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Design and Validation of an Augmented Hematopoietic Cell Transplantation-Comorbidity Index Comprising Pretransplant Ferritin, Albumin, and Platelet Count for Prediction of Outcomes after Allogeneic Transplantation

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A B S T R A C T

Pretransplant values of serum ferritin, albumin, and peripheral blood counts were previously suggested to provide prognostic information about hematopoietic cell transplantation (HCT) outcomes. Whether these "biomarkers" have prognostic value independent of each other and the HCT-comorbidity index (HCT-CI) is unknown. We analyzed data from 3917 allogeneic HCT recipients at multiple sites in the United States and Italy using multivariate models including each biomarker and the HCT-CI. Data from all sites were then randomly divided into a training set (n = 2352) to develop weights for the relevant biomarkers to be added to the HCT-CI scores and a validation set (n = 1407) to validate an augmented HCT-CI compared with the original index. Multivariate analysis with data from one site showed that ferritin, albumin, and platelets—not neutrophils or hemoglobin—were independently associated with increased nonrelapse mortality (NRM) and decreased overall survival. Findings were validated in data from the other sites. Subsequently, in a training set from all sites, ferritin >2500 mg/dL (hazard ratio [HR], 1.69); albumin 3 to 3.5 g/dL (HR, 1.61) and <3.0 g/dL (HR, 2.27); and platelets 50 to <100,000 (HR, 1.28), 20 to <50,000 (HR, 1.29), and <20,000 (HR, 1.55) were statistically significantly associated with NRM. Weights were assigned to these laboratory values following the same equation used to design the original index. In the validation set, the addition of the biomarkers to the original index to develop an augmented HCT-CI resulted in a statistically significant increase in a higher *c*-statistic estimate for prediction of NRM ($P = .0007$). Ferritin, albumin, and platelet counts are important prognostic markers that further refine the discriminative power of the HCT-CI for transplant outcomes.

INTRODUCTION

Development of an optimal model for predicting prognosis after hematopoietic stem cell transplantation (HCT) remains an active area of research. Certainly, disease and treatment characteristics play a large role. Additional contributions arise from the physical abilities of patients to tolerate allogeneic HCT. The HCT-comorbidity index (HCT-CI) was developed in 2005 to measure relationships between medical comorbidities and nonrelapse mortality (NRM) after HCT [1]. This index has now been validated in multi-institutional studies [2-4]. The HCT-CI is being used to

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counsel patients about prognosis and to risk-stratify patients in studies examining outcomes after HCT [5,6]. Previously, the use of objective laboratory measures within the HCT-CI has improved its performance compared with the Charlson comorbidity index [7]. Whether the discriminative capacity of the HCT-CI could be further augmented by adding additional laboratory values is not known.

Previous studies have shown that a number of additional objective laboratory "biomarkers" are of interest if pre-HCT risk assessment is to be optimized. Serum albumin inversely correlates with age, smoking, obesity, and hypertension; serves as a marker of inflammatory status; and predicts cardiovascular mortality [8,9]. Serum ferritin is an acute phase reactant, and elevated levels suggest iron overload, which has been linked to post-HCT infections, hepatic, and pulmonary complications [10-13]. Finally, cytopenias, as represented by absolute neutrophil count (ANC), hemoglobin (Hgb), or platelet count, could indicate poor marrow function related to persistent malignancy or effects of prior treatment [14-16].

Here, we analyzed the independent prognostic role of 5 readily available biomarkers (albumin, ferritin, ANC, Hgb, and platelet count) in a large group of patients treated with allogeneic HCT at multiple centers in the United States and Italy. We asked two main questions: (1) Which, if any, of these 5 biomarkers is independently associated with risks of NRM and OS? (2) Could we integrate the relevant biomarkers into the HCT-CI to improve its performance?

METHODS

Patients

We retrospectively collected data from 3917 patients who received allogeneic HCT at the Fred Hutchinson Cancer Research Center (FHCRC) (n = 1789) and the Dana Farber Cancer Institute (DFCI) (n = 716) in the United States and at Gruppo Italiano Trapianto di Midollo Osseo (GITMO) (n = 1412), a network of institutions in Italy. The study was approved by the internal review boards of the FHCRC, DFCI, and the GITMO centers. Patients were included in the analysis if they received allogeneic HCT with either high-dose or reduced intensity/nonmyeloablative conditioning regimens, as previously defined [17], and received either HLA-matched related or unrelated donor grafts. Informed consent was obtained from all patients at the time of transplantation in accordance with the Declaration of Helsinki.

Definitions

HCT-CI scores were calculated by investigators at each institution according to previously published criteria [1]. Physical function before HCT was assessed using Karnofsky performance status (KPS). Low-risk diseases included chronic myeloid leukemia in first chronic phase, acute leukemia in first complete remission, myelodysplasia-refractory anemia or refractory anemia with ringed sideroblasts, and nonmalignant hematologic diseases. High-risk diseases included all other diagnoses.

The values of ferritin, albumin, ANC, Hgb, and platelet count obtained closest to and up to day −10 before HCT were used in the analysis. Ferritin concentrations were evaluated in increments of ≤1000, 1000 to 2500, and ≥2500 mg/dL consistent with cutoffs used in prior studies [18-20]. Serum albumin concentrations were divided into 3 categories, ≥3.5, 3.0 to 3.5, and <3.0 g/dL, also similar to previous studies [21,22]. ANC values were evaluated in increments of >1500, 1000 to 1500, 500 to 1000, and <500/μL. Hgb values were evaluated at cutoff values of >10, 9 to 10, and <9/μL. Platelet counts were evaluated in 4 increments: >100,000, 50,000 to 100,000, 20,000 to 50,000, and <20,000/μL.

Statistical Analysis

Overall survival (OS) was estimated by the Kaplan-Meier method. Cumulative incidence of NRM was estimated by standard methods, with relapse and progression treated as competing risks. Cox regression models were used to evaluate the association between each of the laboratory variables and risk of NRM, adjusting for HCT-CI score (0, 1, 2, 3, 4+), donor type (related, unrelated), patient cytomegalovirus serology results (−, +), regimen intensity (high-dose, reduced-intensity/nonmyeloablative), patient age (<50, ≥50 years), diagnosis category (myeloid versus others), relapse risk (low, high), and KPS. Analysis was stratified by institution. Missing information on any biomarker was included in the models as a separate variable.

Table 1
Patient Characteristics

	All Patients (n = 3917) n (%)	FHCRC (n = 1789) n (%)	DFCI/GITMO (n = 2128) n (%)
Donor			
Related	1962 (50)	900 (50)	1062 (50)
Unrelated	1942 (50)	889 (50)	1053 (50)
Missing	13		
Disease risk			
Low	1606 (41)	740 (41)	866 (43)
High	2206 (56)	1049 (59)	1157 (57)
Missing	105		
Age			
<50 yr	2145 (55)	1025 (57)	1120 (53)
≥50 yr	1772 (45)	764 (43)	1008 (47)
Conditioning			
High dose	2083 (53)	983 (55)	1100 (52)
RIC/NMA	1810 (46)	806 (45)	1004 (48)
Missing	24		
Patient CMV status			
−	1278 (33)	773 (43)	505 (24)
+	2596 (66)	1016 (57)	1581 (76)
Missing	42		
KPS			
≤90	1335 (34)	691 (39)	644 (33)
90-100	2402 (61)	1098 (61)	1304 (67)
Missing	180		

RIC/NMA indicates reduced-intensity/nonmyeloablative conditioning; CMV, cytomegalovirus.

To ensure that any notable associations between the biomarkers of interest and NRM were reproducible across institutions, we first assessed their effect in a data set from a single institution (FHCRC, n = 1789). Biomarkers that showed statistically significant independent associations with risks of NRM in the FHCRC population were then assessed using similar statistical methods in a larger, more heterogeneous data set from the remaining 2 institutions (DFCI and GITMO, n = 2128).

In order to develop and assign weights to biomarkers, patients from all centers were then randomly divided into 2 cohorts: 2352 (60%) patients were assigned to a training set; the remaining 40% were assigned to a validation set (n=1565). Patients with missing albumin and platelet data were then excluded from the validation set (n=158), with a final sample of 1407 patients contributing to the validation analysis. Integer weights for biomarkers were derived from Cox proportional hazards modeling applied to the training set, with NRM as the outcome of interest. Hazard ratios (HRs) for NRM were calculated for each biomarker value, controlling for the presence of all covariates described above, including HCT-CI scores, and were stratified by institution. Multivariate *P* values for each variable were based on adjustment for all other variables in the model. All *P* values were derived from likelihood ratio statistics and were 2-sided. The adjusted HRs were converted to integer weights according to our previously published criteria [1]. The augmented HCT-CI score for each patient was the sum of the score assigned to the HCT-CI plus that assigned to each biomarker value.

In the validation set, we compared the capabilities of the HCT-CI versus the augmented model to discriminate risks of NRM and overall mortality. Comparisons were done by computing *c*-statistic estimates [23] with the same interpretation of results as previously described [1]. The *c*-statistic was computed based on time-to-event data using the entire follow-up period. Standard errors for the *c*-statistic and differences between *c*-statistics for the original and augmented HCT-CI were evaluated in 50 bootstrap samples and then analyzed by paired *t*-tests.

RESULTS

Patient Characteristics

Forty-five percent of patients were ≥50 years of age. Approximately half of the patients received grafts from HLA-matched related donors, and the remainder received HLA-matched unrelated donor grafts. A slight majority of patients (58%) were considered to have high-risk disease. Fifty-four percent of patients received high-dose conditioning. The remaining 46% received either reduced-intensity or nonmyeloablative regimens. A significant number of patients