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# 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

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## 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,