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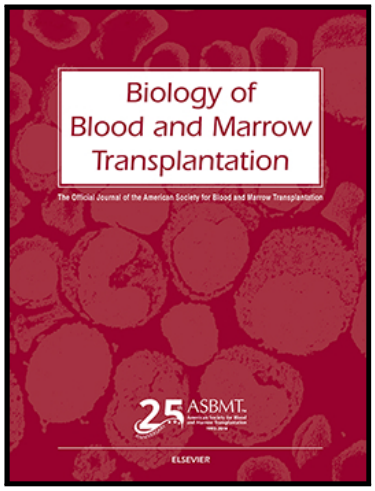

Predicting mortality after autologous transplant: Development of a novel risk score

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PII: S1083-8791(20)30405-5
DOI: https://doi.org/10.1016/j.bbmt.2020.06.028
Reference: YBBMT 56060

To appear in: *Biology of Blood and Marrow Transplantation*

Received date: 19 March 2020
Accepted date: 29 June 2020

Please cite this article as: Mariano Berro , Saurabh Chhabra , José Luis Piñana , Jorge Arbelbide , Maria M Rivas , Ana Lisa Basquiera , Adriana Vitriu , Alejandro Requejo , Vera Milovic , Sebastian Yantorno , Gonzalo Bentolila , Juan Jose Garcia , Martin Castro , Silvina Palmer , Martin Saslavsky , Patricio Duarte , Amalia Cerutti , Gustavo Jarchum , Matias Tisi Baña , Bicky Thapa , Carlos Solano , Anna Sureda , Montserrat Rovira , Bronwen E Shaw , Gustavo Kusminsky , Predicting mortality after autologous transplant: Development of a novel risk score, *Biology of Blood and Marrow Transplantation* (2020), doi: https://doi.org/10.1016/j.bbmt.2020.06.028

Highlights

- Variables other than comorbidities affect NRM after Autologous Transplant
- We developed, in a large cohort, a novel score combining HCT-CI, age, disease and sex.
- The new score predicts early morbidity events and long term NRM and OS.
- The score was validated in an independent large cohort.

Predicting mortality after autologous transplant: Development of a novel risk score

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Short Title: GATMO score

Abstract

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-SCT and validated for ASCT, however 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 non-relapse mortality (NRM), overall survival (OS) and early morbidity end-points (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 (10/2002-06/2017) for multiple myeloma or lymphoma. For the validation cohort, we analyzed 2168 ASCT performed in the Medical College of Wisconsin and Spanish stem cell transplant group (GETH) (01/2012-12/2018).
We first performed a multivariate analysis for NRM in order to select and assigned weight to the risk factors included in the score (male patients, age 55-64 and ≥65 years, HCT-CI ≥3, HL and NHL). The hazard ratio for NRM increased proportionally with the score. Patients were grouped as low risk (LR) with a score 0-1 (686, 33%), intermediate risk (IR) score 2-3 (1109, 53%), high risk (HR) score 4 (198, 10%) and very high risk (VHR) score ≥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 (day 100: 1.5% vs 2.4% vs 7.6% vs. 17.6%) as well as long term (1-3 years 1.8-2.3% vs. 3.8-4.9% vs. 11.7-14.5% vs. 25.0-27.4% respectively, p<0.0001) and OS (1-5 years 94-73% vs. 89-75% vs. 76-47% vs. 65-52% respectively, p<0.0001). 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 two large cohorts of more than 2000 autologous transplant patients. This tool can be useful for tailoring conditioning regimens or defining risk for transplant programs decision-making.
Keywords

Non-Relapse portality; Lymphoma; Multiple Myeloma; Comorbidities

Introduction

Autologous stem cell transplantation (ASCT) is the standard of care for many hematologic malignancies like multiple myeloma (MM) and lymphomas as a fist line or second line treatment[1,2]. Although the morbidity and mortality of ASCT is 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 and colleagues described the association of the international prognostic factors project for Hodgkin Lymphoma patients after ASCT[5], as Brockelmann et al developed a new score for this group of patients that predicts progression free survival and overall survival (OS)[6]. Similarly, the International Prognostic Index showed a significant impact on transplant outcomes for Non-Hodgkin Lymphoma patients[7].

The only score applicable to different diseases is the Hematopoietic Cell Transplant-Comorbidity Index (HCT-CI) score, originally described by Sorror *et al* for allogeneic HCT[8]. 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 Non-Relapse Mortality (NRM) compared to low and intermediate risk. To our knowledge there is no score that combines comorbidities with patient- and disease-related clinical factors that predicts NRM after ASCT for different hematological 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. Median follow up was 1.1 years (range, 100 days-14 years). Variables included in the analysis were age, gender, disease, disease status at the time of ASCT, lines of chemotherapy (defining as heavily pretreated with ≥3 lines), HCT-CI (according to the original description)[8] and CD34+ cell dose received during ASCT (defining as low dose $<3x10^6$/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-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 Inc, Chicago, IL, USA), R version 3.2 (http://r-project.org) and Stata version 14.0. We compared NRM and relapse

with cumulative incidence (CI) (Grey's test; relapse was the competing risk for NRM), OS with Kaplan-Meier (log-rank test). Early morbidity outcomes were defined as oro-tracheal intubation (OTI), shock or dialysis before day +100, and were compared with 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 <0.2. Age was analyzed in 10 years cut-point fashion (15-24 years, 25-34, 35-44, 45-54, 55-64 and ≥65). 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 the 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, 15-74); 59% were male, 52% had MM, 30% non-Hodgkin lymphoma (NHL) and 18% Hodgkin lymphoma. Fifty three percent were in complete response (CR), 44% in partial response (PR) and 3% stable disease (SD)/progressive disease (PD); 13% received three or more chemotherapy lines before ASCT (heavily pre-treated). Regarding comorbidities, 58% were HCT-CI low-risk (score 0), 29% intermediate-risk (1-2) 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%.

Based on univariate analysis, the variables included in the first multivariate analysis were age, gender, disease, HCT-CI, lines of chemotherapy and disease status (see supplementary data: figures S1-5, table S6). In the analysis according to age the four 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: male patients (1 point), age (55-64 years=1 point, ≥65 years=2 points), HCT-CI ≥3 (1 point), 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 (figure S7). Patients were grouped as low-risk (LR) with a score 0-1 (686 patients, 33%), intermediate-risk (IR) score 2-3 (1109 patients, 53%), high-risk (HR) score 4 (198 patients, 10%) and very high-risk (VHR) score ≥5 (75 patients, 4%).

The score was significantly associated with the three early morbidity endpoints (table 3) as well as early NRM (day +100: 1.5% vs. 2.4% vs. 7.6 vs. 17.6 for LR, IR, HR and VHR, respectively, p<0.001) (Table 3). Regarding long-term outcomes, the score discriminates four risk groups with statistically significant differences for NRM (at 1 and 3 years, 1.8% and 2.3% vs. 3.8% and 4.9% vs. 11.7% and 14.5% vs. 25.0% and 27.4%, respectively, p<0.001, Hazard Ratio, 95% CI ref. LR: IR 2.16, 1.19-3.93; HR 6.43, 3.33-12.41; VHR 12.80, 6.29-26.04) (Figure 1) (Table IV) and OS (at 1 and 5 years, 94% and 73% vs. 89% and 64% vs. 76% and 48% vs. 65% and 52%, respectively, p<0.001, Hazard Ratio, 95% CI ref. LR: IR 1.43, 1.11-1.84; HR 2.54, 1.79-3.60; VHR 3.99, 2.60-6.13) (Figure 2) (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-statistics of 0.68.

Validation cohort

The important validation cohort characteristics are listed in Table S8. Comparing to the training cohort, transplants were performed later (median transplant year 2016). Median age was 60 years (range, 15-81); 60% were male, 61% had MM, 31% non-Hodgkin lymphoma and

8% Hodgkin lymphoma. Regarding comorbidities, 16% were HCT-CI low-risk (score 0), 44% intermediate-risk (1-2) 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 outcomes (see supplementary data S9), 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% vs. 2.2% and 5.8% vs. 4.7% and 8.2% vs. 8.5% and 11.2%, respectively, p<0.001, Hazard Ratio, 95% CI ref. LR: IR 2.38, 1.08-5.23; HR 3.78, 1.64-8.69; VHR 5.74, 2.39-13.77) (Figure S10) (Table 4) and lower OS (at 1 and 5 years, 96% and 81% vs. 93% and 68% vs. 88% and 57% vs. 81% and 60%, respectively, p<0.001, Hazard Ratio, 95% CI ref. LR: IR 1.56, 1.08-2.25: HR 2.98, 1.60-3.59; VHR 3.04, 0.93-4.79) (Figure S11) (Table 4).

Discussion

We developed a novel score that combines comorbidities (HCT-CI) with three 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 higher NRM rate compared to intermediate- and low-risk groups, with no clear difference between these two groups[9]. Moreover, although long-term OS was significantly lower in high-risk patients, the difference was less than 10% compared to low-risk. 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[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 55-64 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 NHL patients showed slightly higher NRM rates than HL and clear significant increased risk compared to MM[9,11,17,21]. Other variables were tested like 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, have more impact on relapse and disease-free survival[22].

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 disease like NHL or HL[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. described the first composite score combining HCT-CI with alcohol abuse and age in around 750 ASCT patients with lymphoma[23]. 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 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 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* showed in a 1000 transplant patient cohort, 3% patients needed vasopressors and this subgroup had a mortality rate higher than 70%[29].

We consider our analysis has several strengths. First, the sample size of 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 every day practice. Possible limitations are the median follow up time, around one year, with long term NRM as main outcome. The retrospective nature of the analysis made impossible to add other variables like alcohol abuse or albumin described in previous studies[23,30].

In conclusion, this composite score that combines three 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 outpatients transplant candidates.

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Table 1. Training cohort characteristics (N 2068)		N (%)
Age, median 54 years (range 15-75 years)	<55 years	1067 (52)
	55-64 years	685 (33)
	≥65 years	316 (15)
Gender	Male	1211 (59)
	Female	857 (41)
Disease	Multiple Myeloma	1069 (52)
	Hodgkin Lymphoma	382 (18)
	Non-Hodgkin Lymphoma	617 (30)
Pre-trasplante chemotherapy lines	1 line	955 (46)
	2 lines	838 (41)
	≥3 lines	275 (13)
Pre-transplant 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)
CD 34+ cell infusion	<3x10.6/kg	539 (27)
	≥3x10.6/kg	1427 (73)
	Missing data	102
Follow up for survivors (median, range)		1.1 years (100 days-14y)
Transplant year, median (range)		2013 (2002-2017)

Table 2 Multivariate analysis for Non-Relapse Mortality					
		P value	HR	CI 95%	
				Lower	Upper
Age	<55 years	ref.			
	55-64 years	<0.001	2.68	1.62	4.41
	≥65 years	<0.001	4.53	2.64	7.77
Male gender		0.01	1.68	1.09	2.58
Desease	Multiple Myeloma	ref.			
	Hodgkin Lymphoma	<0.001	3.43	1.82	6.44
	Non/Hodgkin Lymphoma	<0.001	3.69	2.38	5.72
HCT-CI high risk		0.006	1.96	1.21	3.17

Table 3. GATMO score impact on early morbidity and mortality					
	Low Risk	Interm. Risk	High Risk	Very High Risk	P (univ)
Events (%)					
NRM	1.5	2.4	7.6	16.0	<0.0001
Mechanical ventilation	2.9	4.9	10.6	22.7	<0.0001
Vasopressors	1.9	5.1	9.1	18.7	<0.0001
Dialysis	1.0	2.1	4.0	5.3	<0.01
Abbreviations: Interm., intermediate					

Table 4. GATMO score impact on Nor Relapse Mortality and Overall Survival					
		P value	Odds Ratio	95% CI	
				Lower	Upper
Non Relapse Mortality					
Training Cohort	Low Risk	ref.			
	Intermediate Risk	0.011	2.16	1.19	3.93
	High Risk	<0.001	6.43	3.33	12.41
	Very High Risk	<0.001	12.80	6.29	26.04
Validation Cohort	Low Risk	ref.			
	Intermediate Risk	0.030	2.38	1.08	5.23
	High Risk	0.002	3.78	1.64	8.69
	Very High Risk	<0.001	5.74	2.39	13.77
Overall Survival					
Training Cohort	Low Risk	ref.			
	Intermediate Risk	0.006	1.42	1.11	1.84
	High Risk	<0.001	2.54	1.79	3.60
	Very High Risk	<0.001	3.99	2.60	6.13
Validation Cohort	Low Risk	ref.			
	Intermediate Risk	0.018	1.56	1.08	2.25
	High Risk	<0.001	2.98	1.60	3.59
	Very High Risk	<0.001	3.04	1.93	4.79
CI: confidence interval; ref. referencce					

Figure Legends

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%) vs. intermediate risk (red line) (3.8% and 4.9%) vs. high risk (green line) (11.7% and 14.5%) vs. very high risk (blue line) (25.0% and 27.4%) (p<0.0001).

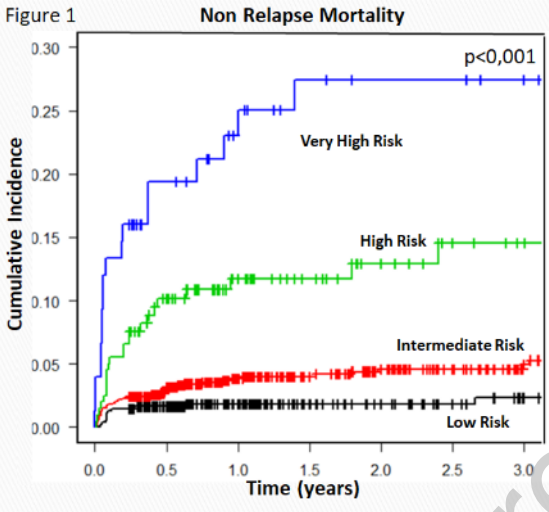
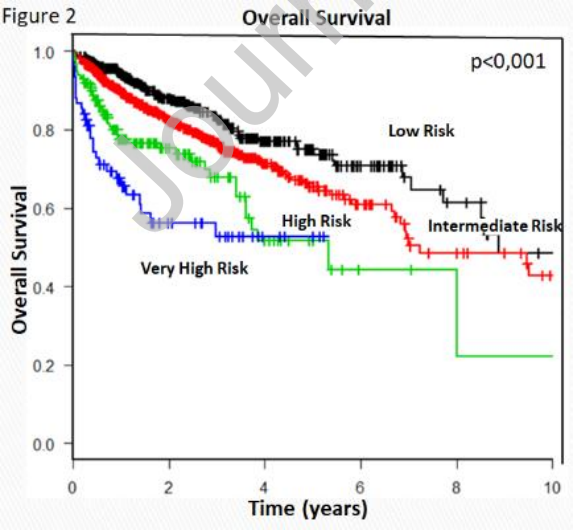


Figure 2: Overall survival in the training cohort according to GATMO score. Probability of OS at 1 and 5 years for low risk (black line) (94% and 73%) vs. intermediate risk (red line) (89% and 75%) vs. high risk (green line) (76% and 74%) vs. very high risk (blue line) (65% and 52%) (p<0.001).



Graphical abstract