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Autologous

Predicting Mortality after Autologous Transplant: Development of a Novel Risk Score

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A B S T R A C T

There have been several efforts to predict mortality after autologous stem cell transplantation (ASCT), such as the hematopoietic cell transplant-comorbidity index (HCT-CI), described for allogeneic stem cell transplantation and validated for ASCT, but there is no composite score in the setting of ASCT combining comorbidities with other clinical characteristics. Our aim is to describe a comprehensive score combining comorbidities with other clinical factors and to analyze the impact of this score on nonrelapse mortality (NRM), overall survival (OS), and early morbidity endpoints (mechanical ventilation, shock or dialysis) after ASCT. For the training cohort, we retrospectively reviewed data of 2068 adult patients who received an ASCT in Argentina (October 2002 to June 2017) for multiple myeloma or lymphoma. For the validation cohort, we analyzed 2168 ASCTs performed in the Medical College of Wisconsin and Spanish stem cell transplant group (Grupo Español de Trasplante Hematopoyético (GETH)) (January 2012 to December 2018). We first performed a multivariate analysis for NRM in order to select and assign weight to the risk factors included in the score (male patients, aged 55 to 64 and ≥65 years, HCT-CI ≥3, Hodgkin lymphoma and non-Hodgkin lymphoma). The hazard ratio for NRM increased proportionally with the score. Patients were grouped as low risk (LR) with a score of 0 to 1 (686, 33%), intermediate risk (IR) with a score of 2 to 3 (1109, 53%), high risk (HR) with a score of 4 (198, 10%), and very high risk (VHR) with a score of ≥5 (75, 4%). The score was associated with a progressive increase in all the early morbidity endpoints. Moreover, the score was significantly associated with early NRM

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(day 100: 1.5% versus 2.4% versus 7.6% versus 17.6%) as well as long term (1 to 3 years; 1.8% to 2.3% versus 3.8% to 4.9% versus 11.7% to 14.5% versus 25.0% to 27.4%, respectively; $P < .0001$) and OS (1 to 5 years; 94% to 73% versus 89% to 75% versus 76% to 47% versus 65% to 52% respectively; $P < .0001$). The score was validated in an independent cohort (N = 2168) and was significantly associated with early and late events. In conclusion, we developed and validated a novel score predicting NRM and OS in 2 large cohorts of more than 2000 autologous transplant patients. This tool can be useful for tailoring conditioning regimens or defining risk for transplant program decision making.

INTRODUCTION

Autologous stem cell transplantation (ASCT) is the standard of care for many hematologic malignancies such as multiple myeloma (MM) and lymphomas as a first-line or second-line treatment [1,2]. Although the morbidity and mortality of ASCT are lower than allogeneic transplant, deaths still occur [3,4].

Several attempts to predict mortality after ASCT have been made, mainly as single-disease analysis. Bierman et al. [5] described the association of the international prognostic factors project for patients with Hodgkin lymphoma after ASCT, and Brockelmann et al. [6] developed a new score for this group of patients that predicts progression-free survival and overall survival (OS). Similarly, the International Prognostic Index showed a significant impact on transplant outcomes for patients with non-Hodgkin lymphoma [7].

The only score applicable to different diseases is the hematopoietic cell transplant-comorbidity index (HCT-CI) score, originally described by Sorror et al. [8] for allogeneic hematopoietic cell transplant. The utility of this score in ASCT has been validated in a large Center for International Blood and Marrow Transplant Research (CIBMTR) cohort and by other groups, including ours [9-12]. High-risk HCT-CI patients had a significant increase in nonrelapse mortality (NRM) compared with low- and intermediate-risk patients. To our knowledge, there is no score that combines comorbidities with patient- and disease-related clinical factors that predicts NRM after ASCT for different hematologic malignancies.

Our objective was to develop a comprehensive score that combines comorbidities with other clinical factors and to analyze the impact of this score on OS and NRM after ASCT. The secondary objective was to evaluate the impact of the score on early morbidity.

MATERIALS AND METHODS

For the training cohort, we conducted a retrospective analysis of 2068 adult patients who received an ASCT in Argentina between October 2002 and June 2017 for treatment of MM or lymphoma. Centers were affiliated to Grupo Argentinon de Trasplante de Médula Ösea (GATMO). Median follow up was 1.1 years (range, 100 days to 14 years). Variables included in the analysis were age, sex, disease, disease status at the time of ASCT, lines of chemotherapy (defined as heavily pretreated with ≥3 lines), HCT-CI (according to the original description) [8], and $CD34^+$ cell dose received during ASCT (defined as low dose $<3 \times 10^6$/kg).

The validation cohort consisted of 2168 adult ASCT patients with MM or lymphoma at the Medical College of Wisconsin (MCW) (N = 890) and within the Spanish cooperative stem cell transplant group (GETH) (N = 1278) between January 2012 and December 2018. Median follow-up was 1.3 years (range, 100 days to 7.5 years). Early morbidity outcomes (see statistical methods) were validated in the MCW cohort only. The institutional review boards at all the sites approved the study.

Statistical analysis was performed using SPSS version 23.0 (SPSS, Chicago, IL), R version 3.2 (Austria), and Stata version 14.0 (StataCorp LLC, Texas, USA). We compared NRM and relapse with cumulative incidence (Grey's test; relapse was the competing risk for NRM) and OS with Kaplan-Meier (log-rank test). Early morbidity outcomes were defined as orotracheal intubation, shock, or dialysis before day +100 and were compared with the chi-square test. Multivariate analysis for NRM was done with Fine-Gray regression and for OS with Cox regression.

For the model development, we included in the multivariate analysis all the factors that after univariate analysis for NRM had a P value of <0.2. Age was analyzed in 10-year cut-point fashion (15 to 24, 25 to 34, 35 to 44, 45 to 54, 55 to 64, and ≥65 years). In a forward-stepwise method, the variables that showed an independent association were finally included in the model. The other variables were excluded or grouped with the reference variable. We assigned a score of 1 if the hazard ratio in multivariate model was <3.5 and a score of 2 if it was ≥3.5. The discrimination power of the model on NRM was tested with Harrell's C-concordance index.

RESULTS

The main training cohort characteristics are listed in Table 1. Median transplant year was 2013. Median age was 54 years (range, 15 to 74 years); 59% were male, 52% had MM, 30% had non-Hodgkin lymphoma (NHL), and 18% had Hodgkin lymphoma. Fifty-three percent were in complete response, 44% had a partial response, and 3% had stable disease/progressive disease; 13% received 3 or more chemotherapy lines before ASCT (heavily pretreated). Regarding comorbidities, 58% were HCT-CI low risk (score 0), 29% intermediate risk (1 to 2), and 13% high risk (≥3). Early NRM (day +100) was 3.1%, long-term NRM (at 1 and 3 years) was 4.7% and 5.8%, and OS (at 1 and 5 years) was 89% and 65%.

Table 1
Training Cohort Characteristics (N = 2068)

Variable		Value
Age, median 54 yr (range, 15 to 75 years)	<55 yr	1067 (52)
	55-64 yr	685 (33)
	≥65 yr	316 (15)
Sex	Male	1211 (59)
	Female	857 (41)
Disease	Multiple myeloma	1069 (52)
	Hodgkin lymphoma	382 (18)
	Non-Hodgkin lymphoma	617 (30)
Pretransplant chemotherapy lines	1 line	955 (46)
	2 lines	838 (41)
	≥3 lines	275 (13)
Pretransplant status	Complete remission	972 (53)
	Partial remission	812 (44)
	Stable/progressive	43 (3)
	Missing data	241
HCT-CI score	Low risk (0)	1207 (58)
	Intermediate risk (1-2)	605 (29)
	High risk (≥3)	256 (13)
$CD34^+$ cell infusion	<3 × 10.6/kg	539 (27)
	≥3 × 10.6/kg	1427 (73)
	Missing data	102
Follow-up for survivors (median, range)		1.1 yr (100 d to 14 yr)
Transplant year, median (range)		2013 (2002-2017)

Values are presented as number (%) unless otherwise indicated.

Table 2
Multivariate Analysis for Nonrelapse Mortality

Variable		*P* Value	HR	95% Confidence Interval	
				Lower	Upper
Age, yr	<55	Reference			
	55-64	<.001	2.68	1.62	4.41
	≥65	<.001	4.53	2.64	7.77
Male sex		.01	1.68	1.09	2.58
Disease	Multiple myeloma	Reference			
	Hodgkin lymphoma	<.001	3.43	1.82	6.44
	Non/Hodgkin Lymphoma	<.001	3.69	2.38	5.72
HCT-CI high risk		.006	1.96	1.21	3.17

Table 3
GATMO Score Impact on Early Morbidity and Mortality

Event	Low Risk, %	Intermediate Risk, %	High Risk, %	Very High Risk, %	*P* Value (Univariate)
NRM	1.5	2.4	7.6	16.0	<.0001
Mechanical ventilation	2.9	4.9	10.6	22.7	<.0001
Vasopressors	1.9	5.1	9.1	18.7	<.0001
Dialysis	1.0	2.1	4.0	5.3	<.01

Based on univariate analysis, the variables included in the first multivariate analysis were age, sex, disease, HCT-CI, lines of chemotherapy, and disease status (see Supplementary Figures S1 to S5, Supplementary Table S1). In the analysis according to age, the 4 groups under 55 years showed similar outcomes (supplementary data) and therefore were grouped together for the multivariate analysis. The variables that showed an independent significant impact on NRM after adjusting for covariates and were included in the score were as follows: male patients (1 point), age (55 to 64 years = 1 point, ≥65 years = 2 points), HCT-CI ≥3 (1 point), and disease (Hodgkin lymphoma = 1 point, non-Hodgkin lymphoma = 2 points) (Table 2).

The hazard ratio for NRM increased proportionally with the score (expressed as hazard ratio, reference score 0): score 1 = 1.4, score 2 = 1.9, score 3 = 4.3, score 4 = 8.5, score 5 = 16.8, and score 6 = 30 (Supplementary Figure S7). Patients were grouped as low risk (LR) with a score of 0 to 1 (686 patients, 33%), intermediate risk (IR) with a score of 2 to 3 (1109 patients, 53%), high risk (HR) with a score of 4 (198 patients, 10%), and very high risk (VHR) with a score of ≥5 (75 patients, 4%).

The score was significantly associated with the 3 early morbidity endpoints (Table 3) as well as early NRM (day +100: 1.5% versus 2.4% versus 7.6% versus 17.6% for LR, IR, HR, and VHR, respectively; $P < .001$) (Table 3). Regarding long-term outcomes, the score discriminates 4 risk groups with statistically significant differences for NRM (at 1 and 3 years, 1.8% and 2.3% versus 3.8% and 4.9% versus 11.7% and 14.5% versus 25.0% and 27.4%, respectively, $P < .001$; hazard ratio [95% confidence interval]: LR, reference; IR, 2.16 [1.19 to 3.93]; HR, 6.43 [3.33 to 12.41]; VHR, 12.80 [6.29 to 26.04]) (Figure 1 and Table 4) and OS (at 1 and 5 years, 94% and 73% versus 89% and 64% versus 76% and 48% versus 65% and 52%, respectively, $P < .001$; hazard ratio [95% confidence interval]: LR, reference; IR, 1.43 [1.11 to 1.84]; HR, 2.54 [1.79 to 3.60]; VHR, 3.99 [2.60 to 6.13]) (Figure 2 and Table 4). No significant association was observed with relapse risk. Results from the concordance tests showed an appropriate discrimination capacity of the new score for NRM prediction, with a C-statistic of 0.68.

Validation Cohort

The important validation cohort characteristics are listed in Supplementary Table S2. Compared with the training cohort, transplants were performed later (median transplant year 2016). Median age was 60 years (range, 15 to 81 years); 60% were male, 61% had MM, 31% had non-Hodgkin lymphoma, and 8% had Hodgkin lymphoma. Regarding comorbidities, 16% were HCT-CI low risk (score 0), 44% intermediate risk (1 to 2), and 40% high risk (≥3). Early NRM (day +100) was 0.6%, long-term NRM (at 1 and 3 years) was 2.9% and 6.2%, and OS (at 1 and 5 years) was 92% and 66%.

The results were confirmed in the validation cohort. The score was significantly associated with the early morbidity

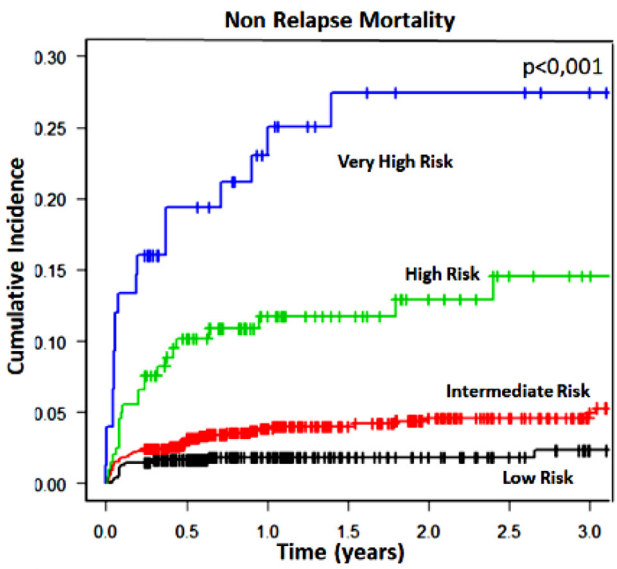

Figure 1. Cumulative incidence of NRM in the training cohort according to GATMO score. Probability of NRM at 1 and 3 years for low risk (black line) (1.8% and 2.3%) versus intermediate risk (red line) (3.8% and 4.9%) versus high risk (green line) (11.7% and 14.5%) versus very high risk (blue line) (25.0% and 27.4%) ($P < .0001$).

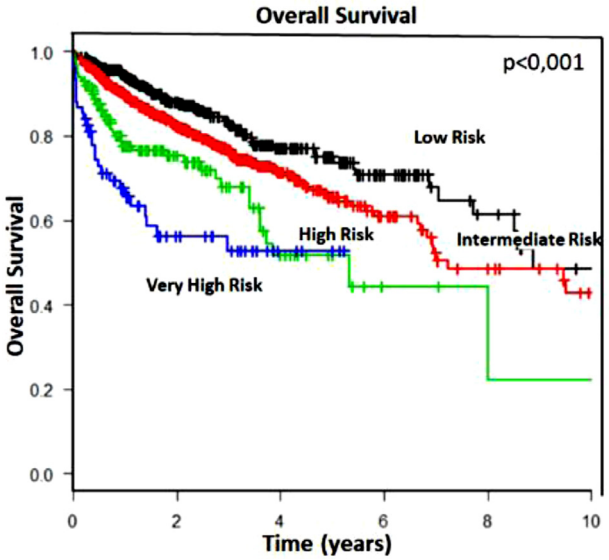

Figure 2. Overall survival in the training cohort according to GATMO score. Probability of OS at 1 and 5 years for low risk (black line) (94% and 73%) versus intermediate risk (red line) (89% and 75%) versus high risk (green line) (76% and 74%) versus very high risk (blue line) (65% and 52%) ($P < .001$).

outcomes (see Supplementary data Table S3), evaluated in the MCW cohort. Regarding long-term outcomes, the score was significantly associated with a higher probability for NRM (at 1 and 3 years, 0.9% and 3.1% versus 2.2% and 5.8% versus 4.7% and 8.2% versus 8.5% and 11.2%, respectively, $P < .001$; hazard ratio [95% confidence interval]: LR, reference; IR, 2.38 [1.08 to 5.23]; HR, 3.78 [1.64 to 8.69]; VHR, 5.74 [2.39 to 13.77]) (Supplementary Figure S7 and Table 4) and lower OS (at 1 and 5 years, 96% and 81% versus 93% and 68% versus 88% and 57% versus 81% and 60%, respectively, $P < .001$; hazard ratio [95% confidence interval]: LR, reference; IR, 1.56 [1.08 to 2.25]; HR, 2.98 [1.60 to 3.59]; VHR, 3.04 [0.93 to 4.79]) (Supplementary Figure S8 and Table 4).

DISCUSSION

We developed a novel score that combines comorbidities (HCT-CI) with 3 clinical factors (age, sex, and disease) in patients undergoing ASCT, which had a significant association with early morbidity events as well as long-term OS and NRM. All outcome risks increased proportionally with the score.

In the CIBMTR ASCT validation of HCT-CI score, high-risk patients showed a higher NRM rate compared with intermediate- and low-risk groups, with no clear difference between these 2 groups [9]. Moreover, although long-term OS was significantly lower in high-risk patients, the difference was less than 10% compared with low-risk patients. In our previous collaborative analysis evaluating HCT-CI in ASCT, we confirmed the increased risk in NRM for high-risk patients and no significant difference between intermediate- and low-risk patients [10].

Other clinical variables are associated with ASCT outcomes. Older age was associated with an increased risk of mortality after ASCT for MM [13] and NHL (diffuse large B cell) [14,15]. Moreover, in the allogeneic setting, age was incorporated with comorbidities into a composite score, and 1 point was added to the original HCT-CI score for patients older than 40 years [16]. In our analysis, groups younger than 55 years showed similar NRM, with an increase between 55 and 64 years and especially over 64 years.

Male sex, although with conflicting results in some studies, has been independently associated with worse outcomes following ASCT for MM and lymphomas [17-19]. The reasons for these results are not clear. Possible explanations could be other comorbidities not included in the HCT-CI score or a higher prevalence of risk factors such as hypertension or smoking or another unexplained biologic reason [20].

Although the impact of the diagnosis (MM, different type of lymphomas) was not directly compared, generally patients with NHL showed slightly higher NRM rates than Hodgkin lymphoma and clear significant increased risk compared with MM [9,11,17,21]. Other variables were tested, such as chemotherapy lines before transplant or disease status, but no clear association was found. In accordance with previous publications, these variables linked with the disease biology and had more impact on relapse- and disease-free survival [22].

Table 4
GATMO Score Impact on Nonrelapse Mortality and Overall Survival

		P value	Odds Ratio	95% Confidence Interval	
				Lower	Upper
Nonrelapse mortality					
Training cohort	Low risk	Reference			
	Intermediate risk	.011	2.16	1.19	3.93
	High risk	<.001	6.43	3.33	12.41
	Very high risk	<.001	12.80	6.29	26.04
Validation cohort	Low risk	Reference			
	Intermediate risk	.030	2.38	1.08	5.23
	High risk	.002	3.78	1.64	8.69
	Very high risk	<.001	5.74	2.39	13.77
Overall survival					
Training cohort	Low risk	Reference			
	Intermediate risk	.006	1.42	1.11	1.84
	High risk	<.001	2.54	1.79	3.60
	Very high risk	<.001	3.99	2.60	6.13
Validation cohort	Low risk	Reference			
	Intermediate risk	.018	1.56	1.08	2.25
	High risk	<.001	2.98	1.60	3.59
	Very high risk	<.001	3.04	1.93	4.79

There is no other score that combines comorbidities with clinical variables applicable to ASCT for different diseases in a large cohort analysis. There are few publications restricted to certain diseases such as NHL or Hodgkin lymphoma [7,22]. Both analyses evaluated the applicability of international prognostic indices developed for the diagnostic period of the particular disease and were associated with relapse- and disease-free survival. Graf et al. [23] described the first composite score combining HCT-CI with alcohol abuse and age in around 750 ASCT patients with lymphoma. The authors concluded that high HCT-CI score, age over 50 years, and alcohol abuse were independently associated with NRM and OS.

Early morbidity outcomes were defined differently than classic transplant toxicity scales [24]. We considered that requirement of mechanical ventilation, vasopressor therapy, or renal replacement therapy reflects more severe events with a clear impact on transplant-related morbidity, mortality, and health care costs [25-28]. Patients admitted to an intensive care unit after transplant present a higher mortality rate, especially when they require mechanical ventilation, and that can be as high as 50% [25]. Similarly, Trinkaus et al. [29] showed in a 1000-transplant patient cohort that 3% patients needed vasopressors, and this subgroup had a mortality rate higher than 70%.

Our analysis has several strengths. First, the sample size of both, the training and the validation cohort. Second, although the training cohort represents a wide period of time, the validation cohort corresponds to a modern period. Third, the variables included are used in everyday practice. Possible limitations are the median follow-up time, around 1 year, with long-term NRM as the main outcome. The retrospective nature of the analysis made it impossible to add other variables such as alcohol abuse or albumin described in previous studies [23,30].

In conclusion, this composite score that combines 3 simple clinical factors (age, sex, and disease) with HCT-CI can independently predict NRM and OS after ASCT by putting patients into categories with clinically meaningful and statistically significant differences among them. This tool can be used to define transplant eligibility criteria, adjust conditioning regimen doses, and define algorithms to select outpatient transplant candidates.

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