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The EBMT Risk Score in the Presence of Graft Versus Host Disease in Allogeneic Stem Cell Transplantation in Adult Acute Myelogenous Leukemia: A Multistate Model for Competing Risks

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ABSTRACT

The aim of this study was to assess the predictive effect of the EBMT risk score on the outcomes of allogeneic stem cell transplantation in a relatively homogenous group of acute myelogenous leukemia (AML) patients regarding the occurrence of acute and chronic graft versus host disease (GVHD).

This historical cohort study included adult patients (≥ 15 years old) with AML (n=363) who received allogeneic peripheral blood stem cell transplantation from HLA-identical sibling donors in the first or higher complete remission following myeloablative conditioning regimens between 2004 and 2011.The patients recruited in this study were followed-up until January 2013. Patients with acute promyelocytic leukemia (APL) were excluded from the study. Early outcomes until day +100 and events after day +100 were regarded for acute and chronic GVHD, respectively. A multi state model for competing risks was applied.

We found that the EBMT risk score was a good predictor for overall survival (OS) and relapse incidence; however, it was not associated with transplant-related mortality (TRM). The EBMT risk score was not associated with acute and chronic GVHD. For early outcomes, the predictive effect of the EBMT risk score was not statistically significant in the presence of acute GVHD; however, in the presence of chronic GVHD, it was a significant predictor of relapse but not for TRM. It seems that the effect of EBMT risk score on OS and relapse incidence cannot be affected by GVHD. Although the results were insignificant, there was evidence that the EBMT risk score can predict early outcomes, while for late outcomes, it works well for relapse and OS but not for TRM.

KEYWORDS: Acute myeloid leukemia; Peripheral blood stem cell transplantation; Graft versus host disease; Survival analysis; Competing risks; Multistate model

INTRODUCTION

Allogeneic stem cell transplantation (SCT) from an HLA-identical sibling donor following a myeloablative conditioning regimen is a powerful treatment in reducing the risk of relapse in patients with acute myelogenous leukemia (AML), especially in first complete remission (CR).[1-4] However, the main part of this benefit is affected by complications due to allogeneic SCT. These complications which are related to toxicity,

infections and graft-versus-host disease (GVHD) may cause transplant-related mortality (TRM).[5, 6] Moreover, peripheral blood stem cells (PBSC), as a source of hematopoietic stem cells, has increasingly replaced bone marrow (BM) in allogeneic SCT for more than one decade[7-10] which causes faster neutrophil and platelet recovery.[3, 7-11] Lack of anemia, no anesthesia and hospitalization for donors and cost reduction are among the other advantages of PBSCT compared to BMT.[12] Nevertheless, because of the greater number of T-cells in PBSCT, there is concern that the allogeneic PBSCT results in higher rates and severity of GVHD.[7]

Decision whether to go forward with allogeneic SCT can be improved by assessing the potential risks before allogeneic SCT.[13-16] The European group of blood and marrow transplantation (EBMT) risk score for CML was introduced more than 10 years ago[17] which was then extended to other malignancies, especially acute leukemias.[15, 18] The EBMT risk score includes the recipient's age, donor/recipient gender combinations, disease stage at the time of transplantation, donor type, and the time interval from diagnosis to transplant. As Gratwohl[18] mentioned, pre-transplant factors can be influenced by transplant techniques, conditioning regimen, GVHD prevention and stem cell source.

The aim of the present study was to assess the predictive effect of the EBMT risk score on the results of AML patients who underwent allogeneic PBSCT from HLA-identical sibling donors with the same transplant technique, conditioning regimen and GVHD prophylaxis regarding the occurrence of acute and chronic GVHD.

PATIENTS AND METHODS

This historical cohort study was conducted on 377 patients who were transplanted at the Hematology-Oncology and Stem Cell Transplantation Research Center (Tehran, Iran), a tertiary referral center, from January 2004 to December 2011 and were followed up until January 2013. Patients' and donors' information including demographic characteristics and clinical data before and after transplant were collected from hospital archives, follow-up clinic records and database. Moreover, their disease and survival status were completed until Jan 2013. The eligibility criteria included AML adult patients (≥ 15 years old) other than acute promyelocytic leukemia in the first or higher CR who were transplanted from an HLA-identical sibling donor with PBSC. They were all administered a myeloablative conditioning regimen including oral BU 4 mg/kg/day for 4 days from day -6 to -3 and intravenous CY 60 mg/kg/day for 2 days from -3 to -2 before transplant. All patients received GVHD prophylaxis regimen containing intravenous cyclosporine 1.5 mg/kg/day from day -3 which increased to 3 mg/kg/day from day +8 plus a short course of methotrexate 10 mg/m^2 on day +1 and 6 mg/m^2 on days +3, +6, and +11. Cyclosporine (6 mg/kg/day) was continued orally as soon as oral tolerance until day +80. It was then followed by a tapering dose until 6 to 7 months after HSCT and discontinued in the absence of GVHD. The protocol of this study was approved by the Research Board of Tehran University of Medical Sciences.

The neutrophil recovery time was defined as the time to the first day of 3 consecutive post SCT days with a persistent ANC count ≥0.5 × 10^9/L, and the platelet recovery time was defined as the time to the first day of platelet count ≥20 × 10^9/L independent of platelet transfusions for at least the last 7 days.

Acute GVHD (aGVHD) was classified from grade 0 to 4 according to the Seattle criteria.[19] Chronic GVHD (cGVHD) in types of de novo, progressive, and interrupted was graded as limited or extensive[20] and was defined for patients who survived at least 100 days after transplant.

The EBMT risk score ranged from 0 for good to 7 for the worst with the following pre-transplant risk factors; recipient's age below 20, 20 to 40, and above 40 years scored 0, 1, and 2, respectively. Female donor to male recipient scored 1, and 0 was given to other gender combinations. Patients transplanted in CR1, CR2, and CR3+ scored 0 to 2, respectively. A time interval more than 1 year from diagnosis to transplant received 1 score; however, this scoring was not applicable for patients in CR1. Donor types other than an HLA-identical sibling scored 1. As only transplants from HLA-identical siblings were considered, the latter item was zero in this study. The EBMT risk score was categorized into three groups of zero or 1, 2, and 3 or greater scores

(3+) to ensure enough data in each group. In analysis of some states where no event was observed in group 3+, the EBMT risk score was categorized into two groups of 0 or 1, and scores 2 or higher (2+).

Overall survival (OS) was defined as the time from transplant to death from any cause. Leukemia-free survival (LFS) was defined for patients in remission as the time from transplant to hematologic relapse or death from any cause, whichever came first. Relapse incidence was defined for patients who were previously in disease remission as time from transplant to hematologic relapse. TRM was defined as death without relapse and was considered as a competing event for relapse. Patients who were alive without event at their last follow-up were considered as censored observations.

Events occurred in the first 100 days after transplant were defined as early outcomes and events after day +100 were considered as late outcomes.

Time to onset of aGVHD in the first 100 days after transplant was defined as a secondary outcome and either death or relapse before aGVHD was considered as its competing event. Likewise, time to onset of cGVHD was defined as another secondary endpoint after 100 days post-transplant and death or relapse before cGVHD was regarded as its competing event.

Statistical methods

Data were presented through median with range (minimum, maximum) and frequency with percentage for continuous and categorical variables, respectively. Survival curves were calculated using the Kaplan-Meier method and the 95% confidence interval (CI) for survival rates was calculated using the log-transformed method. The effect of covariates on OS and LFS was assessed by applying the Cox proportional hazards (PH) model and was reported through hazard ratio (HR) with 95% CI. Cumulative incidence functions were computed for relapse and TRM in a competing risks setting. The effect of covariates on relapse and TRM was evaluated using Fine & Gray competing risks regression, and sub-distribution hazard ratio (SHR) with 95% CI was reported.[21] This method was also applied to assess the association of the EBMT risk score and its components with acute and chronic GVHD.

Although the outcomes can be influenced by GVHD, it's incidence as a post-transplant risk factor is unknown at the time of transplant. Hence, a multistate approach was applied for competing risks[22] to consider the information of GVHD as an intermediate event in addition to relapse and TRM in the analyses. The four final states considered in this model were the combination of two levels of GVHD (presence/absence) and two causes (relapse/TRM). The scheme of this model is shown in Figure 1. This model was used to assess the effect of the EBMT risk score on early outcomes with aGVHD as an intermediate event and on late outcomes with cGVHD as an intermediate event, separately. The statistical packages "survival",[23] "cmprsk",[24] and "mstate"[25] in R software version 3.0.0[26] were used to perform the analyses.

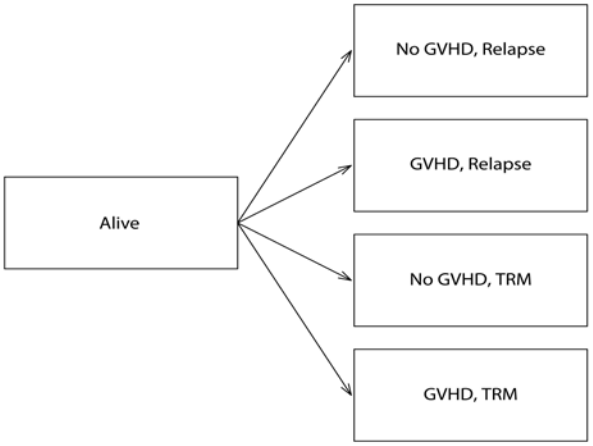

Figure 1. Multistate model for competing risks with four final states to take into account the information about the occurrence of GVHD

RESULTS

Three hundred and seventy-seven out of 426 patients who received allogeneic transplants between 2004 and 2011 met the study criteria, among whom, 14 (3.7%) were completely lost to follow-up after discharge and were excluded from the study. Out of the remaining 363 patients, 34 recipients (9.4%) had incomplete follow-up visits so that 11 had less than one year follow-up. However, the authors decided to include them in
the analysis. The median follow-up time of the survivors was 52.3 months (range: 2.6 to 108.5).

Demographic and baseline characteristics of the study patients are shown in Table 1.

Table 1. Demographic and baseline characteristics of the study patients

Characteristics	Number (%)
Recipient's gender	
Male	195 (53.7)
Female	168 (46.3)
Recipient's age at transplant (year)[1]	30 (15, 60)
Donor's gender	
Male	221 (60.9)
Female	142 (39.1)
Donor's age (year)[1]	29 (8, 63)
Donor/Recipient CMV serostatus	
+/+	335 (92.3)
+/-	11 (3.0)
-/+	13 (3.6)
-/-	4 (1.1)
Time interval between diagnosis and transplant (month)[1]	6.3 (1.3,114.6)
Status of disease at transplant	
CR1	293 (80.7)
CR2	61 (16.8)
CR3+	9 (2.5)
Karnofsky performance score	
>=90	299/325 (92.0)
<90	26/325 (8.0)

[1]Median (range); CMV, cytomegalovirus

Table 2 represents the characteristics of the outcomes and intermediate events. Ninety-nine percent of the recipients had neutrophil and 96% had platelet recovery. AGVHD occurred in about two-thirds of the recipients and nearly two-thirds of the survivors experienced cGVHD on day +100 after transplant (Table 2).

One-, two-, and five-year LFS were 72.8% (95% CI: 68.4-77.6%), 65.6% (95% CI: 60.8-70.8%) and 56.7% (95% CI: 51.3-62.6%), respectively (Figure 2.a). Additionally, one-, two-, and five-year OS were 76.4% (95% CI: 72.1-81.0%), 68.5% (95% CI: 63.8-73.6%), and 59% (95% CI: 53.6-64.9%, Figure 2.a), respectively. The most common causes of death were relapse, GVHD and infection.

Table 2. Characteristics of outcomes and intermediate events

Event characteristics	Frequency (%)
Neutropenic fever	281 (77.4)
Neutrophil recovery	
Yes	360 (99.2)
Never dropped	0 (0.0)
No	3 (0.8)
Time to neutrophil recovery (day)[1]	12 (7, 42)
Platelet recovery	
Yes	347 (95.6)
Never dropped	12 (3.3)
No	4 (1.1)
Time to platelet recovery (day)[1]	13 (7, 49)
Hospitalization days	27 (7, 98)
Acute GVHD	235 (64.7)
Acute GVHD grade	
I	63/235 (26.8)
II	64/235 (27.2)
III	79/235 (33.6)
IV	29/235 (12.3)
Time to acute GVHD (day)[1]	12 (7, 80)
Chronic GVHD	216/328 (65.9)
De novo	69/216 (31.9)
Progressive	73/216 (33.8)
Interrupted	74/216 (34.3)
Chronic GVHD extensity	
Limited	127/216 (58.8)
Extensive	89/216 (41.2)
Time to chronic GVHD (day)[1]	153 (101, 952)
Relapse	88 (24.2)
Survival status	
Alive	223 (61.4)
Dead	140 (38.6)
Main causes of death	
Relapse	80/140 (57.1)
GVHD	29/140 (20.7)
Infection	13/140 (9.3)
Other	18/140 (12.9)
Follow-up (month)[1]	51.5 (2.6, 108.5)

[1] Median (range)

The cumulative incidence of relapse at one, two, and five years after transplant was 16.8% (95% CI: 13.1-20.9%), 20.8% (95% CI: 16.7-25.3%), and 25.7% (95% CI: 21.0-30.7%), respectively while the cumulative incidence of TRM at one, two, and five years after transplant was 10.3% (95% CI: 7.4-13.7%), 13.6% (95% CI: 10.3-17.4%), and 17.6% (95% CI: 13.6-22.0%, Figure 2.a), respectively.

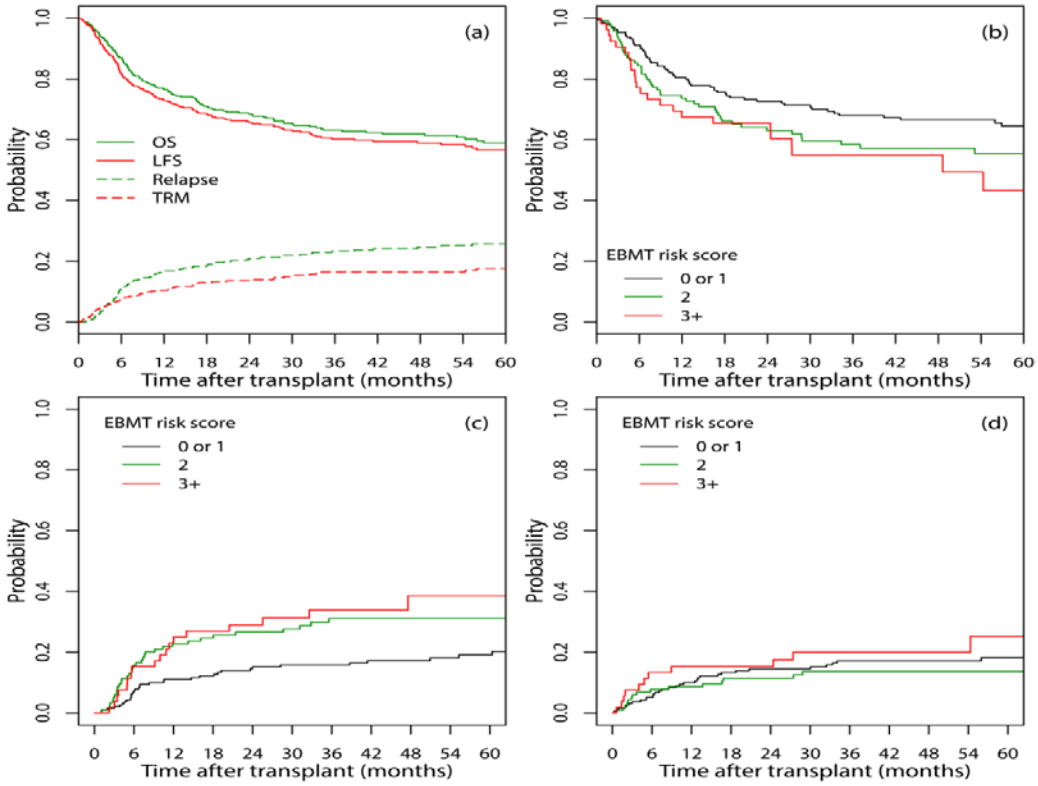

Figure 2. (a) OS, LFS, Relapse incidence, and TRM curves for all study patients; (b) OS, (c) cumulative incidence of relapse, and (d) cumulative incidence of TRM for different EBMT risk scores

Characteristics of the EBMT risk score and its components are shown in Table 3. The correlation between the disease status at transplant and the time interval from diagnosis to transplant was 34.6%. This correlation increased to 60.2% between the disease stage and interval score. The status of the disease, and time interval longer than one year were the dominant pre-transplant risk factors of the EBMT risk score on outcomes.

The univariate effect of covariates on OS, TRM and relapse are shown in Table 4. The EBMT risk score had a significant effect on OS (p=0.045) and relapse incidence (p=0.003). The higher the EBMT risk score, the higher the hazard of death (Table 4, Figure 2.b) and the incidence of relapse (Table 4, Figure 2.c). The effect of the EBMT risk score on TRM was not statistically significant (p=0.51, Table 4, Figure 2.d).

Table 3. Characteristics of the EBMT risk score and its components

Variables	score	Frequency (%)
Age at transplant		
<20	0	45 (12.4)
20 - 40	1	237 (65.3)
>40	2	81 (22.3)
Gender combination		
Other	0	296 (81.5)
Female donor to male recipient	1	67 (18.5)
Disease status at transplant		
CR1	0	293 (80.7)
CR2	1	61 (16.8)
CR3+	2	9 (2.5)
Time from diagnosis to transplant		
<1 year	0	335 (92.3)
>1 year	1	28 (7.7)
EBMT risk score		
0		22 (6.1)
1		171 (47.1)
2		117 (32.2)
3		45 (12.4)
4		7 (1.9)
5		1 (0.3)

Table 4. The univariate effect of covariates on OS, Relapse, and TRM

Variables	Overall Survival		Relapse		TRM	
	HR (95% CI)	p	SHR (95% CI)	p	SHR (95% CI)	p
Gender (Male)	1.20 (0.85, 1.67)	0.298	1.22 (0.80, 1.87)	0.346	1.30 (0.78, 2.18)	0.311
Age at transplant	1.00 (0.99, 1.02)	0.877	1.00 (0.98, 1.02)	0.772	1.00 (0.98, 1.03)	0.807
Donor's gender (Male)	1.13 (0.80, 1.59)	0.497	1.61 (1.02, 2.55)	0.039	0.74 (0.45, 1.23)	0.250
Donor's age	1.00 (0.98, 1.01)	0.573	0.99 (0.97, 1.01)	0.241	1.01 (0.99, 1.03)	0.475
Time from diagnosis to transplant	1.01 (1.00, 1.03)	0.166	1.01 (1.00, 1.03)	0.176	1.01 (0.98, 1.03)	0.645
Recipient's CMV status (positive)	0.85 (0.38, 1.93)	0.700	0.63 (0.26, 1.52)	0.300	2.51 (0.34, 18.72)	0.370
Donor's CMV status (positive)	1.25 (0.51, 3.05)	0.630	0.95 (0.34, 2.65)	0.918	2.93 (0.41, 21.23)	0.286
Karnofsky performance score (<90)	1.07 (0.61, 1.86)	0.822	1.40 (0.73, 2.68)	0.316	0.82 (0.33, 2.00)	0.656
Hospitalization days	1.01 (0.99, 1.02)	0.509	1.00 (0.98, 1.02)	0.764	1.02 (1.00, 1.04)	0.027
Neutropenic fever	1.13 (0.74, 1.72)	0.571	1.04 (0.62, 1.74)	0.877	1.22 (0.64, 2.33)	0.553
Age score						
<20	1.00	0.957	1.00	0.833	1.00	0.589
20-40	1.00 (0.60, 1.66)	0.995	0.95 (0.50, 1.83)	0.888	1.01 (0.48, 2.15)	0.969
>40	0.94 (0.52, 1.70)	0.841	1.11 (0.53, 2.33)	0.774	0.71 (0.28, 1.79)	0.467
Gender combination score F->M	1.12 (0.73, 1.70)	0.606	0.66 (0.36, 1.21)	0.183	1.91 (1.09, 3.35)	0.024
Disease stage						
CR1	1.00	<0.001	1.00	<0.001	1.00	0.055
CR2	2.27 (1.54, 3.33)	<0.001	3.79 (2.41, 5.95)	<0.001	0.76 (0.37, 1.59)	0.472
CR3+	3.51 (1.54, 8.04)	0.003	2.61 (1.06, 6.46)	0.037	3.71 (1.17, 11.82)	0.026
Interval score >1 year	1.82 (1.07, 3.12)	0.028	2.22 (1.20, 4.10)	0.011	1.11 (0.43, 2.85)	0.823
EBMT risk score						
0 or 1	1.00	0.045	1.00	0.003	1.00	0.510
2	1.40 (0.97, 2.02)	0.076	1.94 (1.21, 3.11)	0.006	0.81 (0.45, 1.47)	0.490
3+	1.70 (1.07, 2.70)	0.024	2.31 (1.33, 4.00)	0.003	1.29 (0.65, 2.56)	0.480

SHR, sub-distribution hazard ratio; CMV, Cytomegalovirus

In the first 100 days after transplant, 13 (3.6%) patients experienced relapse, 18 (5.0%) died due to causes other than relapse, and 4 (1.1%) recipients were lost to follow-up from day 79 to 99. The EBMT risk score showed no statistically significant effect on aGVHD incidence (p=0.933).

Table 5 represents that the association between the EBMT risk score and its components with the incidence of aGVHD was not statistically significant.

By using a multistate model, it was resulted that the effect of the EBMT risk scores 2 and 3+ versus 0 or 1 in the absence of aGVHD on early relapse were 2.59 (95% CI: 0.43-15.51, p=0.297) and 3.84 (95% CI: 0.54-27.25, p=0.179), respectively (Figure 3.a). However, when aGVHD was present, the hazard of early relapse in patients with the EBMT risk score 2+ was 2.31 (95% CI: 0.42-12.63, p=0.333) times more than score 0 or 1 (Figure 3.b). Likewise, for patients with scores 2 and 3+, the hazard of TRM in the absence of aGVHD was 0.84 (95% CI: 0.08-9.29, p=0.889) and 1.84 (95% CI: 0.17-20.33, p=0.618) times the hazard of patients with score 0 or 1 (Figure 3.c). These measures were 2.00 (95% CI: 0.61-6.57, p=0.251) and 2.25 (95% CI: 0.54-9.43, p=0.266) in the presence of aGVHD, respectively (Figure 3.d).

Table 5. The effects of the EBMT risk score and its components on acute and chronic GVHD

Variables	acute GVHD		chronic GVHD	
	SHR (95% CI)	p	SHR (95% CI)	p
Age score				
<20	1.00	0.570	1.00	0.778
20-40	1.12 (0.74, 1.69)	0.598	1.00 (0.69, 1.45)	0.989
>40	0.96 (0.60, 1.53)	0.859	1.11 (0.74, 1.68)	0.614
Gender combination score F->M	1.24 (0.91, 1.70)	0.174	1.12 (0.82, 1.53)	0.473
Disease stage				
CR1	1.00	0.649	1.00	0.054
CR2	0.89 (0.63, 1.26)	0.516	0.72 (0.48, 1.07)	0.106
CR3+	1.23 (0.64, 2.36)	0.544	1.94 (0.90, 4.18)	0.090
Interval score >1 year	0.91 (0.56, 1.48)	0.702	0.50 (0.26, 0.96)	0.038
EBMT risk score				
0 or 1	1.00	0.933	1.00	0.904
2	0.96 (0.73, 1.26)	0.760	0.94 (0.70, 1.25)	0.660
3+	1.02 (0.71, 1.46)	0.910	0.96 (0.66, 1.41)	0.847

SHR, sub-distribution hazard ratio

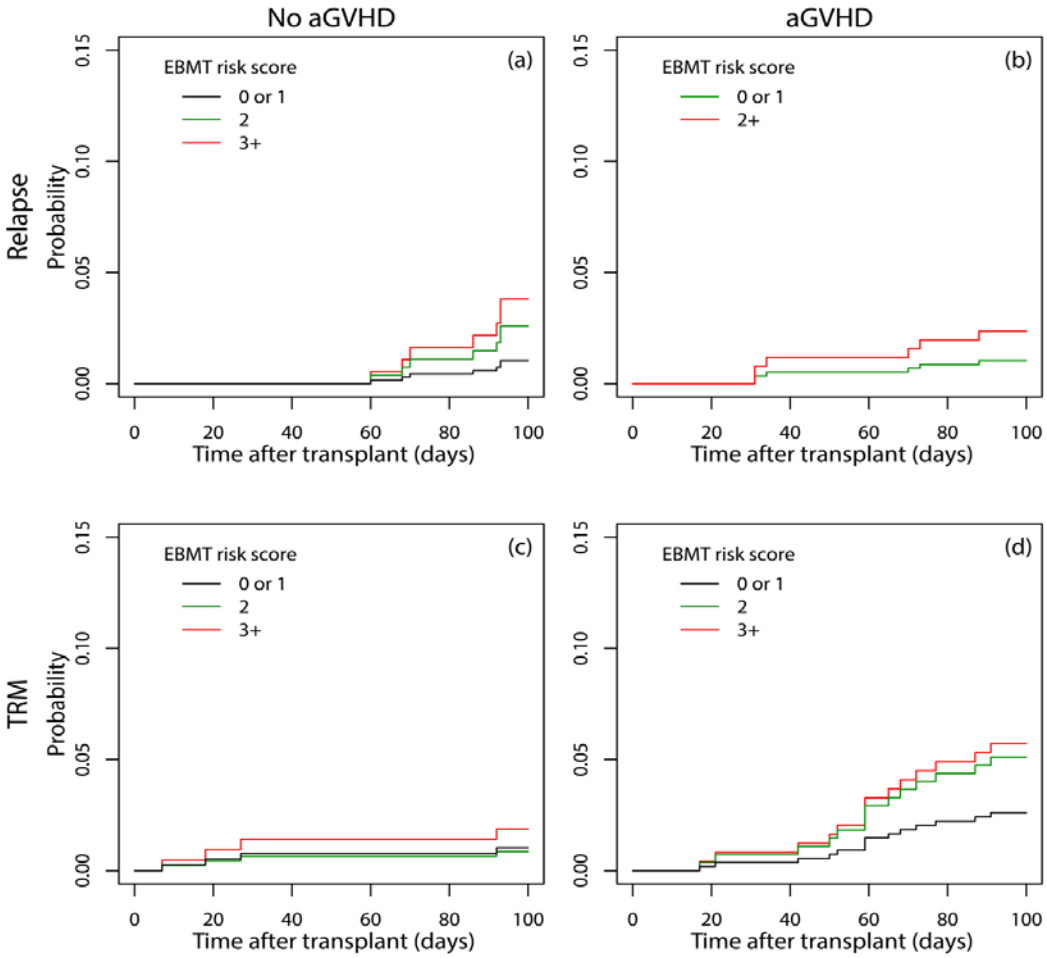

Figure 3. Cumulative incidence of early relapse (a, b) and TRM (c, d) considering the occurrence of aGVHD in the first 100 days after transplant in different EBMT risk scores using a multistate approach for competing risks

Among 328 survivors and event-free recipients, 75 (22.9%) relapsed and 42 (12.8%) died due to TRM on day +100 after transplant. Among 112 recipients who did not experience cGVHD, 65 (58%) had a history of aGVHD (21 grade I, 22 grade II, 17 grade III, and 5 grade IV). AGVHD [grade I =18 (24.7%),

grade II= 11 (15.1%), grade III=32 (43.8%), grade IV=12 (16.4%)] was observed in 73 patients with progressive cGVHD and 74 recipients [grade I= 22 (29.7%), grade II=25 (33.8%), grade III=20 (27.0%), grade IV=7 (9.5%)] with interrupted cGVHD.

The predictive effect of the EBMT risk score on the incidence of cGVHD was not statistically significant (p=0.904). However, the interval score and status of disease, as the two components of the EBMT risk score, had statistically significant protective (p=0.038) and borderline (p=0.054) effect on the incidence of cGVHD (Table 5). All 269 patients who achieved CR1 were transplanted less than one year, while 25 out of 59 (42.4%) patients who were in CR2+ were transplanted after one year of diagnosis.

When the multistate model was applied, the hazard of late relapse in the absence of cGVHD in patients with scores 2 and 3+ were 2.20 (95% CI: 1.12-4.32, p=0.022) and 2.62 (95% CI: 1.15-5.96, p=0.021) times the hazard of patients with score 0 or 1, respectively (Figure 4.a); Similarly, when cGVHD was present, these measures were 1.54 (95% CI: 0.68-3.48, p=0.301) and 3.21 (95% CI: 1.33-7.76, p=0.010, Figure 4.b), respectively. The hazard of late TRM in patients with score 2+ in the absence of cGVHD was half (95% CI: 0.10-2.52, p=0.403) the hazard in patients with score 0 or 1 (Figure 4.c). When cGVHD was present, the hazard of late TRM in patients with the EBMT risk scores 2 and 3+ to those with scores 0 or 1 were 0.60 (95% CI: 0.25-1.43, p=0.251) and 1.37 (95% CI: 0.57-3.27, p=0.480), respectively (Figure 4.d).

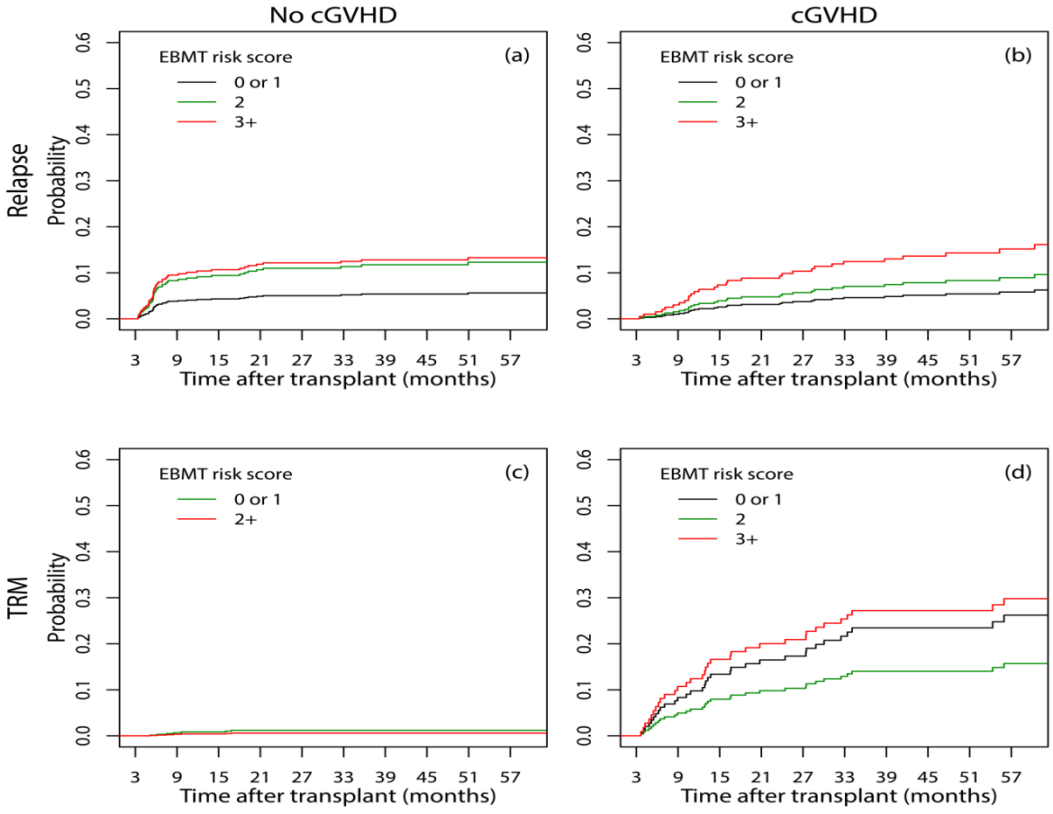

Figure 4. Cumulative incidence of relapse (a, b) and TRM (c, d) considering the occurrence of cGVHD for patients at risk on the day 100 post-transplant in different EBMT risk scores using a multistate approach for competing risks

DISCUSSION

The long-term estimates of LFS, OS, relapse incidence, and TRM of the whole study patients were very close to the 5-year report released by Keating et al from CIBMTR[1] on AML patients (n=425) who received allogeneic PBSCT from HLA-identical sibling donors (54%, 59%, 26% and 20%, respectively).

Our results revealed that the main dominant pre-transplant risk factors of the EBMT risk score were the disease status and time interval between diagnosis and transplant which were moderately correlated. In general, we found that the EBMT risk score was a good predictor for OS and relapse incidence; however, it was not associated with TRM. Similarly, Hemmati et al.,[27] reported a strong correlation between the time interval from diagnosis to transplant and disease status at transplant and found that their proposed modified EBMT risk score was highly predictive for OS and relapse.

Risk factors such as CMV serostatus and Karnofsky score did not have significant effect on outcomes in our study. This may be because of the high prevalence of CMV seropositive status among recipients and donors, and high frequency of Karnofsky performance score more than 90 in our data.

Our findings showed that the EBMT risk score did not have any association with the incidence of acute and chronic GVHD, but the time interval between diagnosis and transplant had significant protective effect on cGVHD. Since all patients who were transplanted more than one year after diagnosis were in CR2+, the protective effect of time interval on cGHVD might be due to higher relapse and mortality in patients in CR2+ which precluded the chance of experiencing cGVHD.

In a multistate setting, the results demonstrated that in the presence or absence of aGVHD in the first 100 days, the association between the EBMT risk score and relapse incidence was not statistically significant; however, there was evidence that the higher the EBMT risk score, the higher the hazard of relapse incidence. This is also true for TRM with weaker evidence in the presence of aGVHD. After the day +100, in the presence or absence of cGVHD, the predictive effect of the EBMT risk score for relapse incidence was found to be statistically significant. However, this effect is not only statistically insignificant but also there exists no trend for the association of the EBMT risk score and TRM. Therefore, it seems that the effect of EBMT risk score on OS and relapse incidence cannot be affected by GVHD.

One of the advantages of this study was to better evaluation of the predictive effect of the EBMT risk score on post-transplant events in relatively homogenized patients by considering the influential factors such as conditioning regimen, source of stem cell and donor type as Gratwohl[18] mentioned. This study suffered a small sample size since it was a single-center study and we did not have access to cytogenetic risk reports at diagnosis. Insufficient sample size resulted in a small number of events in the first 100 days after transplant which led to statistically insignificant results. Moreover, inaccessibility to cytogenetic risk reports at diagnosis, identified as the strongest predictor of relapse[28, 29] , made it impossible to distinguish high and intermediate risk in AML patients.

Gratwohl et al.,[15] extended the EBMT risk score based on almost 50,000 allogeneic HSCT EBMT mega data from data registry, which is more heterogeneous than our single-center data. Therefore, it seems that the heterogeneous nature of the information helps the EBMT risk score to distinguish the patients much better in international data registries, as compared to homogeneous single-center data.

Despite these facts, although the EBMT risk score "explains at best 63% of the outcome" as Gratwohl et al mentioned, "the overall risk score retains its primary value as a rapid and instant tool for basic assessment".[18] Eventually, according to our data, it seems that the EBMT risk score predicts early TRM better than late TRM and works well for predicting relapse. However, the results of a single center study cannot be generalized with certainty.

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CONFLICT OF INTEREST

All authors declare no conflict of interest.

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