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# Prognostic Performance of the Augmented Hematopoietic Cell Transplantation-Specific Comorbidity/Age Index in Recipients of Allogeneic Hematopoietic Stem Cell Transplantation from Alternative Graft Sources

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A B S T R A C T

The Hematopoietic Cell Transplantation-Specific Comorbidity Index (HCT-CI) was developed and validated to weigh the burden of pretransplantation comorbidities and estimate their impact on post-transplantation risks of nonrelapse mortality (NRM). Recently, the HCT-CI was augmented by the addition of both age and the values of 3 markers: ferritin, albumin, and platelet count. So far, research involving The HCT-CI has been limited almost exclusively to recipients of allogeneic hematopoietic cell transplantation (HCT) from HLA-matched grafts. To this end, we sought to investigate the discriminative capacity of an augmented comorbidity/age index among 724 recipients of allogeneic HCT from HLA-mismatched (n = 345), haploidentical (n = 117), and umbilical cord blood (UCB; n = 262) grafts between 2000 and 2013. In the overall cohort, the augmented comorbidity/age index had a higher c-statistic estimate for prediction of NRM compared with the original HCT-CI (.63 versus .59). Findings were similar for recipients of HLA-mismatched (.62 versus .59), haploidentical (.60 versus .54), or UCB grafts (.65 versus .61). Compared with patients with an HCT-CI score ≥4, those with a score <4 had a higher survival rate among recipients of HLA-mismatched (55% versus 39%; $P < .0008$), HLA-haploidentical (58% versus 38%; $P = .01$), or UCB (67% versus 48%; $P = .004$) grafts. Our results demonstrate the utility of the augmented comorbidity/age index as a valid prognostic tool among recipients of allogeneic HCT from alternative graft sources.



## INTRODUCTION

Allogeneic hematopoietic cell transplantation (HCT) is a curative therapeutic modality for most malignant and nonmalignant hematologic disorders. However, this treatment is associated with a substantial risk of subsequent nonrelapse mortality (NRM). Pretransplantation comorbidities, as evaluated by the Hematopoietic Cell Transplantation-Specific Comorbidity Index (HCT-CI), have been shown to provide accurate estimates of the risk of post-allogeneic HCT NRM [1]. The prognostic value of the HCT-CI was further augmented by the addition of a score of 1 for age ≥40 years [2] and scores for serum ferritin level, albumin level, and platelet count [3] in an "augmented comorbidity/age" index. Nevertheless, the prognostic validity of the comorbidities has been studied almost exclusively in recipients of HLA-matched donor grafts in both retrospective and prospective multicenter studies, with consistent agreement regarding its validity across the majority of these studies [4-7].

In the United States, more than 12,000 patients annually are diagnosed with a life-threatening hematologic disorder that necessitates curative allogeneic HCT. According to data from the National Marrow Donor Program, a suitable HLA-matched family member is potentially available for only approximately 30% of allogeneic HCT candidates. The remaining 70% of patients are otherwise offered allogeneic HCT using alternative graft sources. For those patients, cure might still be

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achieved by offering HLA-mismatched grafts, haploidentical grafts, or umbilical cord blood (UCB). However, allogeneic HCT using such graft sources is potentially associated with a higher risk of NRM compared with HLA-matched allogeneic HCT, for several reasons. For example, the use of HLA-mismatched and haploidentical grafts has been shown to carry higher risks of graft rejection and severe graft-versus-host disease (GVHD) [8,9]. The use of a cyclophosphamide-dependent conditioning regimen in part addressed these problems but at the expense of a higher rate of relapse [10]. Likewise, UCB grafts have been associated with relatively higher risks of delayed engraftment and subsequent infection given the potentially insufficient cell dose [11]. Currently, there are insufficient data to support the superiority of one graft source over the others.

According to data from the Center for International Blood and Marrow Transplant Research, recipients of unrelated grafts, including HLA-mismatched and UCB grafts, constitute the largest group of allogeneic HCT recipients in the United States. The expansion in this group compared with recipients of related donor grafts was most noticeable after 2006, with the gap between these 2 groups steadily widening thereafter on an annual basis. Further analysis reveals an increasing proportion of transplantations performed using UCB grafts in 2008 to 2012 compared with previous periods, constituting 40% and 10% of all donor sources for pediatric and adult patients, respectively. In addition, the percentage of haploidentical graft recipients increased steadily between 2011 and 2015 [12]. Whether comorbidities may have a sufficient prognostic influence on outcomes for counseling patients regarding their most suitable graft source remains to be investigated. A limited number of studies have examined the prognostic value of comorbidities among alternative donor graft recipients [13,14], but none has investigated the impact of incorporating both laboratory values and age into the HCT-CI in a single model.

In the present study, we explored whether (1) an augmented comorbidity/age index could stratify outcomes after allogeneic HCT from UCB, HLA-mismatched, or HLA haploidentical donors, and (2) whether this index could guide appropriate graft source selection for patients without a suitable HLA-matched donor.

## METHODS

### *Patients*

Eligible patients were recipients of allogeneic HCT from an HLA-mismatched donor, a haploidentical donor, or UCB graft at the Fred Hutchinson Cancer Research Center between 2000 and 2013. Patients with any hematologic diagnosis, including nonmalignant disease, were included, as were patients from all age groups. We retrospectively identified 724 patients as eligible candidates for the study, divided as follows: HLA-mismatched graft recipients, n = 345; haploidentical graft recipients, n = 117; and UCB recipients, n = 262.

The following data were obtained by extensive review of the patients' medical records: demographic data, including patient age and sex, donor age and sex, and Karnofsky Performance Status (KPS) score; disease-related data, including type, date of diagnosis, risk category, and status at time of transplantation; and transplantation-related data, including stem cell source, conditioning regimen intensity, GVHD prophylaxis protocol, cytomegalovirus (CMV) serostatus, date of transplantation, pretransplantation serum albumin, ferritin, and platelet count; and cause of death. Augmented comorbidity/age scores for all patients were calculated by a single investigator in accordance with recently published guidelines [15].

### *Transplantation Procedure*

Conditioning regimens were categorized based on intensity as high-dose, reduced-intensity, or nonmyeloablative. The specific regimen was chosen according to the active research protocols at Fred Hutchinson Cancer Research Center at the time of transplantation.

For recipients of HLA-mismatched grafts, high-dose regimens consisted of busulfan and cyclophosphamide (BU/CY), CY and high-dose total body irradiation (TBI; 1200 to 1440 cGy depending on the protocol), or etoposide and high-dose TBI. Reduced-intensity and nonmyeloablative regimens consisted of CY and low-dose TBI (200 to 450 cGy depending on the protocol), or fludarabine (FLU) and low-dose TBI, or BU for 2 days and FLU. In this group, HLA typing was determined at all loci by high-resolution techniques, and all donors were HLA-mismatched at 1 or 2 loci (9/10 or 8/10) (HLA-A, -B, -C, -DRB1, and -DQB1). The majority of donors (87%) were unrelated.

For recipients of UCB grafts, high-dose regimens consisted of BU/CY with or without melphalan or CY/high-dose TBI with or without FLU. Reduced-intensity and nonmyeloablative regimens consisted of treosulfan/FLU/low-dose TBI or CY/FLU/low-dose TBI. More than one-half of the patients (58%) received 2 units with HLA matching of 6/6, 5/6, or 4/6 in 1 or both units.

For recipients of haploidentical grafts, high-dose regimens consisted of BU/CY, CY/high-dose TBI, or thiotepa/FLU/high-dose TBI. Reduced-intensity and nonmyeloablative regimens consisted of CY/low-dose TBI, CY/FLU/low-dose TBI, or thiotepa/FLU/TBI. Related donors with HLA mismatches at more than 2 loci were categorized as haploidentical donors.

The vast majority of GVHD prophylaxis regimens consisted of a combination of a calcineurin inhibitor (cyclosporine or tacrolimus) and methotrexate or mycophenolate mofetil with or without sirolimus. Among haploidentical graft recipients, post-transplantation CY (PTCY) was administered for T cell depletion in 96% of patients (n = 112), whereas the remaining 5 patients received a non-PTCY alternative. Donors and recipients were categorized as CMV positive or negative based on CMV IgG serostatus.

### *Definitions*

The incidence of 2-year NRM was defined as the proportion of patients dying between the date of allogeneic HCT (day 0) to 2 years post-transplantation from causes other than disease relapse. Low- risk diseases included acute leukemia in first complete remission (CR), chronic myelogenous leukemia in first chronic phase, chronic lymphocytic leukemia in CR, myelodysplasia-refractory anemia or refractory anemia with ringed sideroblasts, lymphoma in CR at the time of HCT, and nonmalignant disorders. All other diagnoses were considered high risk. Comorbidities were collected in accordance with previously published guidelines [15]. The augmented comorbidity/age index was defined as the sum of the original HCT-CI scores with the addition of scores for age ≥40 years and pretransplantation biomarkers serum ferritin, serum albumin, and platelet count as described previously (Table 1) [3]. Conditioning regimens were classified as high dose, reduced intensity, or nonmyeloablative based on previously published criteria [16].

### *Statistical Methods*

Cumulative incidence estimates were used to evaluate NRM, and Kaplan-Meier estimates were used to assess survival. Relapse or progression of the primary disease was treated as a competing risk for NRM. Events were analyzed over the entire follow-up period. For each donor graft source, adjusted hazard ratios (HRs) of the augmented comorbidity/age scores for 2-year NRM were derived from multivariate models adjusting for known confounders: age (as a continuous variable), conditioning intensity (high-dose versus reduced-intensity versus nonmyeloablative), CMV serostatus (positive versus negative), disease risk (high versus low), KPS score (≤80 versus >80), and year of transplantation (2000 to 2004, 2005 to 2009, and 2010 to 2013). Multivariate *P* values were based on adjustment for all other variables in the model. All *P* values were 2-sided and derived from Wald statistics. C-statistics were computed for predicting NRM and OS by the 2 indices as continuous predictors using previously published methods [17]. Standard errors for the c-statistics and *P* values comparing c-statistics between indices were estimated from 50 bootstrap samples. All calculations and analyses were carried out in SAS (SAS Institute, version 8, Cary, NC).

## RESULTS

### *Patient Characteristics*

The patients were divided into 3 cohorts according to graft source. A total r of 724 patients were included in this analysis, of whom 345 received an HLA-mismatched graft, 117 received a haploidentical graft, and 262 received a UCB graft. Table 2 summarizes characteristics of the 3 patient cohorts. Among recipients of allogeneic HCT using an HLA-mismatched graft, 66% received a high-dose conditioning regimen. The majority of these patients (61%) had high-risk disease, and 52% had an augmented comorbidity/age score ≥4 at the time of transplantation. The vast majority of patients in this cohort (88%) had a KPS score ≥80.

The recipients of allogeneic HCT using UCB grafts were notably younger, with 61% under age 40 years. Patients in this cohort had a similar distribution of low-risk and high-risk

**Table 1**
Definitions of Comorbidities Included in the Augmented Comorbidity/Age Index and Their Corresponding Scores

| Comorbidity | Definition | Score |
|---|---|---|
| HCT-CI | | |
| Arrhythmia | Any type of arrhythmia that has necessitated the delivery of a specific antiarrhythmia treatment at any time point in the patient's past medical history | 1 |
| Cardiac | Coronary artery disease,[§] congestive heart failure, myocardial infarction, or EF ≤50% | 1 |
| Inflammatory bowel disease | Crohn's disease or ulcerative colitis necessitating treatment at any time point in patient's past medical history | 1 |
| Diabetes | Requiring treatment with insulin or oral hypoglycemic agents continuously for 4 wk before the start of conditioning | 1 |
| Cerebrovascular disease | Transient ischemic attack or cerebrovascular accident | 1 |
| Psychiatric disturbance | Any disorder requiring continuous treatments for 4 wk before start of conditioning | 1 |
| Hepatic, mild | Chronic hepatitis, bilirubin > ULN to 1.5 times the ULN, or AST/ALT > ULN to 2.5 times the ULN; at least 2 values of each within 2 or 4 wk before start of conditioning | 1 |
| Obesity | Patients with a body mass index >35 kg/m$^2$ for patients age >18 yr or a BMI-for-age ≥95th percentile for patients age ≤18 yr | 1 |
| Infection | Requiring antimicrobial treatment starting from before conditioning and continued beyond day 0 | 1 |
| Rheumatologic | Requiring specific treatment at any time point in the patient's past medical history | 2 |
| Peptic ulcer | Based on previous endoscopic or radiologic diagnosis | 2 |
| Moderate/severe renal | Serum creatinine >2 mg/dL (at least 2 values of each within 2 or 4 wk before start of conditioning), on dialysis, or previous renal transplantation | 2 |
| Moderate pulmonary | Corrected DLCO (via Dinakara equation) and/or FEV$_1$ of 66%-80% or dyspnea on slight activity | 2 |
| Previous malignancy | Treated at any time point in the patient's history, excluding nonmelanoma skin cancer | 3 |
| Heart valve disease | Of at least moderate severity, prosthetic valve, or symptomatic mitral valve prolapse as detected by echocardiography | 3 |
| Severe pulmonary | Corrected DLCO (via Dinakara equation) and/or FEV$_1$ ≤65% or dyspnea at rest or requiring oxygen | 3 |
| Moderate/severe hepatic | Liver cirrhosis, bilirubin >1.5 times the ULN, or AST/ALT >2.5 times the ULN; at least 2 values of each within 2 or 4 wk before the start of conditioning | 3 |
| Augmented comorbidity/age index: all of the above plus | | |
| High ferritin | Value ≥2500 at the measurement nearest the start of conditioning | 1 |
| Mild hypoalbuminemia | Value <3.5-3.0 at the measurement nearest the start of conditioning | 1 |
| Moderate hypoalbuminemia | Value <3.0 at the measurement nearest the start of conditioning | 2 |
| Thrombocytopenia | Value <100,000 at the measurement nearest the start of conditioning | 1 |
| Age | ≥40 yr | 1 |

EF indicates ejection fraction; ULN, upper limit of normal; AST, aspartate aminotransferase ; ALT, alanine aminotransferase; DLCO, diffusion capacity of carbon monoxide: FEV$_1$, forced expiratory volume in 1 second.
[*]One or more vessels with coronary artery stenosis requiring medical treatment, stent, or bypass graft.

disease, at 49% and 51%, respectively. Patients with an augmented comorbidity/age score ≥4 constituted 48% of the cohort, with most patients (89%) having a KPS score of ≥80.

Haploidentical graft recipients received nonmyeloablative and reduced-intensity conditioning regimens almost exclusively (97%). This cohort had the highest percentage of patients with high-risk disease (66%), and 57% of patients within this cohort had an augmented comorbidity/age score ≥4.

The most predominant comorbidities among the 3 cohorts were moderate pulmonary comorbidity and infections. The frequencies of various components of the augmented comorbidity/age index in the 3 alternative donor groups are presented in Table 3.

### *Prognostic Value of the Augmented Comorbidity/Age Index among the Entire Cohort and Relative to the HCT-CI Alone*

The prognostic capability of the augmented comorbidity/age index was compared with that of the original HCT-CI as determined by c-statistics estimates for different outcomes. Among the entire study cohort, the augmented comorbidity/age index had higher c-statistics estimates for 2-year NRM compared with the original HCT-CI (.63 versus .59; $P = .0001$), respectively. Similarly, the augmented comorbidity/age index provided better prognostication of 2-year OS (c-statistics estimates of .60 versus .57; $P = .0001$). C-statistics estimates were higher for the augmented comorbidity/age index among individual donor groups as well (Table 4). Thus, we elected to use the augmented comorbidity/age index for the remainder of the analysis. The augmented comorbidity/age index scores were collapsed into 2 binary risk groups with relatively equal patient sample distributions, with scores of <4 (48%) and ≥4 (52%), considered low-risk and high-risk groups, respectively. Figure 1A and B illustrates the incidence of NRM, the rate of OS, and the numbers of patients remaining at risk annually following transplantation among the entire patient cohort as stratified by the augmented comorbidity/age index.

### *Performance of the Augmented Comorbidity/Age Index among Recipients of HLA-Mismatched Grafts*

Higher augmented comorbidity/age index scores were statistically significantly associated with lower OS and higher NRM. Patients with a score ≥4 had almost double the risk of 2-year NRM compared with those with a score <4 (41% versus 23%; $P < .0001$) (Figure 2A). Two-year OS rates were higher among patients with low-risk versus high-risk scores (55% versus 39%; $P < .0008$) (Figure 2B). In regression models adjusted for conditioning intensity, age, CMV serostatus, disease risk, KPS score, and year of transplantation, the risk of 2-year NRM was significantly higher with an increasing augmented comorbidity/age index score, with a hazard ratio (HR) of 1.52 (95% confidence interval [CI], 1.00 to 2.30; $P = .05$). The 2-year OS had a HR of 1.29 (95% CI, .94 to 1.75; $P = .11$) (Table 5). C-statistics estimates were .62 for 2-year NRM and .60 for 2-year OS when the augmented comorbidity/age score was treated as a continuous variable.

### *Performance of the Augmented Comorbidity/Age Index among Recipients of Haploidentical Grafts*

The cumulative incidence of 2-year NRM was not statistically significantly different between patients with a lower

**Table 2**
Patient Characteristics According to Graft Source

| Characteristic | HLA-Mismatched Graft Recipients (N = 345) | UCB Graft Recipients (N = 262) | Haploidentical Graft Recipients (N = 117) |
|---|---|---|---|
| Conditioning regimen, % | | | |
| High dose | 66 | 55 | 3 |
| Nonmyeloablative/reduced-intensity conditioning | 35 | 45 | 97 |
| ATG use | 4 | 18 | 0 |
| Age, yr, median (range) | 45 (.6-76) | 37 (.4-73) | 37 (.5-74) |
| <40 | 37 | 61 | 45 |
| ≥40 | 63 | 39 | 55 |
| Disease risk, % | | | |
| Low | 39 | 49 | 34 |
| High | 61 | 51 | 66 |
| CMV serostatus, % | | | |
| Negative | 43 | 40 | 32 |
| Positive | 57 | 60 | 68 |
| Donor type, % | | | |
| Related | 13 | | 100 |
| Unrelated | 87 | 100 | |
| Stem cells source, % | | | |
| Peripheral blood stem cells | 73 | | 19 |
| Bone marrow | 27 | | 81 |
| Umbilical cord blood | — | 100 | — |
| Single unit | — | 42 | — |
| Two units | — | 58 | — |
| Augmented comorbidity/age index, % | | | |
| <4 | 48 | 52 | 43 |
| ≥4 | 52 | 48 | 57 |
| Median (range) | 4 (0-14) | 3 (0-13) | 4 (0-14) |
| KPS score, % | | | |
| >80 | 88 | 89 | 81 |
| ≤80 | 13 | 11 | 19 |
| Year of transplantation, % | | | |
| 2000-2004 | 43 | 6 | 14 |
| 2005-2009 | 38 | 40 | 45 |
| 2010-2010 | 29 | 55 | 41 |
| Follow-up of survivors, yr, median (range) | 8.0 (1.2-16.1) | 4.1 (1.7-12.9) | 5.0 (.2-11.4) |

*Missing for 1 HLA-mismatched recipient and 6 UCB recipients.

(<4) and those with a higher (≥4) augmented comorbidity/age score (34% versus 41%; $P$ = .07) (Figure 3A). However, lower comorbidity burden was associated with a significantly higher 2-year OS (58% in patients with an augmented comorbidity/age score <4 versus 38% in patients with an augmented comorbidity/age score ≥4; $P$ = .01) (Figure 3B). In models adjusted for previous risk factors, higher augmented comorbidity/age score was not

**Table 3**
Distribution of the Different Components of the Augmented Comorbidity/Age Index among the 3 Donor Groups

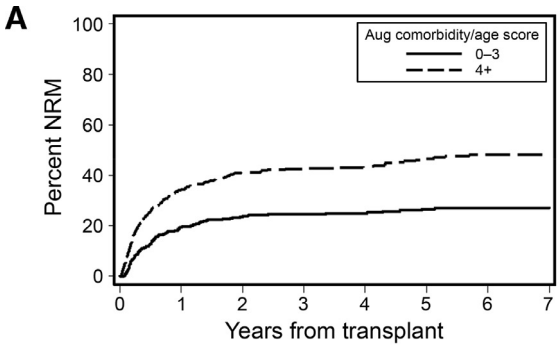
| Component | HLA-Mismatched (N = 345), % (n) | UCB (N = 262), % (n) | Haploidentical (N = 117), % (n) |
|---|---|---|---|
| Arrhythmia | 6 (20) | 5 (12) | 7 (8) |
| Cardiac disease | 10 (33) | 7 (18) | 8 (9) |
| Inflammatory bowel disease | .2 (1) | .7 (2) | .9 (1) |
| Diabetes | 8 (29) | 7 (19) | 5 (6) |
| Cerebrovascular disease | 4 (14) | 4 (10) | 3 (3) |
| Psychiatric disturbance | 21 (71) | 15 (40) | 23 (27) |
| Hepatic disease, mild | 12 (40) | 18 (49) | 14 (16) |
| Obesity | 7 (25) | 6 (16) | 8 (9) |
| Infection | 22 (76) | 35 (93) | 26 (30) |
| Rheumatologic disease | .6 (2) | 2 (5) | 0 |
| Peptic ulcer | 2 (8) | 2 (4) | 3 (3) |
| Moderate/severe renal disease | .9 (3) | .8 (2) | 3 (3) |
| Moderate pulmonary disease | 35 (122) | 33 (86) | 37 (44) |
| Previous malignancy | 10 (36) | 9 (24) | 9 (10) |
| Heart valve disease | 1 (4) | 2 (6) | 2 (2) |
| Severe pulmonary disease | 16 (56) | 16 (43) | 26 (31) |
| Moderate/severe hepatic disease | 3 (11) | 3 (7) | .9 (1) |
| High serum ferritin level | 3 (11) | 3 (8) | 8 (9) |
| Mild hypoalbuminemia | 14 (50) | 11 (29) | 25 (29) |
| Moderate hypoalbuminemia | 7 (23) | 4 (11) | 6 (7) |
| Thrombocytopenia | 44 (152) | 30 (79) | 49 (57) |
| Age ≥40 yr | 62 (215) | 39 (101) | 55 (64) |

**Table 4**
c-Statistic Estimates for the 2 Risk Indices in the Whole Cohort

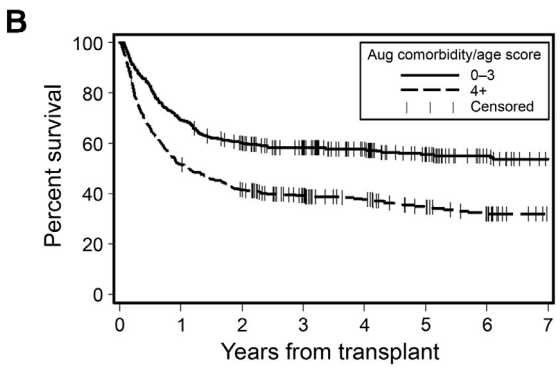
| Parameter | HCT-CI | Augmented Comorbidity/Age Index |
|---|---|---|
| NRM (266 events) | | |
| All donors (n = 724) | .59 (.02) | .63 (.02) |
| Antigen-mismatched (n = 345) | .59 (.02) | .62 (.02) |
| UCB (n = 262) | .61 (.03) | .65 (.03) |
| Haploidentical (n = 117) | .54 (.05) | .60 (.04) |
| OS (406 events) | | |
| All donors (n = 724) | .57 (.02) | .60 (.02) |
| Antigen-mismatched (n = 345) | .58 (.02) | .60 (.02) |
| UCB (n = 262) | .59 (.03) | .61 (.03) |
| Haploidentical (n = 117) | .54 (.03) | .59 (.03) |

SE and *P* values estimated from 50 bootstrap samples.

associated with OS (HR, 1.66; 95% CI, .95 to 2.29; $P = .08$) or NRM (HR, 1.19; 95% CI, .62 to 2.29; $P = .60$) for patients with a score ≥4 (Table 5). Continuous c-statistics estimates were the lowest among the 3 cohorts (.60 for NRM and .59 for OS).




| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| All | 724 | 399 | 329 | 271 | 221 | 177 | 141 | 113 |
| MM | 345 | 177 | 146 | 123 | 108 | 99 | 91 | 79 |
| Cord | 262 | 160 | 139 | 109 | 79 | 55 | 33 | 24 |
| Haplo | 117 | 62 | 44 | 39 | 34 | 23 | 17 | 10 |




| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| All | 724 | 435 | 354 | 292 | 238 | 193 | 154 | 124 |
| MM | 345 | 201 | 159 | 137 | 120 | 111 | 101 | 88 |
| Cord | 262 | 167 | 146 | 112 | 80 | 56 | 34 | 25 |
| Haplo | 117 | 67 | 49 | 43 | 38 | 26 | 19 | 11 |

**Figure 1.** Outcomes of the entire patient cohort as stratified by the augmented comorbidity/age index. (A) Cumulative incidence of NRM among the whole cohort of patients as stratified by the augmented comorbidity/age index. (B) Rates of OS among the whole cohort of patients as stratified by the augmented comorbidity/age index. The table below each graph depicts the number of patients remaining at risk by year from HCT.

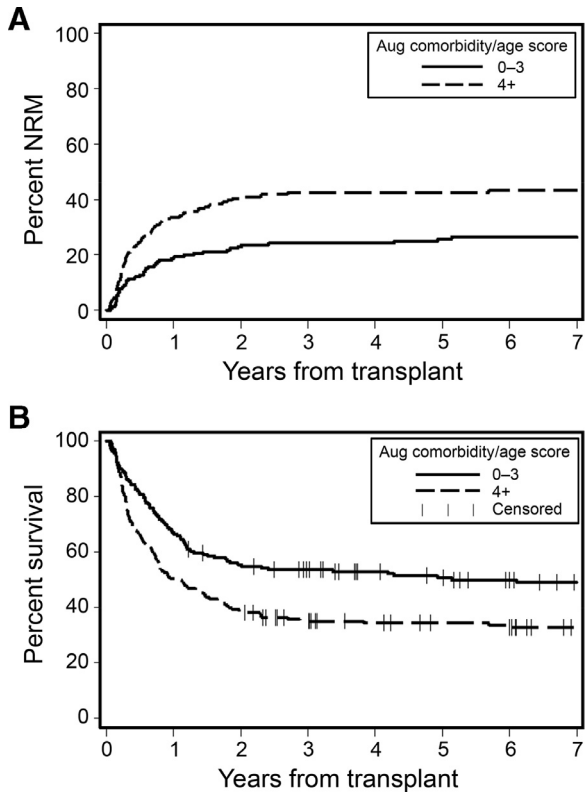



**Figure 2.** Outcomes of recipients of HLA-mismatched grafts as stratified by the augmented comorbidity/age index. (A) Cumulative incidence of NRM among HLA-mismatched grafts recipients as stratified by augmented comorbidity/age index score <4 versus ≥4. (B) Rates of OS among HLA-mismatched graft recipients as stratified by augmented comorbidity/age score <4 versus ≥4.

### *Performance of the Augmented Comorbidity/Age Index among UCB Graft Recipients*

The cumulative incidence of 2-year NRM was 21% in patients with an augmented comorbidity/age score <4 versus 42% in those with a score of ≥4 ($P < .0001$) (Figure 4A). An augmented comorbidity/age score <4 was associated with better 2-year OS compared with a score ≥4 (67% versus 48%; $P = .004$) (Figure 4B). In multivariate regression models adjusted for previously mentioned factors, a higher augmented comorbidity/age score was associated with a significantly higher risk of 2-year NRM (HR, 2.04; 95% CI, 1.20 to 3.47; $P = .008$). The HR of 2-year OS was 1.49 (95% CI, .96 to 2.31; $P = .08$) (Table 5). Continuous c-statistics

**Table 5**
Multivariate Regression Model of the Augmented Comorbidity/Age Index among 3 Donor Graft Sources

| Parameter | Adjusted HR (95% CI) | *P* Value |
|---|---|---|
| NRM | | |
| HLA-mismatched | 1.52 (1.00-2.30) | .05 |
| UCB | 2.04 (1.20-3.47) | .008 |
| Haploidentical | 1.19 (.62-2.29) | .60 |
| OS | | |
| HLA-mismatched | 1.29 (.94-1.75) | .11 |
| UCB | 1.49 (.96-2.31) | .08 |
| Haploidentical | 1.66 (.95-2.92) | .08 |

Augmented comorbidity/age index score ≥4 compared with <4. Adjusted for conditioning (high-dose, reduced-intensity, or nonmyeloablative), age (<50 or ≥50 yr), CMV serostatus (+ or -), disease risk (low or high), and KPS score (≤80 or >80), and year of transplantation (2000-2004, 2005-2009, or 2010-2013).

estimates for the predictive power of the model were .65 for NRM and .61 for OS.

### *Can the Augmented Comorbidity/Age Index Be Used to Choose between Graft Sources?*

In a separate multivariate analysis, we compared the 3 graft sources in terms of NRM and OS in the low-risk (<4) and high-risk groups (≥4) according to the augmented comorbidity/age scores. There were no significant differences in outcomes among the 3 graft sources in both the low-risk and high-risk groups (Table 6).

## DISCUSSION

Outcome research studies focusing on recipients of allogeneic HCT from alternative graft sources are limited. Here we were able to validate the discriminative capacity of a composite model combining an augmented HCT-CI and age in a group of patients receiving HLA-mismatched, HLA-haploidentical, or UCB grafts. Patients with a score ≥4 consistently had worse survival compared with those with a score <4 irrespective of graft source. Our findings are important for counseling patients in the clinic about the risks of HCT. Furthermore, within the limitations of a retrospective study, we found no advantage of one graft source over the others in patients with either low risk or high risk based on augmented comorbidity/age score. Pending prospective randomized studies, our results indicate that either graft source can be suitable for patients of older age or with multiple comorbidities.

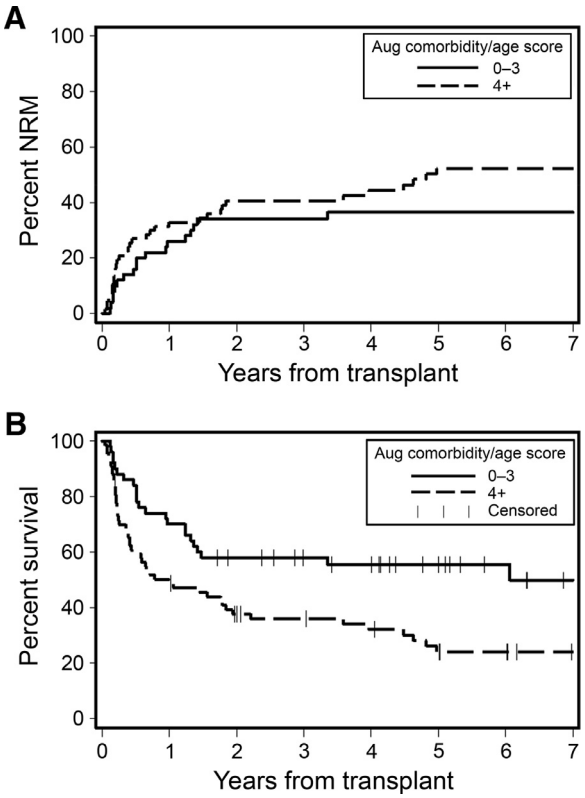



**Figure 3.** Outcomes of recipients of haploidentical grafts as stratified by the augmented comorbidity/age index. (A) Cumulative incidence of NRM among haploidentical graft recipients as stratified by augmented comorbidity/age score <4 versus ≥4. (B) Rates of OS among haploidentical graft recipients as stratified by augmented comorbidity/age score <4 versus ≥4.

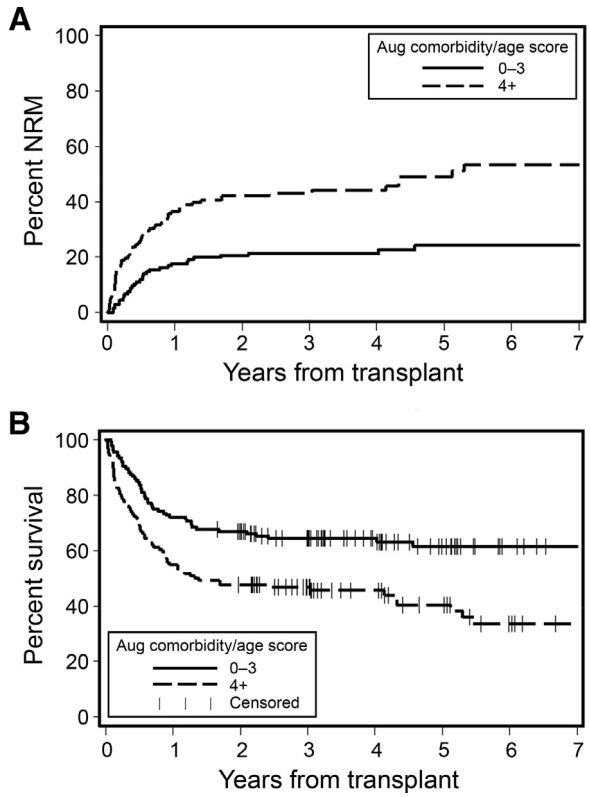



**Figure 4.** Outcomes of recipients of UCB grafts as stratified by the augmented comorbidity/age index. (A) Cumulative incidence of NRM in UCB graft recipients as stratified by augmented comorbidity/age score <4 versus ≥4. (B) Rates of OS among UCB graft recipients as stratified by augmented comorbidity/age score <4 versus ≥4.

In the present analysis, we evaluated the prognostic validity of the augmented comorbidity/age index among recipients of alternative graft sources. We added another layer of data to augment the prognostication provided by the HCT-CI through the inclusion of laboratory serum values of ferritin, albumin, and platelets and age as described previously [2,3]. The augmented comorbidity/age index consistently stratified outcomes across the 3 groups of alternative graft recipients. The augmented comorbidity/age index scores were collapsed into low-risk and high-risk groups with significant differences in outcomes, with the exception of recipients of haploidentical grafts, in whom the difference did not reach statistical significance for NRM. In addition, we confirmed an observation previously reported by our group and others regarding the interpretation of prognostic data provided by the HCT-CI scores in 2 binary risk groups. The HCT-CI score was meant to capture an association between worse OS and increased NRM with higher scores; however, these associations are relative and not absolute [13,18,19].

The incidence of NRM and rate of OS and their respective HRs at 2 years were comparable across recipients of HLA-mismatched, UCB, and haploidentical grafts in each augmented comorbidity/age index risk group. However, it should be noted that this is a retrospective nonrandomized analysis, and that other variables, such as minimal residual disease, could be used to compare outcomes across alternative graft sources [20]. Our findings emphasize the need for prospective randomized trials comparing outcomes among recipients of allogeneic HCT from alternative graft sources to provide information for counseling patients on their most suitable graft source. The

**Table 6**
Adjusted HRs for NRM and OS as Stratified by the Augmented Comorbidity/Age Index Comparing Alternative Graft Sources

| Parameter | HR (95% CI) | *P* Value | Adjusted HR (95% CI)* | Adjusted *P* Value* |
|---|---|---|---|---|
| NRM with augmented comorbidity/age score <4 | | | | |
| Antigen-mismatched | 1.0 | | 1.0 | |
| UCB | .87 (.55-1.38) | .56 | .98 (.59-1.62) | .94 |
| Haploidentical | 1.42 (.82-2.47) | .21 | 1.24 (.58-2.63) | .58 |
| NRM with augmented comorbidity/age score ≥4 | | | | |
| Antigen-mismatched | 1.0 | | 1.0 | |
| UCB | 1.06 (.75-1.48) | .75 | 1.40 (.88-2.24) | .16 |
| Haploidentical | 1.18 (.78-1.77) | .43 | 1.48 (.82-2.66) | .19 |
| OS with augmented comorbidity/age score <4 | | | | |
| Antigen-mismatched | 1.0 | | 1.0 | |
| UCB | .73 (.52-1.04) | .08 | .84 (.58-1.23) | .37 |
| Haploidentical | .96 (.61-1.51) | .86 | .99 (.53-1.86) | .99 |
| OS with augmented comorbidity/age score ≥4 | | | | |
| Antigen-mismatched | 1.0 | | 1.0 | |
| UCB | .87 (.65-1.17) | .36 | .94 (.64-1.36) | .73 |
| Haploidentical | 1.16 (.83-1.63) | .38 | 1.20 (.76-1.91) | .43 |

* Adjusted for conditioning (myeloablative, reduced-intensity, or nonmyeloablative), age (<50 or ≥50 yr), CMV serostatus (+ or -), disease risk (low or high), and KPS score (≤80 or >80).

augmented comorbidity/age index could be used to adjust comparisons in outcomes among different graft sources in these trials. An ongoing multicenter randomized clinical trial is addressing the latter question comparing double-cord versus haploidentical grafts as a source for allogeneic HCT grafts (BMT CTN1101; Clinical Trials.gov identifier NCT01597778). Evaluating outcomes by comorbidity risk group could be important for individualized application of study results according to comorbidity burden.

In the present study, the augmented comorbidity/age scores for all patients were assigned by a single investigator (M.E.) with significant interrater agreement with the principal investigator (M.L.S.) as measured by a weighted $\kappa$ estimate of .95 (SE, .03), indicating excellent agreement on comorbidity coding. This highlights the relevance of adapting consistent guidelines for comorbidity coding when validating the model, as described previously [15]. In addition, the augmented comorbidity/age index risk groups had comparable numbers of patients in the various cohorts, thus providing reliable results.

Nevertheless, our study has some limitations, beginning with its retrospective nature. In addition, the association between the augmented comorbidity/age score and NRM among the haploidentical graft recipients was weak, likely owing to the lower number of patients included in the analysis (n = 117), given that we previously showed that the lowest number of patients required to validate the model is at least 200 patients [4]. Despite this limitation, our cohort is considered among the largest single-center series of haploidentical grafts recipients. Future application on a large cohort of patients with HLA-haploidentical grafts is warranted.

Our results highlight the importance of incorporating the augmented comorbidity/age score into the design and interpretation of trial results. Future research should focus on testing the role of comorbidities in decision making about graft source selection in a large multicenter study.

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