show that after combining both models, patients within low (score = 0) and intermediate (score = 1 to 2) HCT-CI risk groups had similar outcome irrespective of their EBMT score. Moreover, no individual pretransplant characteristics were identified as potential risk factors for NRM in patients with HCT-CI of 0 to 2, suggesting that if medically fit, a patient can handle the risk of having an unrelated donor or an unfavorable gender combination between donor and recipient. However, in patients with more and severer comorbidities (HCT-CI ≥ 3), having a high EBMT score was associated with worse outcome after the

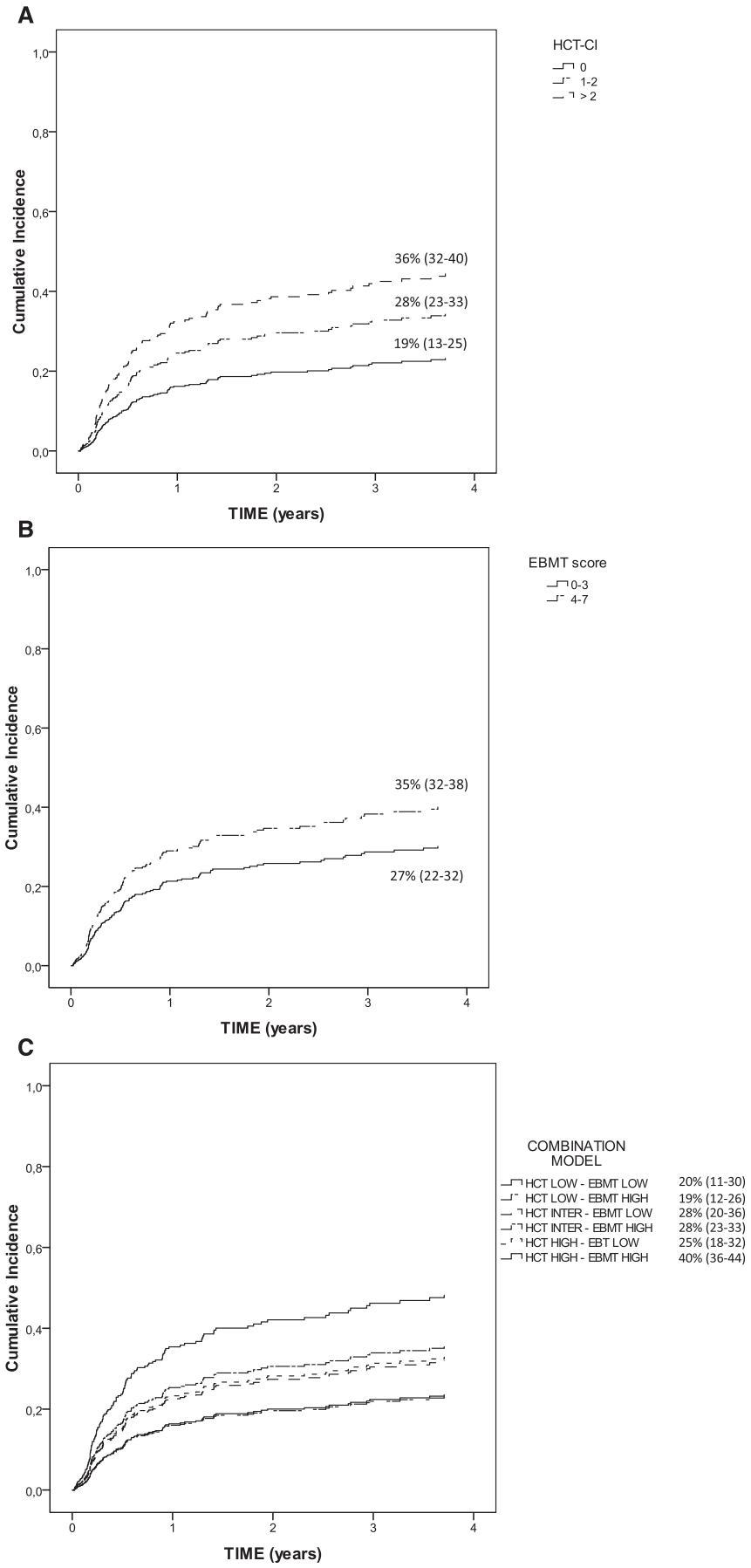

Figure 1. NRM mortality according to the HCT-CI, EBMT score, and the combination model. Cumulative incidence estimates (and 95% CI) of NRM according to the HCT-CI (A), EBMT score (B), and the integration of both models (C).

procedure. In our cohort, patients with HCT-CI $\geq$ 3 and high EBMT scores had a risk of NRM at 4 years of 40%. Thus, patients within this group and at high risk of relapse according to biological characteristics of their diseases (which are not included in the EBMT score) should be carefully selected for allo-HCT due to a very low probability of surviving long term. On the other hand, the risk of NRM for patients with HCT-CI $\geq$ 3 and low EBMT scores (group 5) was similar to the risk of patients with HCT-CI score = 1 to 2 (groups 3 and 4), suggesting that patients with advanced comorbidities and low EBMT scores should be considered similarly to those with intermediate HCT-CI. This information is especially relevant in patients receiving allo-HCT with reduced-toxicity conditioning, because up to two thirds [19,22] of these patients have HCT-CI $\geq$ 3.

We and others have reported that the predictive capacity in an individual patient of these models is lower than 70% [2,23]. In our study, the *c*-statistic for both models was rather low (<.65), and there was a trend to a better predictive capacity for the HCT-CI compared with the EBMT score. Thus, it seems that further efforts are needed in the predictive model field to reach a better characterization of high-risk patients. To that end, the integration of pretransplant models reported herein might be a useful but not the sole strategy to improve their predictive capacity. For instance, it is necessary to update these models to the current HCT practice. Regarding the EBMT score, several groups have suggested some modifications to the model, such as the addition of an extra point to the age category for patients >60 years and the modification of the parameter time from diagnosis to transplant in some baseline diseases [21,24]. Also, the disease risk category could be revised by adding biological characteristics of the diseases, including cytogenetics in AML and histological subtype in lymphomas. Recently, a new risk model considering these biological characteristics has been developed and validated in a large HCT population [4] and could be used as a guide to redefine the disease risk. Regarding the HCT-CI, a more detailed redefinition of some comorbidities such as previous infection could also be considered. Another important issue is the standardization and simplification of data collection. To that end, some general recommendations, web-based tools, and training programs have been proposed and have shown positive results in the improvement of the interobserver agreement rate [25].

The limited predictive capacity of the EBMT score in our cohort is a limitation of our study and might be explained by the simplification of the EBMT scores into 2 groups and the heterogeneity of baseline diseases. Other limitations might be derived from the retrospective perspective of the study.

In conclusion, our study demonstrates that the combination of HCT-CI and the EBMT score is feasible and might contribute to a better identification of high-risk patients, improving selection of best allo-HCT candidates. Our results suggest that patients with advanced comorbidities but low EBMT scores should be considered similarly as patients with intermediate HCT-CI, whereas patients with high HCT-CI and EBMT scores have a very high probability of developing transplant-related complications. However, these findings should be confirmed in independent populations of HCT recipients before their implementation in clinical practice.

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.bbmt.2013.10.011.

REFERENCES

1. Xhaard A, Porcher R, Chien JW, et al. Impact of comorbidity indexes on non-relapse mortality. *Leukemia*. 2008;22:2062-2069.
2. 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.
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. Armand P, Gibson CJ, Cutler C, et al. A disease risk index for patients undergoing allogeneic stem cell transplantation. *Blood*. 2012;120:905-913.
5. Parimon T, Au DH, Martin PJ, Chien JW. A risk score for mortality after allogeneic hematopoietic cell transplantation. *Ann Intern Med*. 2006;144:407-414.
6. Farina L, Bruno B, Patriarca F, et al. The hematopoietic cell transplantation comorbidity index (HCT-CI) predicts clinical outcomes in lymphoma and myeloma patients after reduced-intensity or non-myeloablative allogeneic stem cell transplantation. *Leukemia*. 2009;23:1131-1138.
7. Smith AR, Majhail NS, MacMillan ML, et al. Hematopoietic cell transplantation comorbidity index predicts transplantation outcomes in pediatric patients. *Blood*. 2011;117:2728-2734.
8. Rezvani K, Kanfer EJ, Marin D, et al. EBMT risk score predicts outcome of allogeneic hematopoietic stem cell transplantation in patients who have failed a previous transplantation procedure. *Biol Blood Marrow Transplant*. 2012;18:235-240.
9. Lodewyck T, Oudshoorn M, van der Holt B, et al. Predictive impact of allele-matching and EBMT risk score for outcome after T-cell depleted unrelated donor transplantation in poor-risk acute leukemia and myelodysplasia. *Leukemia*. 2011;25:1548-1554.
10. Kataoka K, Nannya Y, Ueda K, et al. Differential prognostic impact of pretransplant comorbidity on transplant outcomes by disease status and time from transplant: a single Japanese transplant centre study. *Bone Marrow Transplant*. 2010;45:513-520.
11. Valcárcel D, Martino R, Caballero D, et al. Sustained remissions of high-risk acute myeloid leukemia and myelodysplastic syndrome after reduced-intensity conditioning allogeneic hematopoietic transplantation: chronic graft-versus-host disease is the strongest factor improving survival. *J Clin Oncol*. 2008;26:577-584.
12. Bacigalupo A, Ballen K, Rizzo D, et al. Defining the intensity of conditioning regimens: working definitions. *Biol Blood Marrow Transplant*. 2009;15:1628-1633.
13. Ruutu T, Volin L, Beelen DW, et al. Reduced-toxicity conditioning with treosulfan and fludarabine in allogeneic hematopoietic stem cell transplantation for myelodysplastic syndromes: final results of an international prospective phase II trial. *Haematologica*. 2011;96:1344-1350.
14. Martino R, Piñana JL, Parody R, et al. Lower respiratory tract respiratory virus infections increase the risk of invasive aspergillosis after a reduced-intensity allogeneic hematopoietic SCT. *Bone Marrow Transplant*. 2009;44:749-756.
15. Piñana JL, Martino R, Barba P, et al. Cytomegalovirus infection and disease after reduced intensity conditioning allogeneic stem cell transplantation: single-centre experience. *Bone Marrow Transplant*. 2010;45:534-542.
16. Iacobelli S. Suggestions on the use of statistical methodologies in studies of the European Group for Blood and Marrow Transplantation. *Bone Marrow Transplant*. 2013;48(Suppl. 1):S1-S37.
17. Kaplan EL, Meier P. Non parametric estimation from incomplete observations. *J Am Stat Assoc*. 1958;53:457-481.
18. Harrell FE Jr, Lee KL, Califf RM, et al. Regression modelling strategies for improved prognostic prediction. *Stat Med*. 1984;3:143-152.
19. Birninger N, Bornhäuser M, Schaich M, et al. The hematopoietic cell transplantation-specific comorbidity index fails to predict outcomes in high-risk AML patients undergoing allogeneic transplantation—

investigation of potential limitations of the index. *Biol Blood Marrow Transplant*. 2011;17:1822-1832.
20. 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*. 2011;46:1000-1005.
21. Terwey TH, Hemmati PG, Martus P, et al. A modified EBMT risk score and the hematopoietic cell transplantation-specific comorbidity index for pre-transplant risk assessment in adult acute lymphoblastic leukemia. *Haematologica*. 2010;95:810-818.
22. Sorror ML, Sandmaier BM, Storer BE, et al. Comorbidity and disease status based risk stratification of outcomes among patients with acute myeloid leukemia or myelodysplasia receiving allogeneic hematopoietic cell transplantation. *J Clin Oncol*. 2007;25:4246-4254.
23. 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.
24. Gratwohl A. The EBMT risk score. *Bone Marrow Transplant*. 2012;47:749-756.
25. Sorror ML. How I assess comorbidities before hematopoietic cell transplantation. *Blood*. 2013;121:2854-2863.