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Hematopoietic Cell Transplantation–Specific Comorbidity Index Predicts Morbidity and Mortality in Autologous Stem Cell Transplantation

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A B S T R A C T

The hematopoietic cell transplantation–specific comorbidity index (HCT-CI) score is a useful tool to assess the risk for nonrelapse mortality (NRM) after allogeneic hematopoietic stem cell transplantation. Although the HCT-CI has been investigated in autologous stem cell transplantation (ASCT), its use is limited. To improve on the current use of the HCT-CI score on the morbidity and mortality after ASCT, we assessed the 100-day morbidity defined as orotracheal intubation (OTI), dialysis or shock (vasopressors need), 100-day NRM, early composite morbidity–mortality (combined endpoint that included any previous endpoints), and long-term NRM. We retrospectively reviewed a cohort of 1730 records of adult patients who received an ASCT in Argentinean center's between October 2002 and August 2016. Median follow-up was 1.15 years, and median age was 53 years. Diseases were multiple myeloma (48%), non-Hodgkin lymphoma (27%), and Hodgkin lymphoma (17%); 51% were in complete or partial remission; and 13% received ≥ 3 chemotherapy lines before transplant (heavily pretreated). Early NRM (100-day) was 2.7%, 5.4% required OTI, 4.5% required vasopressors, and 2.1% dialysis, with an early composite morbidity–mortality of 6.8%. Long-term (1 and 3 years) NRM was 4% and 5.2% and overall survival 89% and 77%, respectively. High-risk HCT-CI patients had a significant increase in 100-day NRM compared with intermediate and low risk (6.1% versus 3.4% versus 1.8%, respectively; $P = .002$), OTI (11% versus 6% versus 4%, $P = .001$), shock (8.7% versus 5.8% versus 3%, $P = .001$), early composite morbidity–mortality (13% versus 9 % versus 4.7%, $P < .001$), and long-term NRM (1 year, 7.7% versus 4% versus 3.3%; and 3 years, 10.8% versus 4% versus 4.8%, respectively; $P = .002$). After multivariate analysis these outcomes remained significant: early composite morbidity–mortality (odds ratio [95% confidence interval] compared with low risk: intermediate risk 2.1 [1.3 to 3.5] and high risk 3.3 [1.9 to 5.9]) and NRM (hazard ratio [95% confidence interval] compared with low risk: intermediate risk .97 [.8 to 2.4] and high risk 3.05 [1.3 to 4.5]). No significant impact was observed in overall survival. Other than comorbidities, significant impact

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was observed for heavily pretreated patients, age ≥ 55 years, non-Hodgkin lymphoma, and bendamustine-etoposide-citarabine-melphalan conditioning. We confirmed that the HCT-CI had a significant impact on NRM after ASCT, and these findings are mainly due to early toxicity express as 100-day NRM and the 3 main morbidity outcomes as well as the composite endpoint.

INTRODUCTION

Despite current improvement in supportive care, mortality after hematopoietic stem cell transplantation remains high [1]. Autologous stem cell transplantation (ASCT) is the standard of care for many hematologic malignancies and certain solid tumors [2]. Depending on the diagnosis, this procedure is indicated as the frontline treatment and in other cases as salvage regimens but in all cases as part of the treatment of chemosensitive diseases [3,4]. Although the morbidity and mortality of ASCT is lower than allogeneic transplant, deaths still occurs, mainly because of infectious complications [1].

The hematopoietic cell transplantation–specific comorbidity index (HCT-CI) score, described by Sorror et al. [5], is a useful tool to predict the risk for nonrelapse mortality (NRM) after allogeneic hematopoietic stem cell transplantation and is helpful in the pretransplant clinic to define the intensity of the conditioning regimen. Few studies have been published regarding the impact of this score in ASCT [6-9]. A Center for International Blood and Marrow Transplant Research analysis, including US centers, demonstrated a significant association of the score in long-term NRM after ASCT, but not much evidence has been published about the impact of the score in early post-transplant events [10]. The aim of this article is to validate in a large cohort of recent ASCTs performed in Argentina the impact of HCT-CI score on the mortality after transplant and to analyze the association of the score in early morbidity and mortality endpoints.

METHODS

We retrospectively reviewed a cohort of 1730 medical records of patients (age ≥ 15 years) who received an ASCT in 10 Argentinean centers between October 2002 and August 2016. Median follow-up was 1.15 years, with all patients followed to at least day 100. Variables collected were age, gender, disease, lines of treatment before transplant (heavily pretreated defined as 3 or more), pretransplant status (complete remission, partial remission, or progressive/stable disease), conditioning, and low stem cell cellularity (defined as less than $CD34^+$ 3×10^6/kg). Comorbidities were assessed by HCT-CI score as low risk (score 0), intermediate risk (score 1 to 2), or high risk (score ≥ 3). Study endpoints were 100-day morbidity that included orotracheal intubation (OTI), dialysis or shock (defined as need for vasopressors), 100-day NRM, early composite morbidity–mortality (combined endpoint that included any of the previous endpoints), and long-term NRM (at 1 and 3 years). Secondary endpoint was overall survival (OS) (at 1 and 3 years).

Statistical analysis was performed using SPSS version 17.0 (SPSS Inc., Chicago, IL) and R version 3.2 (https://r-project.org). In univariate analysis the OS probability was compared using the log-rank statistic and calculated with the Kaplan-Meier method. For relapse and NRM we used Gray's test and analyzed these outcomes using the cumulative incidence method. The competing event for NRM was relapse and for relapse was death without relapse. For OTI, shock, dialysis, and combined early morbidity–mortality we used the chi-square test. For multivariate analysis we use the Cox regression model for OS, Fine-Gray regression for competing event endpoints (NRM, relapse), and the logistic regression for dichotomous variables. We included all factors in the univariate analysis with a $P < .2$. Outcomes were considered to be significant with $P < .05$, whereas a trend was considered with $P = .05$ to 0.1.

RESULTS

Cohort characteristics are listed in Table 1. Median age was 53 years (range, 15 to 74 years), and 58% were male. Prevalent diseases were multiple myeloma (48%), non-Hodgkin lymphoma (27%), and Hodgkin lymphoma (17%); 51% were in complete remission, 46% in partial remission, and 3% in stable/progressive disease; and 46% received 1 chemotherapy line before transplant, 41% received 2 lines, and 13% received 3 or more (heavily pretreated). Regarding conditionings, melphalan was used in 48% of the cases, carmustine, cyclophosphamide, etoposide in 24%, carmustine, etoposide, cytarabine, melphalan in 8%, and bendamustine-etoposide-citarabine-melphalan (BendaEAM) in 7.5%. Twenty-six percent received an infusion of stem cells $CD34^+ < 3 \times 10^6$/kg. In respect to comorbidities, 60% had low-risk HCT.CI, 29% intermediate risk, and 13% high risk.

Table 1
Cohort Characteristics (N = 1730)

Characteristic		No. of Patients (%)
Age, mean 53 years (range, 15-74)	<55 yr	944 (55)
	≥ 55 yr	786 (45)
Gender	Male	1008 (58)
	Female	722 (42)
Diseases	Multiple myeloma	837 (48)
	Non-Hodgkin lymphoma	475 (27)
	Hodgkin lymphoma	299 (17)
	Acute myeloid leukemia	58 (3.4)
	Others*	61 (3.5)
Pretransplant treatment (chemotherapy lines)	1 line	718 (46)
	2 lines	629 (41)
	≥3 lines	201 (13)
	Missing	182
Pretransplant status	Complete remission	876 (51)
	Partial remission	777 (46)
	Stable-progressive	47 (3)
	Missing	30
Conditioning	Melphalan	833 (48)
	Carmustine, cyclophosphamide, etoposide	407 (24)
	Carmustine, etoposide, cytarabine, melphalan	141 (8)
	BendaEAM	131 (7.5)
	Busulfan-cyclophosphamide	56 (3)
	Others	161 (9.5)
HCT-CI score	Low risk (0)	1032 (60)
	Intermediate risk (1-2)	502 (29)
	High risk (≥3)	196 (11)

* Other diseases includes germinal cell tumors, neuroblastoma, meduloblastoma, Ewing sarcoma, and osteosarcoma.

Early NRM (100-day) was 2.8%. By day 100 5.4% required OTI, 4.5% required vasopressors, and 2.1% dialysis, with an early composite morbidity–mortality of 6.8%. Regarding time-dependent variables, NRM at 1 year was 4% and at 3 years 5%, and OS was at 1 year was 85% and at 3 years 75%.

High-risk HCT-CI patients had a significant increase in 100-day NRM compared with intermediate risk and low risk (6.1 versus 3.2% versus 1.8%, respectively; $P = .002$). Similarly, the score increased the need for OTI (11% versus 6% versus 4%, $P = .001$) and vasopressors (8.7% versus 5.8% versus 3%, $P = .001$) and significantly increased the early composite morbidity–mortality endpoint (13% versus 9% versus 4.7%, $P < .001$), whereas it showed a trend with higher dialysis need

Table 2
HCT-CI Score Impact on Morbidity and Mortality after Autologous Hematopoietic Stem Cell Transplantation

Outcomes	Low Risk	Intermediate Risk	High Risk	*P*
Day 100 NRM	1.8	3.2	6.1	.002
OTI	4	6	11	.001
Shock	3	5.8	8.7	.001
Dialysis	1.6	2.4	4.1	.06
Morbidity–mortality	4.7	9	13	<.001

Values are percents.

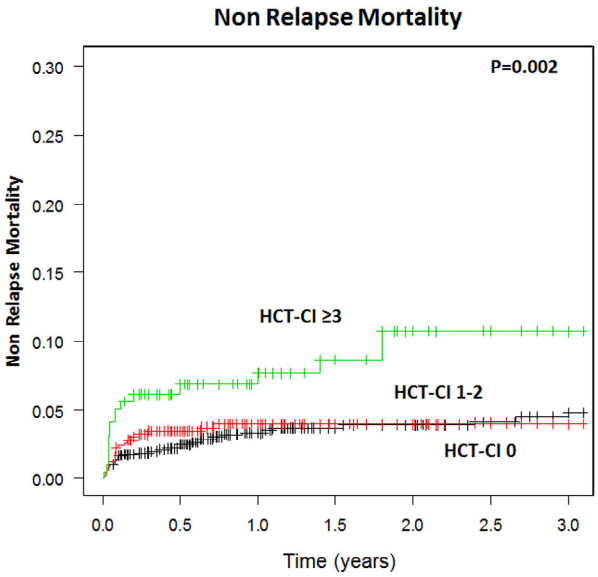

Figure 1. NRM according to HCT-CI score in the full cohort. High Risk HCT-CI patients had a significantly higher NRM compared to Intermediate and Low Risk patients.

(4.1% versus 2.4% versus 1.6%, *P* = .06) (Table 2). Moreover, long-term NRM was significantly increased in high-risk patients compared with intermediate risk and low risk (1 year 7.7% versus 4% versus 3.3%, and 3 years 10.8% versus 4% versus 4.8%, respectively; *P* = .002) (Figure 1). No significant impact was observed on OS (1 year: low risk 89% versus intermediate risk 88% versus high risk 88%; 3 year: low risk 74% versus intermediate risk 78% versus high risk 74%; *P* = .98) (Figure S1, appendix).

After multivariate analysis these outcomes remained significant with a proportional increase in the odds ratio for intermediate-risk and high-risk compared with low-risk HCT-CI score: early composite morbidity–mortality endpoint (intermediate-risk odds ratio, 2.1 [95% confidence interval, 1.3 to 3.5]; high-risk odds ratio, 3.3 [95% confidence interval, 1.9 to 5.9]) (Table 3) as well as all the early morbidity endpoints (appendix, Tables S1 to S5 to S3). Moreover, after multivariate analysis NRM was significantly increased in high-risk patients (hazard ratio for intermediate risk, .97 [95% confidence interval, .7 to 2.3]; hazard ratio high risk, 3.05 [95% confidence interval, 1.3 to 4.5]) (Table 4).

We analyzed the impact of the score on the 2 main diseases subgroups. Multiple myeloma patients (n = 837) had a 100-day NRM rate of 1.2%, 3.9% early composite morbidity–mortality endpoint and long-term NRM (1 and 3 years) of 2% and 2.9%, respectively, with a significantly higher early

Table 3
Multivariate Analysis for Early Composite Morbidity–Mortality

	P	Odds Ratio	95% Confidence Interval	
			Lower	Upper
Patients ≥ 55 yr	.87	1.03	.66	1.60
Non-Hodgkin lymphoma	.001	2.17	1.38	3.40
Heavily pretreated	.06	1.64	.96	2.80
Infusion (CD34 ≥ 3×10^6/kg)	.29	.78	.49	1.23
BendaEAM	.001	2.71	1.52	4.83
HCT-CI				
Low risk (ref.)				
Intermediate risk	.002	2.16	1.32	3.53
High risk	<.001	3.35	1.90	5.92

Table 4
Multivariate Analysis for NRM

	P	Hazard Ratio	95% Confidence Interval	
			Lower	Upper
Patient older than 55 years	.01	2.47	1.13	3.01
Male patients	.04	2.02	1.01	2.87
Pretransplant status				
Complete remission (ref.)				
Partial remission	.13	.70	.41	1.12
Stable/progressive disease	.06	1.83	.94	5.95
Heavily pretreated	.07	1.78	.94	3.05
Non-Hodgkin lymphoma	<.01	3.13	1.31	3.29
BendaEAM	<.001	3.76	1.70	5.44
HCT-CI				
Low risk (ref.)				
Intermediate risk	.33	.97	.75	2.31
High risk	<.01	3.05	1.39	4.53

composite morbidity–mortality for high risk/intermediate risk versus low risk (5.4% versus 2.7%, *P* = .04) but no significant impact in NRM (1 year: 2.1 % versus 2.1% versus 2%; 3 year: 5.5% versus 2.1% versus 2.7%, respectively, for high risk, intermediate risk, and low risk; *P* = .4) (Figure S2, appendix) or OS (Figure S3, appendix). A different impact was observed in lymphoma patients (n = 777). This subgroup showed 4.1% 100-day NRM, 10.2% composite morbidity–mortality and long-term NRM (1 and 3 years) of 6.2% and 8.1%, respectively, with a significant impact of the score (high risk versus intermediate risk versus low risk) in 100-day NRM (12.7% versus 6.1% versus 4.5%, *P* < .001), as well as composite morbidity–mortality (24% versus 13.5% versus 6.6%, *P* < .001), long-term NRM (1 year: 15.1% versus 6.9% versus 4.5%; 3 year: 18.1% versus 6.9% versus 8.1%, respectively; *P* < .001) (Figure 2) and a reduction in OS (high risk versus intermediate/low risk, 1 year: 77% versus 85%; 3 years: 61% versus 72%, respectively; *P* = .03) (Figure 3).

Other than comorbidities, a significant impact was observed in the need for OTI (non-Hodgkin lymphoma, heavily pretreated patients, and BendaEAM conditioning), shock (non-Hodgkin lymphoma, heavily pretreated patients, and BendaEAM conditioning), dialysis (BendaEAM conditioning; appendix, Tables S1–S3), early composite morbidity–mortality (non-Hodgkin lymphoma and BendaEAM conditioning) (Table 3), and NRM (male patients, age ≥ 55 years, non-Hodgkin lymphoma, and BendaEAM conditioning) (Table 4).

DISCUSSION

We confirmed that the HCT-CI had a significant impact on ASCT NRM and the impact was due to early post-transplant

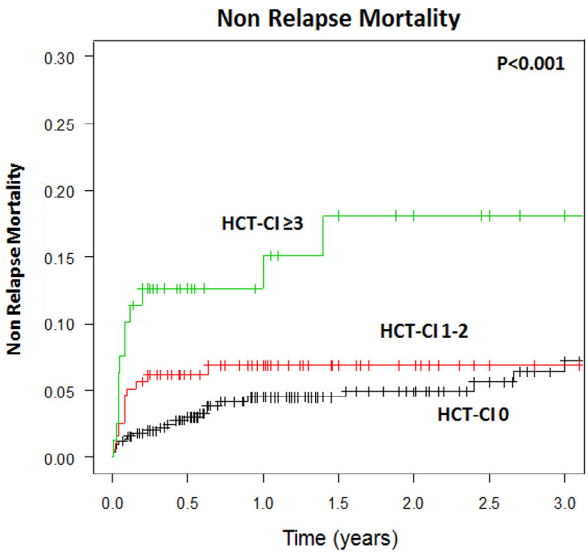

Figure 2. NRM according to HCT-CI score in lymphoma patients. High Risk HCT-CI patients had a significantly higher NRM compared to Intermediate and Low Risk patients.

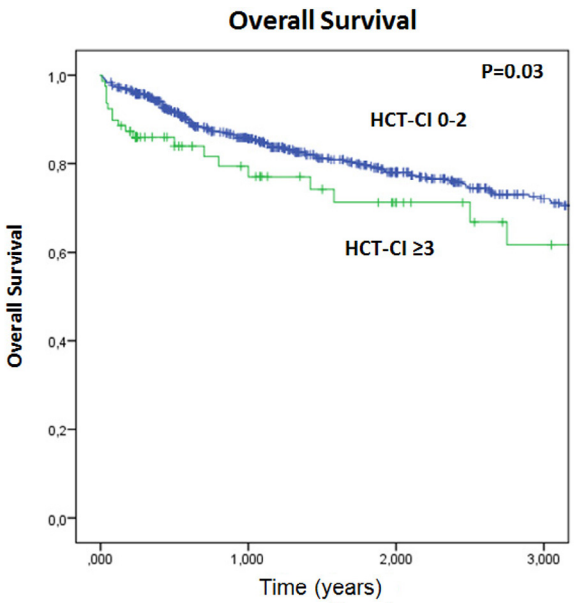

Figure 3. OS according to HCT-CI score in lymphoma patients. High Risk HCT-CI patients had a significantly lower OS compared to Intermediate/Low Risk patients.

toxicity. The outcomes were measured at 100-day NRM, the 3 main morbidity outcomes (OTI, shock, and dialysis), and composite endpoint. Subsequently, long-term NRM was significantly associated with the score. All these endpoints remained significant after multivariate analysis.

The predictive performance of the score is based on few large ASCT cohorts. Labonte et al. [11] described an increased incidence of early toxicity for high-risk HCT-CI patients after ASCT in 125 multiple myeloma patients, without long-term analysis. Jaglowsky et al. [6] found no significant increase in NRM in around 600 patients who underwent an ASCT for multiple myeloma or lymphomas, probably related to the number of patients' included. One of the 2 largest studies was a Center for International Blood and Marrow Transplant Research analysis described by Saad et al. [8] in 1100 multiple myeloma patients, which again found no increase in NRM according to the HCT-CI, probably because this event was very low (1% to 2%). Furthermore, the authors did not report early morbidity endpoints.

Sorror et al. [10] published an additional Center for International Blood and Marrow Transplant Research analysis, including US canters, with more than 11,000 ASCTs for several diseases. Similar to our results, they found a significant association of high-risk HCT-CI score with long-term NRM but no association for intermediate risk. Furthermore, probably because of the larger numbers of this analysis, the score was significantly associated with OS, as was the impact of the score in NRM and OS in multiple myeloma and lymphoma subgroup analyses. Our study adds to this evidence base by providing new analyses on early endpoints and validating the score in a different population.

Other factors were associated with NRM. Apart from the worse outcome of advanced age, male patients, and a trend to a higher NRM for the heavily pretreated patients, non-Hodgkin lymphoma and BendaEAM conditioning were consistently associated with the study endpoints. This conditioning, described by Visani et al. [12] in a phase I to II study, showed a safety profile. Although this study was not designed to analyze this factors, especially the conditioning, undoubtfully BendaEAM was more toxic than traditional regimens used for lymphoproliferative disorders like carmustine, cyclophosphamide, etoposide or carmustine, etoposide, cytarabine, melphalan in consonance with other publications [13,14].

It is common practice to make adjustments in conditioning regimens for older patients, with no rationale for this decision [6,8], and to consider older patients not to be candidates for transplantation based on chronologic age. Surprisingly, after multivariate analysis, age was not associated with early mortality or the combined endpoint but only to long-term NRM. Presumably, this can be explained by the fact that data collection has not assessed correctly the conditioning adjustment according to age and that older patients had a significantly higher prevalence of multiple myeloma than younger patients (70% versus 40%). Although some registry data found a significant impact of age in transplant mortality, the debate is still open [15]. Several publications described no association between advanced age and worst outcome in lymphoma [16-20] and multiple myeloma [21] patients. We and others arrived at a similar conclusion after allogeneic transplantation [22-25].

Our study has several strengths. It is 1 of the largest cohorts reported in this topic. The exclusion criteria for pediatric patients made the cohort more homogeneous. A comprehensive adjusted model with the principal patient characteristics in the multivariate analysis was performed. Limitations are a potential underestimation of high-risk HCT-CI because of the retrospective nature of the cohort, which can be observed in the comparison with the Sorror et al. [5] analysis that described 23% high risk compared with 11% in our cohort. Loss of follow-up can interfere with long-term outcomes like OS. Finally, heterogeneity in practice among practitioners cannot be adjusted for.

In conclusion, we confirmed in a different cohort that the HCT-CI had a significant impact on ASCT NRM basically because of early toxicity expressed as 100-day NRM, the 3 main morbidity outcomes, and the composite morbidity–mortality endpoint. Currently, we are working on a comprehensive score

that not only includes comorbidities but other factors that significantly impact transplant outcomes. This observation can improve patient selection and the intensity of conditioning regimens.

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SUPPLEMENTARY DATA

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