Biology of Blood and Marrow Transplantation 14:985-992 (2008)

1083-8791/08/1409-0001$32.00/0
doi:10.1016/j.bbmt.2008.06.008

Does the Hematopoietic Cell Transplantation Specific Comorbidity Index Predict Transplant Outcomes? A Validation Study in a Large Cohort of Umbilical Cord Blood and Matched Related Donor Transplants

Navneet S. Majhail, Claudio G. Brunstein, Sarah McAvoy, Todd E. DeFor, Ahmed Al-Hazzouri, Daniela Setubal, Mukta Arora, Chap T. Le, John E. Wagner, Daniel J. Weisdorf

Blood and Marrow Transplant Program, University Of Minnesota, Minneapolis, Minnesota

Correspondence and reprint requests: Navneet S. Majhail, MD, MS, Division of Hematology, Oncology and Transplantation, 420 Delaware Street SE, MMC 480, Minneapolis, MN 55455 (e-mail: majha001@umn.edu).

Received April 9, 2008; accepted June 15, 2008

ABSTRACT

The hematopoietic cell transplantation specific comorbidity index (HCT-CI) has been recently proposed to predict the probability of nonrelapse mortality (NRM) and overall survival (OS) in allogeneic HCT recipients while taking into account any pretransplant comorbidity. We tested the validity of the HCT-CI in a cohort of 373 adult HCT recipients (184 matched-related donor and 189 unrelated umbilical cord blood) who received a myeloablative (N = 150) or nonmyeloablative (N = 223) conditioning regimen. HCT-CI scores of 0, 1, 2, and ≥3 were present in 58 (16%), 56 (15%), 64 (17%), and 195 (52%) patients, respectively. Pulmonary conditions were the most common comorbidity. Cumulative incidence of NRM at 2 years was 10%, 20%, 24%, and 28% for HCT-CI scores of 0, 1, 2, and ≥3, respectively ($P = .01$). The corresponding probability of OS at 2 years was 72%, 67%, 51%, and 48%, respectively ($P < .01$). On multivariate analyses adjusted for recipient age, disease risk, donor source, and conditioning regimen intensity, the relative risks for NRM for HCT-CI scores of 1, 2, and ≥3 (compared to a score of 0) were 2.0 (95% confidence intervals, 0.8–5.3), 2.6 (1.0–6.7), and 3.2 (1.4-7.4), respectively. The risks for overall mortality were 1.2 (0.6-2.1), 2.0 (1.1-3.4), and 2.1 (1.3-3.3), respectively. In subgroup analyses, the HCT-CI score did not consistently predict NRM and OS among different donor sources and conditioning regimens. The HCT-CI, although a useful tool for capturing pretransplant comorbidity and risk-assessment, needs to be further validated prior to adopting it for routine clinical use.

KEY WORDS

Allogeneic stem cell transplantation • Umbilical cord blood transplantation • Hematopoietic cell transplantation specific comorbidity index • Nonrelapse mortality

INTRODUCTION

Major advances in the field of allogeneic hematopoietic cell transplantation (HCT) have occurred in the past few decades. However, this procedure can still be associated with significant complications. The advent of nonablative conditioning regimens has led to an increasing use of transplantation in older patients and in patients with comorbidities. Estimating the risk of treatment-related morbidity and mortality (TRM), especially in patients with coexisting comorbidities, is a frequent challenge. A reliable estimation of this risk has important implications for counseling and determining the candidacy of a given patient for allogeneic HCT. The HCT-specific comorbidity index (HCT-CI) has been recently proposed and, using a weighted scoring system, predicts the probability of posttransplant nonrelapse mortality (NRM) and overall survival (OS) while taking into account any pretransplant comorbidities [1]. Early retrospective studies have shown the HCT-CI to be useful for predicting NRM in allogeneic HCT recipients [2,3]. However, this tool has not been independently validated by other transplant centers and has not been explored in recipients of unrelated umbilical cord blood (UCB). We

conducted a retrospective cohort study to determine the validity of this score in a large cohort of matched related donor (MRD) and UCB transplant recipients.

METHODS

Patients and Treatment

This analysis included consecutive adult patients who received an MRD or UCB HCT at our institution between 2000 and 2005. Nineteen patients who received a matched unrelated donor HCT during this time period were excluded from this analysis. Of the 441 eligible patients, 68 did not have adequate data regarding pretransplant comorbidities available to obtain the HCT-CI score. Therefore, the final study cohort consisted of 373 patients, and included 184 MRD and 189 UCB transplant recipients who were transplanted with either a myeloablative (MA, N = 150) or nonmyeloablative (NMA, N = 223) conditioning regimen (Table 1). There was no significant difference in the probability of NRM and OS between the 68 excluded patients and those included in this analysis. All patients were transplanted on protocols approved by our institutional review board.

Eligibility criteria for HCT using NMA conditioning included older age (≥55 years for MRD and ≥45 years for UCB), presence of significant comorbidity (serious organ dysfunction, invasive mold infection within 4 months before transplantation, or Karnofsky performance score of 50-60) or extensive prior therapy (>12 months of alkylator-based chemotherapy, >6 months of alkylator-based chemotherapy and extensive radiation, or history of autologous transplantation). Patients received UCB as a graft source if they had no HLA-compatible related donors. Our UCB selection criteria for adults have been previously published, and allow the use of 2 UCB units to optimize cell dose, if necessary [4-6]. UCB grafts were matched at least 4 of 6 HLA-A,-B (antigen level) and -DRB1 (allele level) to the recipient, and in patients receiving 2 UCB units, also to each other. The MA and NMA conditioning and graft-versus-host disease (GVHD) prophylaxis regimens used at our institution have been described previously [5,7-9]. The dose of total body irradiation (TBI) was 1320 cGy (165 cGy twice daily ×4 days) in MA and 200 cGy (single fraction) in NMA regimens.

Data Collection

Transplant-related and outcome data was retrieved from our Blood and Marrow Transplant Program Database, which prospectively collects these data for all patients receiving HCT at our institution. Data regarding pretransplant comorbidities was extracted from a detailed review of medical charts. Cause of death information was obtained from our database that routinely records the primary cause of death as assigned by the treating physician at the time of patient death using uniform criteria.

Pretransplantation comorbidities were scored retrospectively for all patients using the HCT-CI [1]. The comorbidities captured by this tool include cardiac disorders, cerebrovascular disease, diabetes, altered hepatic function, infection, inflammatory bowel disease, obesity, peptic ulcer disease, psychiatric disturbance, pulmonary abnormalities, renal insufficiency, and rheumatologic disorders. Scores are assigned to various comorbidities based on their severity and a final composite score is then calculated and patients can be assigned to 1 of 3 risk groups: low risk (score 0), intermediate risk (score 1-2), and highrisk (score ≥ 3).

A second investigator independently reviewed medical charts of 110 randomly selected patients and assigned HCT-CI scores. There was good agreement between the scores assigned by the 2 investigators (Kappa coefficient 0.87; 95% confidence intervals [CI], 0.81-0.95). No specific domain was identified where consistent disagreement occurred between the 2 investigators.

Statistical Analysis

The primary endpoints for this analysis were the cumulative incidence of NRM at 1 year and probability of OS at 2 years after allogeneic HCT. NRM was defined as death following HCT without disease progression or relapse. Demographic variables for the patient cohorts were compared across the 2 groups using the chi-square test for categoric variables and the Wilcoxon's rank sum test for continuous variables. Probabilities of NRM were calculated using cumulative incidence curves to accommodate competing risks [10]. Univariate probabilities of OS were calculated using the Kaplan-Meier estimator [11]. Cox regression models were built to determine the independent effect of HCT-CI score on survival [12], and the proportional hazards models of Fine and Gray [13] were used to determine the independent effect of HCT-CI score on NRM. All factors were tested for the proportional hazards assumption. The primary objective was to compare outcomes according to stem cell source and HCT-CI score; these variables were included in all models and were adjusted for age at transplant, conditioning regimen intensity, and disease risk. There were no significant interactions between stem cell source and any other variables, including conditioning regimen intensity. All *P*-values are 2 sided. Analyses were performed using SAS software, version 9.1 (SAS Institute, Cary, NC).

RESULTS

HCT-CI Score

The overall distribution of the HCT-CI score was similar in the 2 groups (Table 1). For the whole cohort,

Table 1. *Patient and Transplant Characteristics*

Factors	Matched Related Donor	Umbilical Cord Blood	*P*-Value
Total	184	189	
Median age at transplant (range), years	48 (18-66)	45 (18-69)	.02
Age at transplant			
<50 years	104 (57%)	117 (62%)	.29
≥50 years	80 (43%)	72 (38%)	
Sex			
Male	108 (59%)	117 (62%)	.53
Female	76 (41%)	72 (38%)	
Karnofsky performance status			.99
≥90	136 (74%)	141 (75%)	
<90	37 (20%)	37 (19%)	
Missing	11 (6%)	11 (6%)	
Median HCT-CI score (range)	3 (0-11)	3 (0-9)	.57
HCT-CI score			.27
0	26 (14%)	32 (17%)	
1	22 (12%)	34 (18%)	
2	36 (20%)	28 (15%)	
3	44 (24%)	34 (18%)	
4	30 (16%)	25 (13%)	
5	12 (7%)	18 (10%)	
≥6	14 (8%)	18 (10%)	
Diagnosis			<.01
Acute myelogenous leukemia	32 (17%)	65 (34%)	
Non-Hodgkin lymphoma	52 (28%)	39 (21%)	
Acute lymphoblastic leukemia	14 (8%)	27 (14%)	
Myelodysplastic syndrome	15 (8%)	15 (8%)	
Hodgkin lymphoma	15 (8%)	12 (6%)	
Multiple myeloma	23 (13%)	4 (2%)	
Chronic myelogenous leukemia	9 (5%)	14 (7%)	
Chronic lymphocytic leukemia	11 (6%)	6 (3%)	
Severe aplastic anemia	6 (3%)	4 (2%)	
Myeloproliferative diseases	3 (2%)	2 (1%)	
Other	4 (2%)	1 (<1%)	
Disease risk*			.23
Standard	39 (21%)	50 (26%)	
High	145 (79%)	139 (74%)	
Donor source			
Bone marrow	10 (5%)	–	
Peripheral blood stem cells	174 (95%)	–	
Single umbilical cord blood	–	38 (20%)	
Double umbilical cord blood	–	151 (80%)	
HLA match†			<.01
6/6	176 (96%)	10 (5%)	
5/6	8 (4%)	40 (21%)	
4/6	0	139 (74%)	
Previous transplant	34 (18%)	33 (17%)	.80
Conditioning regimen			<.01
Myeloablative	88 (48%)	62 (33%)	
Cy/TBI	73	1	
Cy/Flu/TBI	1	59	
Bu/Cy	7	2	
Other	7	0	
Nonmyeloablative	96 (52%)	127 (67%)	
Cy/Flu/TBI	45	70	
Cy/Flu/TBI/ATG	13	37	
Bu/Flu/TBI	22	20	
Other	16	0	
GVHD prophylaxis regimen‡			<.01
CSA/MMF	95 (52%)	188 (99%)	
CSA/MTX	84 (46%)	0	
Other	5 (2%)	1 (<1%)	
Median followup (range), years	3.0 (1.0-7.0)	2.4 (1.0-6.7)	

HCT-CI indicates hematopoietic cell transplantation comorbidity index; HLA, human leukocyte antigen; Cy, cyclophosphamide; TBI, total body irradiation; Flu, fludarabine; Bu, busulfan; ATG, antithymocyte globulin; CSA, cyclosporine; MMF, mycophenolate mofetil; MTX, methotrexate, GVHD, graft-versus-host disease, CSA, cyclosporine; MMF, mycophenolate mofetil; MTX, methotrexate.

*Standard-risk disease included acute leukemia in first complete remission, chronic myeloid leukemia in first chronic phase, myelodysplastic syndrome-refractory anemia, and nonmalignant hematologic disorders; all other diagnoses were categorized as high risk disease.

†Worst match for double umbilical cord blood transplants.

‡Among matched related donor transplants, myeloablative recipients received CSA/MTX, whereas nonmyeloablative recipients received CSA/MMF.

scores of 0, 1, 2, and ≥3 were present in 58 (16%), 56 (15%), 64 (17%), and 195 (52%) patients, respectively. The distribution of HCT-CI scores was also comparable between the 2 conditioning regimens. Scores of 0, 1, 2, and ≥3 were present in 28 (19%), 26 (17%), 27 (18%), and 69 (46%) MA recipients compared to 30 (14%), 30 (14%), 37 (17%), and 116 (52%) in NMA recipients, respectively ($P = .39$). The distribution of scores among the donor and conditioning regimen groups combined (MA MRD, NMA MRD, MA UCB, and NMA UCB) was also comparable.

The distribution of individual comorbidities that define the HCT-CI score is shown in Figure 1. Pulmonary conditions were the most common comorbidity in our cohort (231 [59%] patients). These included 141 patients with moderate and 90 patients with severe pulmonary comorbidity. Other common comorbidities were hepatic (23%), psychiatric (20%), cardiac (14%), and obesity (13%). The distribution of various comorbidities between recipients of MRD and UCB was comparable. Compared to MA HCT recipients, a significantly larger proportion of patients undergoing NMA HCT had cardiac comorbidity (8% versus 18%, $P < .01$) and infection (3% versus 10%, $P = .01$); the

frequencies of specific comorbidities between the 2 conditioning groups was otherwise comparable.

NRM and OS

Figure 2 shows cumulative incidences of NRM for each donor source and conditioning regimen. For the whole cohort, 2-year NRM rates were 10% (95% CI: 2%-18%), 20% (10%-30%), 24% (14%-34%), and 28% (22%-34%) for HCT-CI scores of 0, 1, 2, and ≥3, respectively (P = .01). Within the subgroups of donor source and conditioning regimen, there was no significant difference in the univariate probabilities of NRM for recipients of MRD, UCB, or NMA conditioning for different HCT-CI scores. For patients receiving MA conditioning, the cumulative incidence of NRM at 2 years for the 4 scores was 4%, 19%, 30%, and 30%, respectively (P = .03).

Probabilities of OS are shown in Figure 3. For the whole cohort, probabilities of OS at 2 years for HCT-CI scores of 0, 1, 2, and ≥3 were 72% (95% CI: 61%-83%), 67% (55%-79%), 51% (39%-63%), and 48% (41%-55%), respectively (P < .01). On subgroup analysis, OS by HCT-CI score did not differ significantly for recipients of UCB or NMA conditioning. Two-year OS rates for the 4 scores in MRD recipients was 81%, 63%, 50%, and 49% (P = .03), and for MA conditioning recipients was 82%, 69%, 48%, and 53% (P = .02), respectively.

In multivariate analysis for the whole cohort, HCT-CI scores of 2 and ≥3 were independent

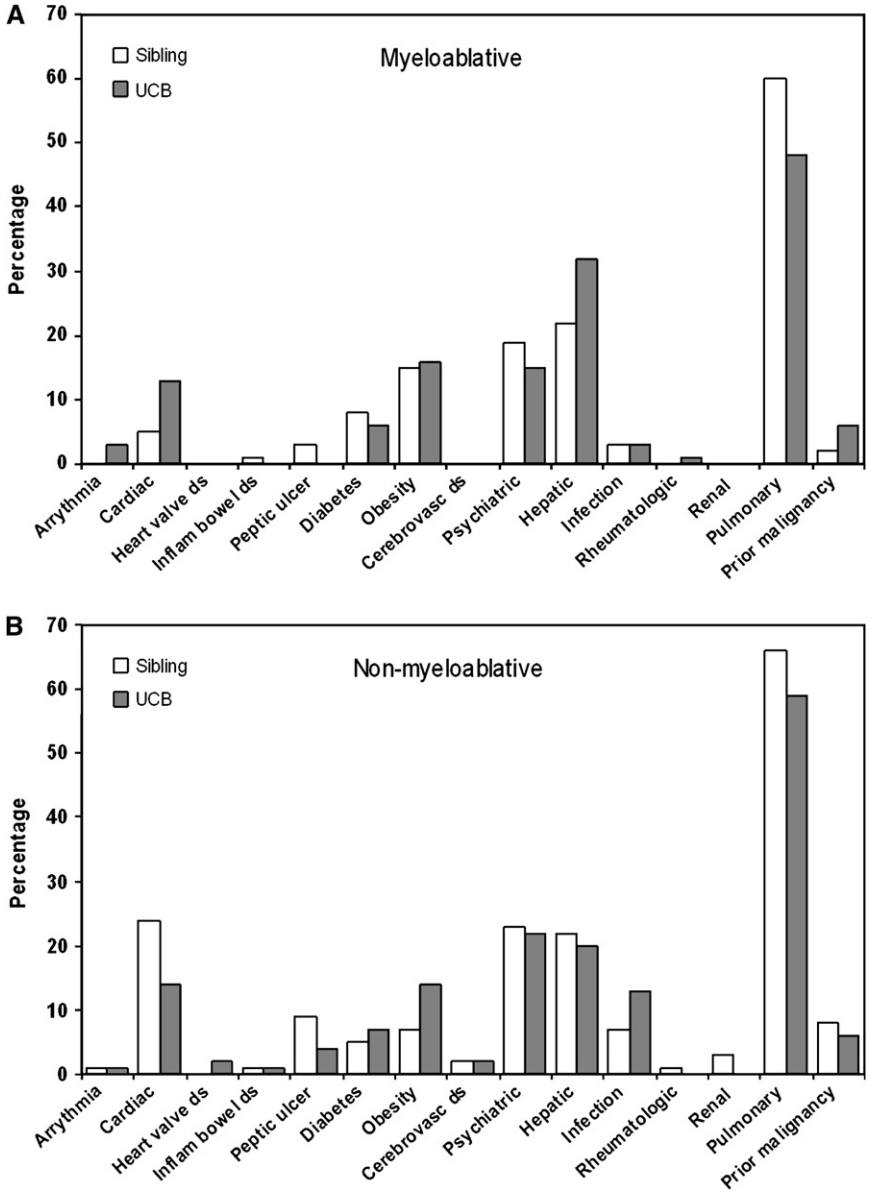

Figure 1. Distribution of comorbidities in MA (N = 150) and NMA (N = 223) hematopoietic cell transplant recipients (Y-axis represents percentage of patients within the cohort with specific comorbidities).

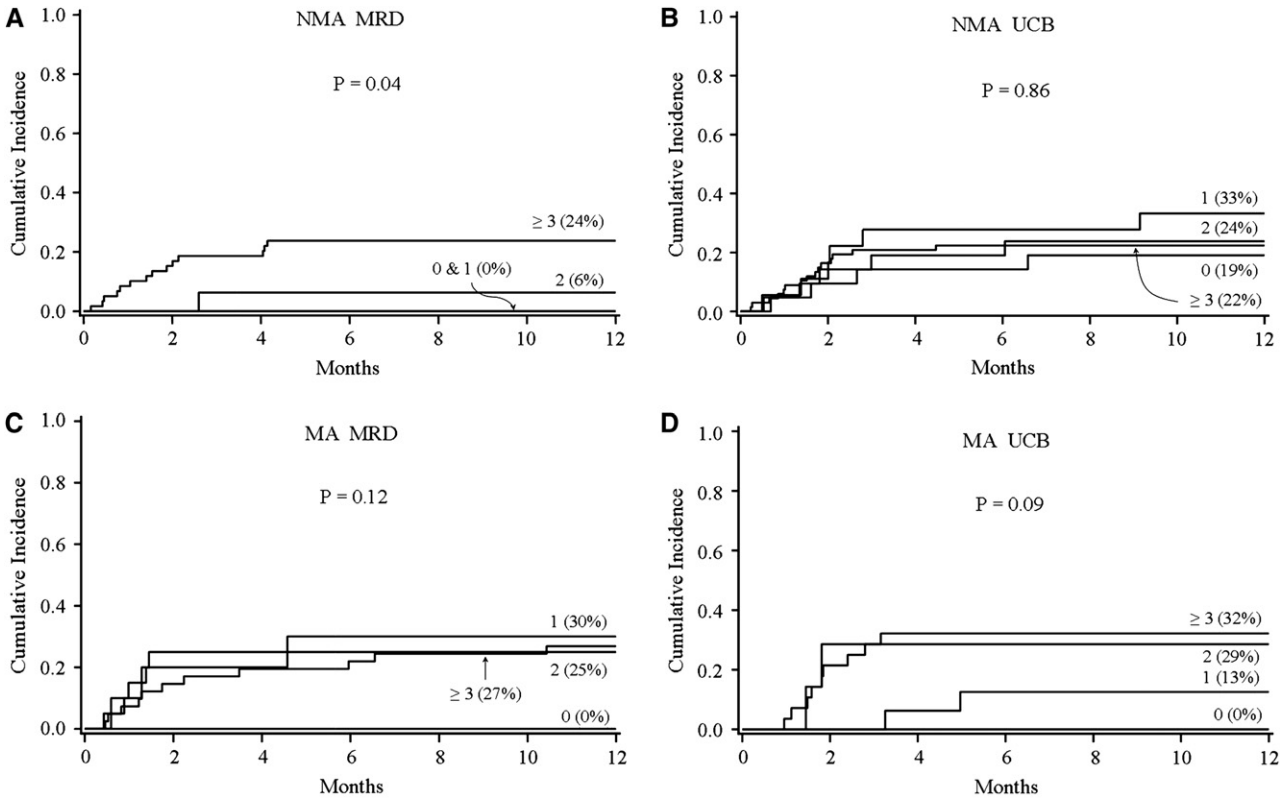

Figure 2. Cumulative incidence of NRM by conditioning regimen and donor source for HCT-CI scores (1-year rates are indicated in brackets; MRD, matched related donor; UCB, umbilical cord blood; MA, myeloablative conditioning; NMA, nonmyeloablative conditioning).

predictors of NRM (Table 2). Similarly, scores of 2 and ≥3 also predicted for OS. In analysis limited to MRD recipients, the relative risks (RR) of NRM did not differ significantly between the 4 HCT-CI score categories. Among UCB recipients, the HCT-CI score again did not have an independent impact on NRM. In multivariate analysis for OS within the MRD cohort, HCT-CI scores of 2 (RR 2.5 [95% CI, 1.1-5.6]) and ≥3 (RR 2.4 [1.2-4.9]) significantly influenced survival, whereas a score of 1 did not (RR 1.7 [0.4-4.1]). Within the UCB cohort, only a score of ≥3 (RR 1.9 [1.0-3.6]) was significantly related with OS, wherease no association was observed for scores of 1 (RR 1.0 [0.4-2.2]) or 2 (RR 1.6 [0.7-3.4]).

Combining scores of 1 and 2 as an "intermediate-risk" group as described in its initial description did not increase the sensitivity of the HCT-CI for NRM or OS. For scores of 0, 1-2, and ≥3, the cumulative incidence of NRM at 2 years was 10% (95% CI: 2%-18%), 22% (15%-29%), and 28% (22%-34%) ($P < .01$) and the probability of OS at 2 years was 72% (61%-83%), 59% (50%-68%), and 48% (41%-55%) ($P < .01$), respectively. In multivariate analyses (compared to score of 0) the RR of NRM for scores of 1-2 and ≥3 was 2.3 (95% CI: 1.0-5.5) and 3.2 (1.4-7.4), respectively. The corresponding risks for OS were 1.6 (0.9-2.6) and 2.1 (1.3-3.3).

Because preexisting pulmonary conditions can significantly contribute to HCT-associated morbidity and mortality and constituted the most common comorbidity in our cohort (59% patients), we estimated the univariate probabilities of NRM for individual scores for pulmonary comorbidity as defined by the HCT-CI. The cumulative incidence of NRM at 1 year was 13% (95% CI: 8%-18%) for patients with no pulmonary comorbidity, 23% (16%-30%) for moderate pulmonary comorbidity, and 32% (22%-42%) for severe pulmonary comorbidity ($P < .01$).

Cause of Death

Causes of death within 1 year posttransplant stratified by HCT-CI scores are displayed in Table 3. Overall, relapse was the most common primary cause of death within the first year (14%), and was followed by organ failure or toxicity (8%), infections (6%), and GVHD (5%). For HCT-CI scores of 0, 1, 2, and ≥3, death could be attributed to organ failure or toxicity in 3%, 5%, 9%, and 10% of patients, respectively.

DISCUSSION

Considering comorbidities during pretransplant risk assessment is a clinical challenge. The HCT-CI combines important comorbidities with varying

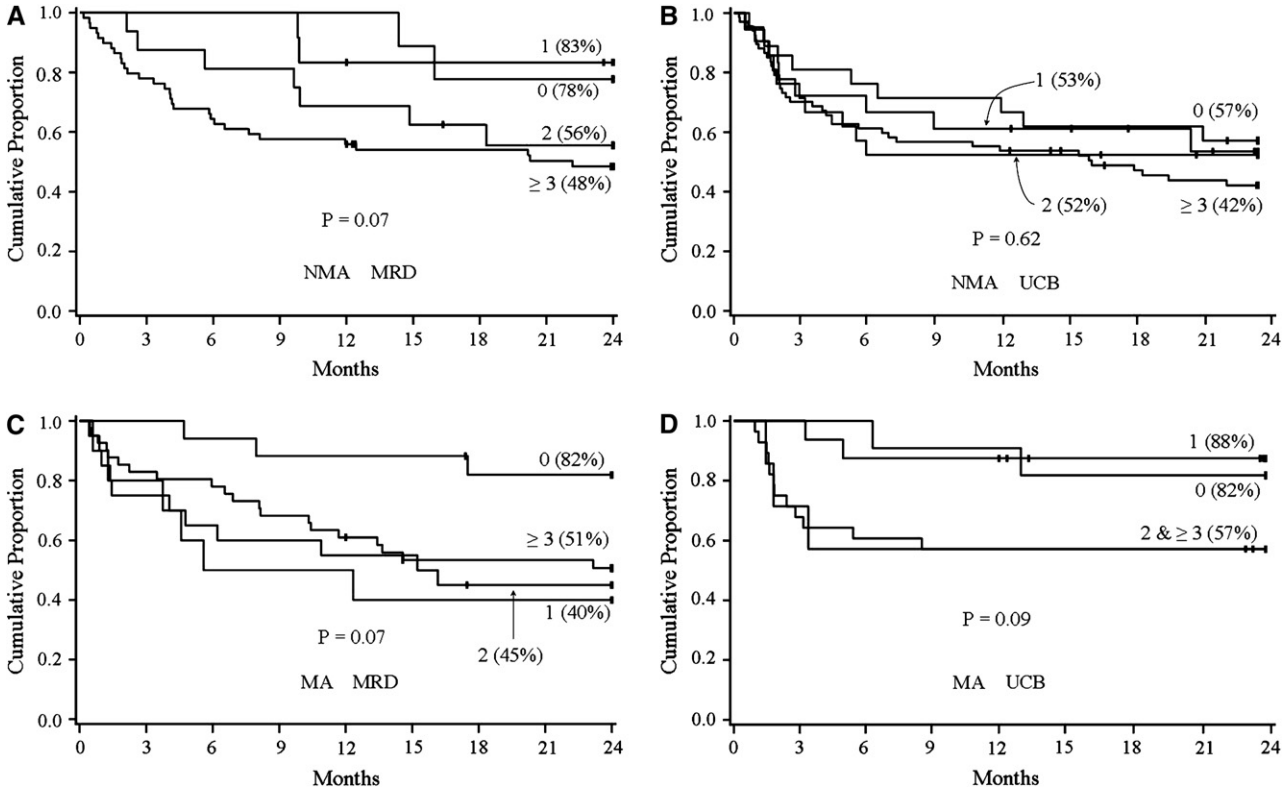

Figure 3. Probability of OS by conditioning regimen and donor source for HCT-CI scores (2-year rates are indicated in brackets; MRD, matched related donor; UCB, umbilical cord blood; MA, myeloablative conditioning; NMA, nonmyeloablative conditioning).

impact on treatment related morbidity and mortality into a single score and is a first step toward incorporating comorbidities in clinical decision analysis for transplantation and for risk adjustment for clinical trials. We found the HCT-CI to be a relatively simple and reliable tool for capturing pretransplant comorbidities. However, in our experience, it did not predict NRM and OS as robustly as has been reported in

Table 2. *Multivariate Analysis for Nonrelapse Mortality and Overall Surviva*

		Nonrelapse Mortality		Overall Survival	
Factor	**N**	**RR (95% CI)**	***P*-value**	**RR (95% CI)**	***P*-value**
HCT-CI score					
0*	**58**	**1.0**		**1.0**	
1	**56**	**2.0 (0.8-5.3)**	**.17**	**1.2 (0.6-2.1)**	**.64**
2	**64**	**2.6 (1.0-6.7)**	**.05**	**2.0 (1.1-3.4)**	**.01**
≥3	**195**	**3.2 (1.4-7.4)**	**<.01**	**2.1 (1.3-3.3)**	**<.01**
Donor source					
Matched related donor*	**184**	**1.0**		**1.0**	
Umbilical cord blood	**189**	**1.2 (0.8-1.8)**	**.49**	**1.1 (0.8-1.5)**	**.49**
Age at transplant					
<50 years*	**221**	**1.0**		**1.0**	
≥50 years	**152**	**1.1 (0.7-1.8)**	**.72**	**1.3 (0.9-1.8)**	**.15**
Disease risk†					
Standard*	**89**	**1.0**		**1.0**	
High	**284**	**1.2 (0.7-2.0)**	**.52**	**1.3 (0.9-1.9)**	**.13**
Conditioning					
Myeloablative*	**150**	**1.0**		**1.0**	
Nonmyeloablative	**223**	**0.8 (0.5-1.4)**	**.49**	**1.0 (0.7-1.4)**	**.87**

HCT-CI indicates hematopoietic cell transplantation comorbidity index; RR, relative risk; CI, confidence intervals.
*Reference value.
†Standard-risk disease included acute leukemia in first complete remission, chronic myelogenous leukemia in first chronic phase, myelodysplastic syndrome-refractory anemia, and nonmalignant hematologic disorders; all other diagnoses were categorized as high-risk disease.

Table 3. *Causes of Death within 1-Year Posttransplant for HCT-CI Scores of 0, 1, 2, and ≥3*

	HCT-CI Score			
Primary Cause of Death	**0 N (%)**	**1 N (%)**	**2 N (%)**	**≥3 N (%)**
Number of patients	**58**	**56**	**64**	**195**
Relapse	**4 (7%)**	**5 (9%)**	**10 (16%)**	**32 (16%)**
Organ failure/toxicity	**2 (3%)**	**3 (5%)**	**6 (9%)**	**19 (10%)**
Graft-versus-host disease	**0**	**3 (5%)**	**6 (9%)**	**11 (7%)**
Infection	**2 (3%)**	**3 (5%)**	**1 (2%)**	**17 (9%)**
Hemorrhage	**0**	**0**	**3 (5%)**	**3 (2%)**
Graft failure	**0**	**2 (4%)**	**0**	**1 (<1%)**
Second cancer	**1 (2%)**	**0**	**0**	**1 (<1%)**
Unknown	**1 (2%)**	**1 (2%)**	**1 (2%)**	**0**

HCT-CI indicates hematopoietic cell transplantation comorbidity index.

previous studies [1-3]. Although there was an overall trend toward worsening outcomes with each increment in the HCT-CI score, this was not consistently noted among different donor sources and conditioning regimens.

This limited generalizability of the HCT-CI in our patient population could be attributed to specific characteristics of our study cohort. First, our study included a large proportion of patients who received UCB as a donor source. Recent analyses have reported a lower risk of acute and chronic GVHD (aGVHD, cGVHD) UCB recipients [14-16], which could be associated with a lower risk of NRM. Compared to published series, our study cohort also had a larger proportion of patients with comorbidities that are captured by the HCT-CI. Only 16% of our patients had no comorbidities (score of 0) compared to 21% to 51% in other reports [1-3,17,18]. Last, the prevalence of comorbidities was also different in our population. For instance, 59% of our patients had pulmonary comorbidity compared to 33% in the initial report of the HCT-CI by Sorror et al. [1]. Comorbidities involving different organ systems could have a differential impact on the risk of NRM after transplantation.

Although the HCT-CI has been recently investigated as a predictor of outcomes in disease-specific analyses [3,18], the ideal tool for capturing pre-HCT comorbidities and integrating them in clinical decision making should be valid across conditioning regimens, donor sources, and transplant practices. The HCT-CI has the potential to be such a universal tool if it could be improved to increase its generalizability. Impact of inclusion of other predictors for NRM and OS such as recipient age and performance status on its sensitivity needs to be explored. Its validity also needs to be tested and confirmed in other transplant centers because variations in the prevalence of comorbidities in different patient populations could affect its performance. Further refinement of the score by exclusion of comorbidities with low prevalence and little impact on NRM could also increase its sensitivity. Its validity also needs to be tested in pediatric HCT recipients.

Our study has the typical limitations of a retrospective cohort study. Furthermore, the overall sample size and number of events within specific subgroups investigated was relatively small. Although clinical and laboratory information needed to calculate the HCT-CI score was abstracted from medical charts, most of these data are routinely collected during pretransplant workup at our institution. Also, we do not anticipate changes in transplant techniques or supportive care to have had a significant impact on outcomes given the contemporary nature of our study cohort.

In conclusion, the HCT-CI is a novel and simple tool that considers the presence or absence of pretransplant comorbidities to predict the risk of death because of transplant-related complications. It has the potential for widespread applicability both in clinical practice and in clinical trials. However, prior to its routine use, its validity and generalizability has to be further investigated, especially in prospective multicenter studies. Its sensitivity could be further increased by including other potential risk factors such as age and excluding comorbidities that may be less prevalent and less important in transplant recipients.

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