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Research Article

Hematopoietic Cell Transplant Specific Comorbidity Index, Disease Status at Transplant and Graft Source as Risk Factors in Patients Undergoing Allogeneic Hematopoietic Stem Cell Transplant

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Abstract

Allogeneic hematopoietic stem cell transplant is an important modality of treatment for patients bearing malignant and benign hematologic diseases, representing a chance of cure. As every treatment, it has a treatment-related mortality influenced by comorbidities. Our objective was to apply the Hematopoietic Cell Transplant Specific Comorbidity Index (HCT-CI) and to find risk factors for Non-Relapse Mortality (NRM) and Overall Survival (OS) in patients who underwent an allogeneic hematopoietic stemcell transplant in our institution, between 1993 and 2010. Medical charts from 457 patients were reviewed. Most patients (59.2%) received score 0, followed by 29.6% of cases with score 1-2 and 11.2% score 3-7. In a univariate analysis, comorbidity score (0 vs. ≥1) had a NRM of 33% vs. 45% (p=0.01) and OS at 5 years of 53% vs. 35% (p=0.001); Disease status at Transplant (low vs. high risk disease) had a NRM of 30% vs. 50% (p<0.0001) and OS of 57% vs. 27% (p<0.0001); graft source (bone marrow vs. peripheral blood) had a NRM of 29% vs. 49% (p<0.0001) and OS 56% vs. 34% (p<0.0001). The multivariate analysis confirmed the influence of HCT-CI score on NRM and OS, Disease Status at Transplant on OS and Graft Source on NRM.. When stratified by comorbidity (0 and ≥1), Disease Status at Transplant and Graft Source influenced NRM and OS in both univariate and multivariate analysis. We were able to validate the HCT-CI in our institution, and the score is used now to guide the treatment strategy of patients with comorbidities.

ABBREVIATIONS

HCT-CI: Hematopoietic Cell Transplant Comorbidity Index; NRM: Non-Relapse Mortality; OS: Overall Survival; HSCT: Hematopoietic Stem Cell Transplant; CCI: Charlson Comorbidity Index; HD: High Dose; LD: Low Dose; CsA: Cyclosporine-A; GvHD: Graft-versus-Host Disease; SPSS: Statistical Package Social Sciences; SAS: Statistical Analysis System; BM: Bone Marrow; PBSC: Peripheral Blood Stem Cell; TRM: Treatment-Related Mortality

INTRODUCTION

Allogeneic Hematopoietic Stem Cell Transplantation (HCST) represents today a chance of cure for patients bearing malignant and benign hematologic diseases. Nevertheless, the mortality related to the procedure is not negligible [1]. The influence of comorbidities on the results of the HSCT is not well defined. Therefore, a tool that could predict the influence of comorbidities on Non-Relapse Mortality (NRM) of HSCT has been sought, and the Hematopoietic Cell Transplant Specific Comorbidity Index (HCT-CI), was created to fulfill this role [2].

In a patient with a given disease under study, a comorbidity refers to any distinct additionally clinical entity that existed previously or that occurs during the clinical course of the disease [3]. Since its definition, several articles have associated comorbidities with worse prognosis, especially in oncology patients [4,5]. One of the firsts attempts to create a score that could predict mortality in cancer patients was the Charlson Comorbidity Index (CCI) [6]. The CCI was developed from the observation of the one-year mortality of 604 patients, and its ability to predict the risk of death was tested, retrospectively, in a cohort of 685 breast cancer patients [6]. By giving weights to the comorbidities, the CCI was able to stratify patients in risk groups regarding the one-year mortality. Several articles validated the CCI as a tool to predict one-year mortality [7-9], and its use was extrapolated to groups of patients undergoing Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) [10,11]. From the observation that some of the 19 comorbidities that composed the CCI were rarely seen in patients undergoing allogeneic HSCT, the HCT-CI was proposed, a specific comorbidity index for transplant patients [2]. Comorbidities of 1055 patients undergoing myeloablative and non-myeloablative allogeneic HSCT were retrospectively analyzed and related to the 2-year NRM. Comorbidities whose hazard ratios were more than 1.2 received an integral weight. The sum of the weights stratified patients in high, intermediate and low risk groups, which could be related to NRM. The HCT-CI was later validated by other groups [12] in the HSCT setting and in other situations, such as induction chemotherapy in acute myeloid leukaemia [13,14]. In the present study, we proposed to apply and validate the HCT-CI in the patients submitted to allogeneic HSCT in our institution. Our secondary aim was to evaluate the HCT-CI, patient, disease, and transplant characteristics as risk factors for NRM and OS.

PATIENTS AND METHODS

A total of 457 patients with malignant and non-malignant hematological diseases submitted to an allogeneic HSCT from 1993 to 2010, at the HSCT unit of the University of Campinas Clinical Hospital, Brazil; they were retrospectively enrolled and 126 (27.6%) were excluded due to underdocumented comorbidities.

After high (HD) or low dose (LD) conditioning regimens, from related and unrelated donors, the comorbidities included in the HCT-CI (Table 1) were recorded and then pts were stratified by risk category. LD conditioning regimen included those using busulfan dose < 9 mg/kg, melphalan dose < 150mg/m^2, and total body irradiation dose of no more than 2Gy. The main indications to LD conditioning regimens were advanced age, the presence of comorbidities and the diagnosis of Non-Hodgkin Lymphoma, Hodgkin Lymphoma and Multiple Myeloma. The majority of patients with the aforementioned diagnoses underwent autologous HSCT prior to allogeneic HSCT. All patients received cyclosporine-A (CsA) with methotrexate [15] or CsA with mycophenolatemofetil [16] as Graft-versus-Host Disease (GvHD) prophylaxis. The diagnosis and clinical grading of acute and chronic GVHD were performed using standard criteria [17-19].

Table 1: Definitions of comorbidities included in the HCT-CI and HCT-CI scores.

Comorbidity	Definitions of comorbidities included in the HCT-CI	HCT-CI weighted scores
Arrhythmia	Atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmias	1
Cardiac	Coronary artery disease, congestive heart failure, myocardial infarction, or EF < 50%	1
Inflammatory bowel disease	Crohn's disease or ulcerative colitis	1
Diabetes	Requiring treatment with insulin or oral hypoglycemics but not diet alone	1
Cerebrovascular disease	Transient ischemic attack or cerebrovascular accident	1
Psychiatric disturbance	Depression or anxiety requiring psychiatric consult or treatment	1
Hepatic, mild	Chronic hepatitis, bilirubin > ULN to 1.5 x ULN, or AST/ALT > ULN to 2.5 x ULN	1
Obesity	Patients with a body mass index > 35 kg/m^2	1
Infection	Requiring continuation of antimicrobial treatment after day 0	1
Rheumatologic	SLE, RA, polymyositis, mixed CTD, or polymyalgia rheumatic	2
Peptic ulcer	Requiring treatment	2
Moderate/severe renal	Serum creatinine> 2 mg/dL, on dialysis, or prior renal transplantation	2
Moderate pulmonary	DLco and/or FEV1 66%-80% or dyspnea on slight activity	2
Prior solid tumor	Treated at any time point in the patient's past history, excluding nonmelanoma skin cancer	3
Heart valve disease	Except mitral valve prolapse	3
Severe pulmonary	DLco and/or FEV1 < 65% or dyspnea at rest or requiring oxygen	3
Moderate/severe hepatic	Liver cirrhosis, bilirubin > 1.5 x ULN, or AST/ALT > 2.5 x ULN	3
Sorror, M. et al Blood 2005;106: 2912-2919		

Severe Aplastic Anemia, Paroxysmal Nocturnal Hemoglobinuria, Acute Leukemia in first complete remission and Chronic Myeloid Leukemia in first chronic phase were defined as Low Risk Disease. Acute Leukemia other than first complete remission, Hodgkin Lymphoma, Non-Hodgkin Lymphoma, Chronic Lymphoid Leukemia, Myelodysplastic disorders, Chronic Myeloid Leukemia other than first chronic phase, Multiple Myeloma and Myelofibrosis were defined as High Risk Disease.

Screening for cytomegalovirus with antigenemia and preemptive treatment with ganciclovir was performed on all patients. Prophylaxis for *Candida* infections was done with fluconazole; ciprofloxacin for bacterial infections; sulfamethoxazole and trimethoprim for *Pneumocystis jirovecii;* and acyclovir for viral agents as herpes simplex virus and varicella zoster virus.

The study was designed in accordance with the requirements for research involving human subjects in Brazil and approved by the Institutional Review Board. Informed consent was obtained at the time of procedure from all patients.

STATISTICAL ANALYSIS

Descriptive statistics summarize patient socio-demographic and transplantation characteristics. As nearly 60% of patients had an HCT-CI score of 0, the outcomes of these patients were compared with those of pts with scores greater than 0. Kaplan-Meier method was used for estimating 5-year overall survival [OS]. The log-rank test was utilized to compare OS curves. Cox Regression was also applied to search independent variables influencing the best results in OS and 2-year NRM. Cumulative incidence was performed to calculate NRM considering a primary disease relapse as a competing risk, using the Gray's test. The SPSS [Statistical Package Social Sciences], version 21.0, was used for major statistical analysis; SAS [Statistical Analysis System] was applied in the cumulative incidence.

Table 2: Patient and transplant characteristics

Characteristics	N=331	
Median age (range), y	36.5	(5-65)
Patient male gender, no. (%)	208	(62.8)
Conditioning Regimen, no. (%)		
Low Dose	82	(25.0)
High Dose	249	(75.0)
Disease status at Transplant *, no. (%)		
Low risk	203	(61.0)
High risk	128	(39.0)
Graft type **, no. (%)		
Bone marrow	179	(54.0)
Peripheral blood	151	(46.0)
Male Receptor Female Donor, no. (%)	96	(29.0)
Donor type, no. (%)		
Related	326	(98.4)
Unrelated	05	(1.6)
Year of transplantation, no. (%)		
1993-2000	146	(44.1)
2001-2005	98	(29.6)
2006-2010	87	(26.3)
Alive pts, no. (%)	154	(46.5)
Alive pts median follow up (range),m	102	(6-206)
Overall median follow up (range), m	21.1	(0-206)

**Low risk*= Severe Aplastic Anemia; PNH= Paroxysmal nocturnal hemoglobinuria; 1ª complete remission of acute Leukemia; 1rst Chronic Phase, chronic myeloid leukemia; *High risk*= different from 1ª complete remission of acute Leukemia; Hodgkin Lymphoma; Non-Hodgkin Lymphoma; Chronic Lymphocytic Leukemia; Myelodysplastic disorders; CML= not first chronic phase; Multiple Myeloma; Myelofibrosis;
** One patient received a cord blood.

Table 3: Distribution of comorbidity scores.

Outcome n= 331	Score 0 n= 196	Score 1-2 n= 98	Score ≥ 3 n= 37
	no. (%)	no. (%)	no. (%)
Alive (n= 154), no. (%)	106 (54)	35 (35.7)	13 (35.1)
Total Deaths (n=177), no. (%)	90 (46)	63 (64.3)	24 (64.9)
Death due to relapse (n=45), no. (%)	22/90 (24.5)	18/63 (28.6)	5/24 (20.8)

RESULTS

Patients

Three hundred and thirty-one patients were analyzed and their detailed characteristics are presented in table 2. In general, 208 (62.8%) were male and their median age were 36 (5.5–65) years. Regarding disease status at transplant, 203 (61%) had a low risk disease and 128 (39%) had a high risk disease. Acute Leukemia was the most frequent transplanted disease (34.8%), followed by Chronic Myeloid leukemia (34.1%) and Severe Aplastic Anemia (12.7%). Bone marrow was the chosen stem cell source in 179 (54%) patients and peripheral blood in 151 (46%). Most of the patients had a HSCT from a related donor (98.4%). One hundred and fifty four patients (46.5%) were alive at the moment of the analysis and the median follow up in this group was 102 months (6-206). The median follow up in the overall group was 21 months (0-206).

HCT-CI distribution

The HCT-CI distribution showed the majority of patients [59.2%] presented score 0, followed by 29.6% with score 1-2 and 11.2% score 3-7. Table 3 presents the number of alive and deceased patients, even the number of deaths due to relapse.

NRM and OS

The univariate analysis of risk factors for 2-year NRM was 33% vs. 45% for HCT-CI score 0 and ≥1, p= 0.01; for disease status at transplant was 30% for low risk vs. 50% for high risk; p< 0.0001; Bone Marrow (BM) and Peripheral Blood Stem Cell (PBSC) graft source was 29% vs. 49%, p< 0.0001. No statistical significance was found between low dose and high dose conditioning type, 35% vs. 39% (Table 4).

The 5-year OS for HCT-CI score 0 vs. score ≥1 was 53% and 35%, p= 0.001; for low and high risk disease was 57% vs. 27%, p< 0.0001; BM graft source was 56% vs. 34% for PB, p< 0.0001.

Table 4: Univariate and Multivariate analyses of risk factors for NRM and OS.

	Univariate	*Multivariate P value*
Comorbidity score (0 vs. ≥ 1)		
NRM	33% vs.45% at 2 years (p=0.01) (HR 0.64; 95%CI: 0.45-0.91)	0.02
OS	53% vs. 35% at 5 years (p= 0.001) (HR 0.62; 95%CI 0.46-0.83)	0.004
Disease status at Transplant (low risk vs. high risk)		
NRM	30% vs. 50% at 2 years (p< 0.0001) (HR 0.53; 95%CI: 0.38-0.76)	0.07
OS	57% vs. 27% at 5 years (p< 0.0001) (HR 0.45; 95%CI: 0.33-0.60)	< 0.0001
Graft source (bone marrow vs. peripheral blood)		
NRM	29% vs. 49% at 2 years (p< 0.0001) (HR 0.52; 95%CI: 0.37-0.74)	0.03
OS	56% vs.34% at 5 years (p< 0.0001) (HR 0.56; 95%CI: 0.41-0.75)	0.19
Conditioning type (low dose vs. high dose)		
NRM	35% vs. 39% at 2 years (p=0.32) (HR 0.81; 95%CI: 0.54-1.23)	0.09
OS	49% vs. 45% at 5 years (p= 0.43) (HR 0.87; 95%CI: 0.61-1.23)	0.11

NRM: non-relapse mortality; OS: overall survival
Low risk= Severe Aplastic Anemia; PNH= Paroxysmal nocturnal hemoglobinuria; 1ª complete remission of acute Leukemia; 1rstChronic Phase, chronic myeloid leukemia; *High risk*= different from 1ª complete remission of acute Leukemia; Hodgkin Lymphoma; Non-Hodgkin Lymphoma; Chronic Lymphocytic Leukemia; Myelodysplastic disorders; CML= 1rstAccelerated Phase, chronic myeloid leukemia; Multiple Myeloma; Myelofibrosis.

Table 5: Univariate and Multivariate analyses of risk factors for NRM and OS according to comorbidity score.

	Univariate	*Multivariate P value*
Comorbidity score = 0		
Conditioning type (low dose, n= 45 vs. high dose, n= 151)		
NRM	29% vs. 35% at 2 years (p=0.31) (HR 0.74; 95%CI: 0.40-1.34)	0.32
OS	56% vs. 52% at 5 years (p= 0.47) (HR 0.83; 95%CI: 0.50-1.38)	0.47
Disease status at Transplant (low risk, n= 128 vs. high risk, n= 68)		
NRM	27% vs. 46% at 2 years (p= 0.006) (HR 0.52; 95%CI: 0.32-0.84)	0.007
OS	64% vs. 33% at 5 years (p< 0.0001) (HR 0.44; 95%CI: 0.29-0.66)	< 0.0001
Graft source (bone marrow, n= 111 vs. peripheral blood, n= 84)		
NRM	28% vs. 40% at 2 years (p= 0.03) (HR 0.60; 95%CI: 0.37-0.97)	0.03
OS	61% vs.43% at 5 years (p= 0.01) (HR 0.60; 95%CI: 0.39-0.91)	0.01
Comorbidity score ≥ 1		
Conditioning type (low dose, n= 37 vs. high dose, n= 98)		
NRM	42% vs. 47% at 2 years (p=0.31) (HR 0.84; 95%CI: 0.48-1.49)	0.56
OS	41% vs. 34% at 5 years (p= 0.52) (HR 0.85; 95%CI: 0.52-1.38)	0.52
Disease status at Transplant (low risk, n= 75 vs. high risk, n= 60)		
NRM	36% vs. 56% at 2 years (p= 0.03) (HR 0.60; 95%CI: 0.36-0.98)	0.04
OS	47vs. 20% at 5 years (p= 0.001) (HR 0.49; 95%CI: 0.32-0.74)	0.001
Graft source (bone marrow, n= 68 vs. peripheral blood, n= 67)		
NRM	32% vs. 60% at 2 years (p= 0.003) (HR 0.47; 95%CI: 0.28-0.78)	0.004
OS	48% vs.23% at 5 years (p= 0.004) (HR 0.54; 95%CI: 0.35-0.83)	0.005

NRM: non-relapse mortality; OS: overall survival
Low risk= Severe Aplastic Anemia; PNH= Paroxysmal nocturnal hemoglobinuria; 1ª complete remission of acute Leukemia; 1rstChronic Phase, chronic myeloid leukemia; *High risk*= different from 1ª complete remission of acute Leukemia; Hodgkin Lymphoma; Non-Hodgkin Lymphoma; Chronic Lymphocytic Leukemia; Myelodysplastic disorders; CML= 1rstAccelerated Phase, chronic myeloid leukemia; Multiple Myeloma; Myelofibrosis.

No statistical significance was found between low dose and high dose conditioning type, 49% vs. 45% (Table 4).

The multivariate analysis for NRM identified the score ≥1 and PB graft source as significantly unfavorable variables. Inasmuch as for OS, the multivariate confirmed that the score ≥1 and high risk disease status at transplant as also a significantly unfavorable variables.

NRM and OS according to HCT-CI

In the univariate and multivariate analyses of risk factors for NRM according to comorbidity score (Table 5), the disease status at transplant and graft source were significant either for comorbidity score=0 and comorbidity score≥1. Also, the outcomes were worse for those patients who had comorbidity score≥1. The figure 1 shows the 2-year NRM and the 5-year OS according to the HCT-CI.

Causes of deaths

Among the 331 patients, 177 (53.4%) died, 45/177 (25.4%) due to relapse and 132/177 (74.6%) due to Treatment-Related Mortality (TRM). The overall cause of transplant-related mortality was 28 (21.2%) bacterial infection; 20 (15.3%) acute GVHD; 16 (12%) fungal infection; 15 (11.4%) chronic GVHD; 12 (9%) organ failure; 10 (7.5%) pneumonia; 9 (7%) CMV; 6 (4.5%) ARDS (adult respiratory distress syndrome); 5 (3.7%) Veno-Occlusive Disease (VOD); 4 (3%) central nervous system (CNS), 3 (2.3%) lung and 3 (2.3%) gastric-intestinal (GIT) haemorrhage; and 1 (0.8%) new malignancy.

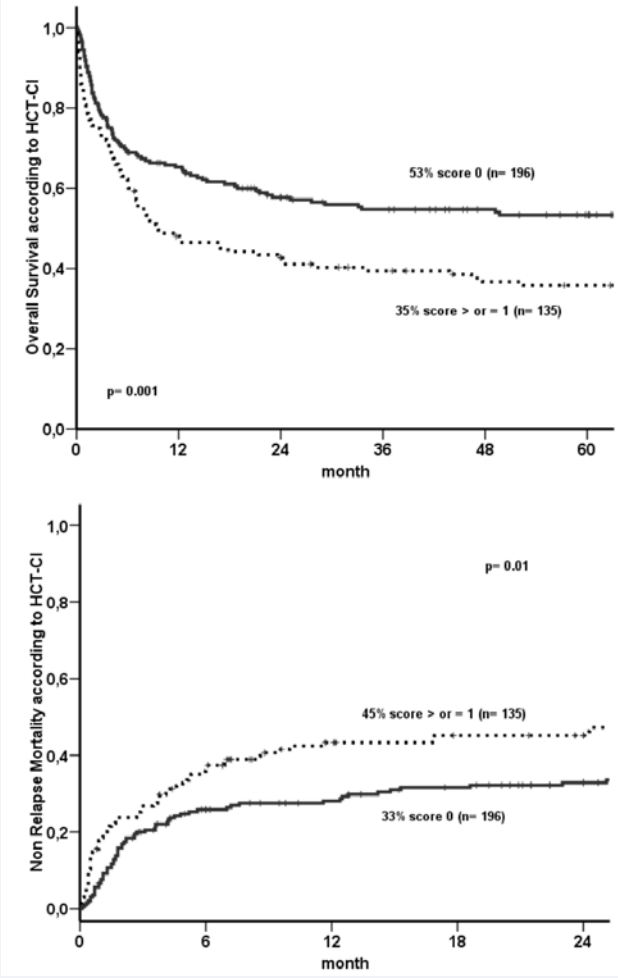

Figure 1 5-year Overall survival and 2-year Non Relapse Mortality according to the HCT-CI.

DISCUSSION

Allogeneic HSCT represents a chance of cure for patients with malignant and benign hematologic disease, but as well as the most treatment modalities, it has a TRM. The HCT-CI is able to predict, based in comorbidities analysis, the NRM of patients submitted to allogeneic HSCT [2]. The main objective of this study was to apply the score in the patients submitted to an allogeneic HSCT in our institution. Based in our data, we were able to validate the HCT-CI. The stratification in groups with score=0 and ≥1 predicted the 5y-OS and 2y-NRM, with statistically significant results. However, many attempts were made with the objective to validate the score in vast variety of scenarios, sometimes with successful results, sometimes not [12, 20-23].

Graft source and disease status also influenced NRM and OS in our analysis. In a paper published in 2012 [24], disease risk and its influence on HSCT results are discussed. Based on this observation, a disease risk index was proposed, and it was able to risk-stratify patients regarding Progression-Free Survival, NRM and OS. The Disease Risk Index was not applied in our analysis. Our data showed that disease status at HSCT had unfavourable influence in 2y-NRM and 5y-OS, even when stratified by comorbidity score.

Bone Marrow and Peripheral Blood Stem Cell are the main options of graft source available, with an increase in the use of PBSC over BM [25]. PBSC is associated with an increased incidence of chronic GvHD and a decreased risk of relapse that would improve survival among patients with high risk diseases [26]. Thus, PBSC is usually used when a high risk disease is present [26,27]. Despite the increased use, there are conflicting results regarding the advantage of exposing the patients with high risk diseases to a higher incidence of chronic GvHD [28]. Our data showed that PBSC is associated with worse 2y-NRM and 5y-OS, probably due to chronic GvHD and the complications related to its treatment. This information must be interpreted carefully, as there was no stratification in disease risk when analysing the PBSC results. We have not been able to stratify the analysis in low risk and high risk diseases because our institution follows a specific protocol regarding graft source. Patients bearing high risk diseases receive PBSC and low risk diseases mainly BM as graft source, which results in unbalanced groups and a inadequate statistical analysis.

The conditioning regimen did not influence OS and NRM in either stratified or non-stratified groups. We expected that this variable would influence the OS and NRM, because some of patients who underwent low dose allogeneic HSCT had comorbidities that prevented them from having a high dose transplant, and more important, many of them had an autologous HSCT previously.

The two main limitation of the present study are the fact that

it is a retrospective study and that we had 27.6% of patients with missing data. Therefore, a prospective study was proposed, with the objective to improve data collection and storage and better address issues as the relation between the score and the other variables.

In conclusion, the HCT-CI proved to be a valid tool to predict outcome after allogeneic HSCT in our population, and should be applied to better guide the treatment strategy of patients with comorbidities, but not prevent them from being transplanted.

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