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The Effect of GVHD on Long-term Outcomes after Peripheral Blood Allogeneic Stem Cell Transplantation from an HLA-identical Sibling in Adult Acute Lymphocytic Leukemia: A Landmark Analysis Approach in Competing Risks

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ABSTRACT

Allogeneic Hematopoietic stem cell transplantation (HSCT) is the most effective therapy to prevent relapse in acute lymphocytic leukemia (ALL). This benefit is affected by non-relapse mortality (NRM) due to complications such as graft versus host disease (GVHD). A new approach in analyzing time-dependent covariates in competing risks is landmark analysis. So, the aim of this study is to evaluate the effect of acute and chronic GVHD on long-term outcomes, relapse and NRM, after allogeneic HSCT in adult ALL using landmark analysis.

This study was conducted on 252 ALL patients who were allogeneic transplanted from an HLA-identical sibling with peripheral blood (PB) as the source of stem cell from 2004 to 2012 and were followed-up until 2013. In the first 100 days after transplant, a landmark analysis on days +10, +11, +12, +17, +24, and +31 was applied to assess the effect of acute GVHD on early relapse and NRM. Similarly, for patients alive and event-free at day +100 after transplant, a landmark analysis at time points day +101, months +4, +5, +6, +9, and +12 was applied to evaluate the effect of chronic GVHD on late relapse and NRM.

Five-year LFS and OS were 35.0% (95% CI: 29.1, 42.2%) and 37.5% (95% CI: 31.3, 45.0%), respectively. Five-year cumulative incidence of relapse was 44.5% (95% CI: 37.9, 51.0%) while this was 20.4% (95% CI: 15.4, 26.0%) for NRM. The landmark analysis in the first 100 days after transplant showed that the grade III/IV of aGVHD has a lower risk of relapse but higher risk of NRM after adjustment for the EBMT risk score. For patients alive at day +100, cGVHD had no significant effect on relapse. Limited cGVHD had lower risk of NRM and after 6 month post-transplant the risk of NRM decreased and there were not important difference between the groups of cGVHD.

Using advanced models enables us to estimate the effects more precisely and ultimately make inference more accurately.

KEYWORDS: Acute Lymphocytic Leukemia; Peripheral Blood Stem Cell Transplantation; Graft versus Host Disease; Survival Analysis; Competing Risks; Landmark Analysis

INTRODUCTION

Acute lymphocytic leukemia (ALL) in adults is still a challenging disease. Although achieving complete remission (CR) is about 80 to 90 percent in ALL patients,[1] 30 to 80% experience relapse which results the probability of long-term survival to reduce to 20-60 percent. Allogeneic hematopoietic stem cell transplantation (HSCT) is the most effective therapy to prevent relapse in ALL, but this benefit is counteracted by high non-relapse mortality (NRM) due to occurrence of complications such as graft versus host disease (GVHD).[2-4] Since GVHD, depending on its severity, reduces the risk of relapse, its presence can improve outcomes after transplant.[5] Despite the fact that acute GVHD (aGVHD) plays an important role in higher NRM and thus it does not improve progression-free survival,[6,7] the occurrence of chronic GVHD (cGVHD) can improve outcomes in comparison with patients without cGVHD.[7, 8]

It is a common mistake that many consider GVHD as a time-fixed covariate in statistical analyses; however the occurrence of GVHD and its time is not known.[9] Therefore, this should be considered as a time-dependent covariate in survival models. One idea to face with such situations is landmark analysis which was first proposed by Anderson.[10] This idea was developed and introduced as a new approach of analysis by Van Houwelingen for dynamic prediction.[11] Moreover, Cortese and Anderson[12] and also Nicolaie et al[13] applied landmark analysis for dynamic prediction in competing risks setting.

Hence, the aim of the present study was to report of the long-term results of peripheral blood (PB) allogeneic HSCT for ALL patients from an HLA-identical sibling in addition to evaluating the impact of acute and chronic GVHD on outcomes using landmark analysis.

PATIENTS AND METHODS

This study included 267 ALL adult patients (≥ 15 year-old) who were allogeneic transplanted in Hematology, Oncology and Stem Cell transplantation Research Center (HORCSCT), Tehran, Iran[14, 15] from 2004 to 2012, and were followed up until 2013. To have more similar patients at the time of transplant, those patients were eligible for this study who had an HLA-identical sibling as donor, PB as the source of stem cell, and transplanted in first or higher complete remission (CR1+). All recipients have been administered myeloablative conditioning regimen including oral BU, 4 mg/kg/day from day -6 to -3 and CY, 60 mg/kg/day from day -3 to -2 before transplant. The protocol of this study was approved by the research board of Tehran University of Medical Sciences.

Patients' demographic and clinical information were gathered from database as well as hospital and follow-up clinic records and the EBMT risk score[16, 17] was computed through the collected data. Neutrophil and platelet recovery times, were determined as the first day of persistent ANC count ≥0.5 × 10/L for three consecutive days, and the first day of platelet count ≥20 × 10/L with at least 7 days independent of platelet transfusion, respectively. Acute GVHD was graded from 0 to 4 in accordance with the Seattle criteria.[18] Chronic GVHD was specified for patients who were alive at least 100 days post HSCT and graded as limited or extensive in types of de novo, progressive, and interrupted.[19]

Overall survival (OS) was defined as time to death from any cause and leukemia-free survival (LFS) was considered as time to hematological relapse or death without relapse, whichever occurred first. Relapse incidence was defined as time to hematological relapse given that the patient was previously in remission. NRM was defined as death without relapse, and was considered as a competing event for relapse incidence. Patients who were alive without event at their last follow-up were regarded as censored observations.

Data were described through median with range (minimum, maximum) and frequency with percentage for continuous and categorical variables, respectively. Survival curves and their 95% confidence interval (CI) were calculated using the Kaplan-Meier and log-transformed methods, respectively. Cox proportional hazards (PH) model was used to assess the effect of covariates on OS and LFS and the effect estimates were reported through hazard ratio (HR) with 95% CI.

In competing risks setting, the cumulative incidence functions were computed for the competing events (relapse and NRM) and Fine & Gray competing risks regression was applied to evaluate the effect of covariates and sub-distribution hazard ratios (SHR) with 95% CI were reported.[20] To assess the impact of acute and chronic GVHD on relapse and NRM, we used the landmark analysis approach.[11, 12] For aGVHD, early outcomes until day +100 were regarded and days +10, +11, +12, +17, +24, and +31 were set as landmark time points. For cGVHD, late outcomes after day +100 were considered for patients alive at least 100 days after HSCT. The landmark time points were then set to day +101, months +4, +5, +6, +9, and +12. At each landmark time, GVHD was regarded as a time fixed covariate and a Cox model for the cause-specific hazards (separately for relapse and NRM) was fitted.

Packages "dynpred",[21] "survival",[22] and "cmprsk"[23] in R software version 3.0.0 [24] were used to prepare landmark data sets and conducting survival and competing risks analyses, respectively.

RESULTS

Out of 403 patients who were allogeneic transplanted from 2004 to 2012, 267 were eligible to enter this study. Among 267 patients, 15 (5.6%) were completely lost to follow-up after discharge and were excluded. So, 252 recipients entered in the analyses of whom 15 (6.0%) had incomplete follow-up visits and did not response at last contact and three of these patients had less than one year follow-up. The median follow-up time was 51 months (range 1.2 to 101.6). Baseline characteristics of the donors and recipients are depicted in Table 1. Almost 96% of the donors and recipients were cytomegalovirus (CMV) seropositive. Table 2 represents characteristics of intermediate events and outcomes. About 70% of the patients experienced aGVHD so that half were in grades III and IV. Also, about 60% of who were alive at day +100 experienced cGVHD in a way that near one third progressed from aGVHD.

Table 1. Patients and Donors Characteristics

	Frequency (%)
Recipient's Gender	
Female	85 (33.7)
Male	167 (66.3)
Recipient's age (year)[1]	22 (15, 53)
Donor's gender	
Female	106 (42.1)
Male	146 (57.9)
Donor's age (year)[1]	24 (7, 60)
Donor to Recipient gender combination	
M -> M	108 (42.9)
M -> F	38 (15.1)
F -> M	59 (23.4)
F -> F	47 (18.7)
Recipient's CMV serostatus	
Negative	10 (4)
Positive	242 (96)
Donor's CMV serostatus	
Negative	12 (4.8)
Positive	240 (95.2)
Donor / Recipient CMV serostatus	
- / -	3 (1.2)
- / +	9 (3.6)
+ / -	7 (2.8)
+ / +	233 (92.5)
Time from Diagnosis to Transplant (month)[1]	7.6 (1.1, 165.8)
Status of disease at transplant	
CR1	190 (75.4)
CR2	53 (21)
CR3+	9 (3.6)
Karnofsky performance score	
≥90	204 / 226 (90.3)
<90	22 / 226 (9.7)
EBMT risk score	
0	39 (15.5)
1	113 (44.8)
2	60 (23.8)
3	30 (11.9)
4	9 (3.6)
5	1 (0.4)

[1] Median (Range); CMV, Cytomegalovirus;

Table 2. Intermediate Events and Outcomes Characteristics

	Frequency (%)
Neutropenic fevere	187 (74.2)
Neutrophil recovery	
No	1 (0.4)
Never dropped	1 (0.4)
Yes	250 (99.2)
Time to Neutrophil recovery (day)[1]	12 (6, 40)
Platelet recovery	
No	4 (1.6)
Never dropped	3 (1.2)
Yes	245 (97.2)
Time to Platelet recovery (day)[1]	14 (7, 42)
Hospital length of stay (day)[1]	27 (15, 166)
aGVHD	
No	77 (30.6)
Yes	175 (69.4)
aGVHD grade	
I	35 (20)
II	51 (29.1)
III	69 (39.5)
IV	20 (11.4)
Time to aGVHD (day)[1]	11 (6, 80)
cGVHD	
No	84 / 218 (38.5)
Yes	134 / 218 (61.5)
cGVHD type	
De novo	39 (30)
Progressive	39 (30)
Interrupted	56 (40)
cGVHD Extensity	
Limited	93 (69.4)
Extensive	41 (30.6)
Time to cGVHD (day)[1]	158 (101, 939)
Relapse	
No	145 (57.5)
Yes	107 (42.5)
Survival status	
Alive	106 (42.1)
Dead	146 (57.9)
Most common causes of death	
Relapse	99 / 146 (67.8)
GVHD	29 / 146 (19.9)
Infection	11 / 146 (7.5)

[1]Median (Range); aGVHD, acute graft versus host disease; cGVHD, chronic graft versus host disease;

The probabilities of outcomes after transplant at one-, three-, and five-year after transplant are shown in Table 3. The univariate effect of variables on OS, relapse, and NRM are presented in Table 4. As it was shown, hospital length of stay affects all three outcomes and higher in hospital stay increases the risk of death and thus NRM. In addition, disease status at transplant affects OS and relapse incidence. As seen in Table 4, the hazard of death in patients transplanted in CR2 versus those in CR1 is 1.66 (95% CI: 1.14, 2.41; p=0.008); and this measure for patients transplanted in CR3+ versus CR1 is 3.31 (95% CI: 1.60, 6.84; p=0.001). Also, the hazard of relapse in CR3+ patients relative to CR1 was 4.00 (95% CI: 1.47, 10.87; p=0.007). The EBMT risk score has a borderline effect on OS.

In the first 100 days after transplant, 25 (9.9%) experienced relapse, 25 (9.9%) died due to causes other than relapse, and 1 patient was lost to follow-up at day +35. Among 175 (69.4%) who experienced aGVHD, 86 (49.1%) patients were in grade I or II, and 89 (50.9%) were in grade III or IV. Table 5 shows the estimated effect of aGVHD on outcomes at different landmark points adjusted for the EBMT risk score. Figure 1 represents the predicted cumulative incidences at each landmark point for a patient with EBMT risk score 2 (Graphs for other EBMT risk scores were not shown). As it was displayed in Figure 1, aGVHD grade III or IV have a protective effect on early relapse on all landmark times relative to patients without aGVHD. Figure 2 shows the predicted cumulative incidences for NRM for a patient with EBMT risk score 2; and the estimated effects are shown in Table 5. The hazard of NRM in patients with aGVHD grade III or IV is higher than patients without aGVHD.

Table 3. Probability of Transplant Outcomes with 95% Confidence Intervals

	1-year	3-year	5-year
OS	63.1% (57.4, 69.4%)	44.0% (38.0, 50.9%)	37.5% (31.3, 45.0%)
LFS	56.9% (51.1, 63.4%)	39.8% (34.0, 46.6%)	35.0% (29.1, 42.2%)
Relapse	28.7% (23.3, 34.4%)	41.8% (35.4, 48.0%)	44.5% (37.9, 51.0%)
NRM	14.3% (10.3, 19.0%)	18.4% (13.8, 23.6%)	20.4% (15.4, 26.0%)

OS, overall survival; LFS, leukemia-free survival; NRM, non-relapse mortality

Table 4. Univariate Effects of Variables

	OS		Relapse		NRM	
	HR (95% CI)	p	SHR (95% CI)	p	SHR (95% CI)	p
Recipient's Gender Male	1.19 (0.84, 1.70)	.328	1.32 (0.87, 2.00)	0.198	1.03 (0.57, 1.88)	0.918
Recipient's age	0.99 (0.97, 1.01)	.516	0.99 (0.96, 1.01)	0.287	1.01 (0.98, 1.04)	0.553
Recipient's CMV positive	1.33 (0.54, 3.25)	.531	1.64 (0.57, 4.67)	0.357	0.93 (0.23, 3.83)	0.919
Donor's Gender Male	0.97 (0.70, 1.35)	.873	0.87 (0.60, 1.28)	0.483	0.98 (0.56, 1.73)	0.953
Donor's age	1.00 (0.98, 1.02)	.953	1.00 (0.98, 1.02)	0.792	1.00 (0.97, 1.03)	0.877
Donor's CMV positive	0.76 (0.35, 1.62)	.476	0.67 (0.29, 1.55)	0.352	1.12 (0.27, 4.67)	0.880
Time from Diagnosis to transplant (month)	1.00 (0.99, 1.01)	.740	1.00 (0.99, 1.01)	0.463	1.00 (0.99, 1.02)	0.572
Disease status at transplant		<0.001		0.010		0.277
CR1	1.00		1.00		1.00	
CR2	1.66 (1.14, 2.41)	.008	1.45 (0.93, 2.26)	0.105	1.59 (0.86, 2.95)	0.140
CR3+	3.31 (1.60, 6.84)	.001	4.00 (1.47, 10.87)	0.007	0.60 (0.08, 4.55)	0.624
Hospital length of stay (day)	1.01 (1.00, 1.01)	.084	0.99 (0.98, 1.00)	0.025	1.02 (1.00, 1.03)	0.005
Karnofsky performance score <90	1.02 (0.57, 1.80)	.953	0.76 (0.37, 1.57)	0.457	1.28 (0.50, 3.28)	0.606
EBMT Risk Score		.051		0.191		0.242
0 or 1	1.00		1.00		1.00	
2	1.30 (0.88, 1.92)	.180	1.01 (0.64, 1.59)	0.965	1.63 (0.86, 3.12)	0.137
3+	1.66 (1.09, 2.55)	.019	1.62 (0.95, 2.75)	0.076	1.59 (0.77, 3.25)	0.207

OS, overall survival; NRM, non-relapse mortality; HR, hazard ratio; SHR, subdistribution hazard ratio; CMV, Cytomegalovirus; CR, complete remission;

Table 5. Acute and Chronic GVHD Effects on Relapse and NRM in Landmark Points

acute GVHD				chronic GVHD			
	Landmark point	Relapse HR (95% CI)	NRM HR (95% CI)		Landmark point	Relapse HR (95% CI)	NRM HR (95% CI)
Grade I / II	**+10**	0.88 (0.26, 2.97)	0.93 (0.27, 3.15)	**Limited**	**day +101**	0.89 (0.43, 1.87)	0.37 (0.05, 2.84)
	+11	0.96 (0.36, 2.58)	1.80 (0.66, 4.90)		**month +4**	1.09 (0.57, 2.09)	0.32 (0.04, 2.43)
	+12	1.13 (0.44, 2.90)	1.88 (0.67, 5.30)		**month +5**	1.17 (0.64, 2.12)	0.63 (0.17, 2.27)
	+17	1.43 (0.60, 3.41)	2.66 (0.89, 7.92)		**month +6**	1.09 (0.59, 2.03)	1.03 (0.30, 3.54)
	+24	1.21 (0.50, 2.90)	1.93 (0.62, 6.01)		**month +9**	1.13 (0.57, 2.21)	1.60 (0.44, 5.82)
	+31	1.36 (0.55, 3.33)	2.31 (0.65, 8.22)		**month +12**	0.99 (0.45, 2.18)	3.15 (0.64, 15.41)
Grade III / IV	**+10**	0.31 (0.04, 2.32)	1.16 (0.39, 3.45)	**Extensive**	**day +101**	0.80 (0.35, 1.85)	1.80 (0.60, 5.38)
	+11	0.20 (0.03, 1.55)	2.29 (0.91, 5.75)		**month +4**	0.87 (0.40, 1.90)	1.23 (0.36, 4.24)
	+12	0.39 (0.09, 1.70)	2.95 (1.19, 7.34)		**month +5**	1.25 (0.63, 2.50)	1.13 (0.32, 3.98)
	+17	0.35 (0.08, 1.57)	4.12 (1.53, 11.09)		**month +6**	1.03 (0.48, 2.19)	2.20 (0.71, 6.82)
	+24	0.27 (0.06, 1.22)	3.32 (1.23, 8.94)		**month +9**	0.87 (0.35, 2.12)	0.75 (0.13, 4.43)
	+31	0.27 (0.06, 1.24)	3.81 (1.20, 12.11)		**month +12**	0.83 (0.31, 2.21)	1.30 (0.17, 9.89)

GVHD, graft versus host disease; NRM, non-relapse mortality;

Among 218 (86.5%) patients who were alive and event-free at day +100, 99 relapsed and 24 died from causes other than relapse. Out of 134 (61.5%) patients who experienced cGVHD, 93 (69.4%) were limited and 41 (30.6%) were extensive. Out of the 39 patients who had progressive cGVHD, 6 (15.4%), 11 (28.2%), 15 (38.5%), and 7 (17.9%) were in grades I, II, III, and IV of aGVHD, respectively. Similarly, among 56 patients with interrupted cGVHD, 13 (23.2%), 17 (30.4%), 22 (39.3%), and 4 (7.1%) had a history of grade I, II, III, and IV of aGVHD in the first 100 days after transplant, respectively. The estimated effects of limited and extensive cGVHD on relapse and NRM adjusted for the EBMT risk score are shown in Table 5. As it was shown in Figure 3, there is no statistically significant difference between the effect of limited and extensive cGVHD on relapse incidence as compared to no cGVHD patients. Figure 4 demonstrates that the effect of extensive cGVHD on NRM is higher than limited cGVHD but this effect is reversed 6 months after transplant.

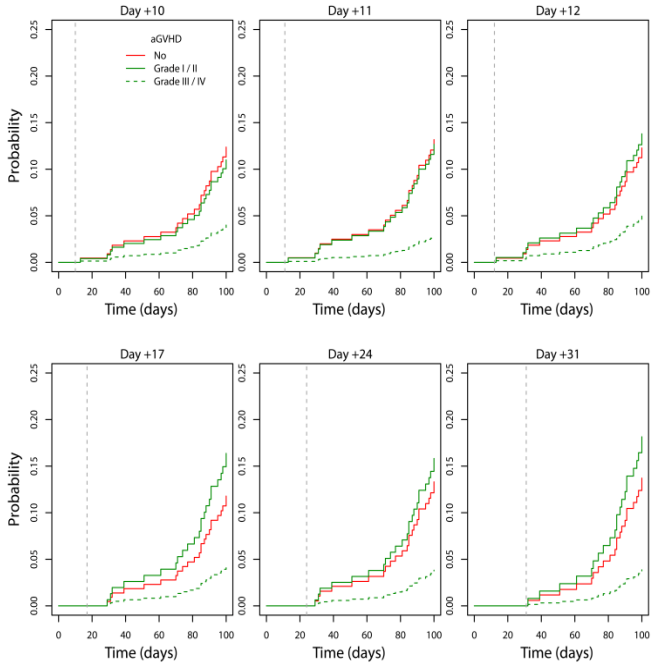

Figure 1. Estimated conditional cumulative incidence functions for relapse separated by no aGVHD, grade I or II of aGVHD, and grade III or IV of aGVHD. Predictions are for a patient with EBMT risk score 2, and are calculated at different landmark time points.

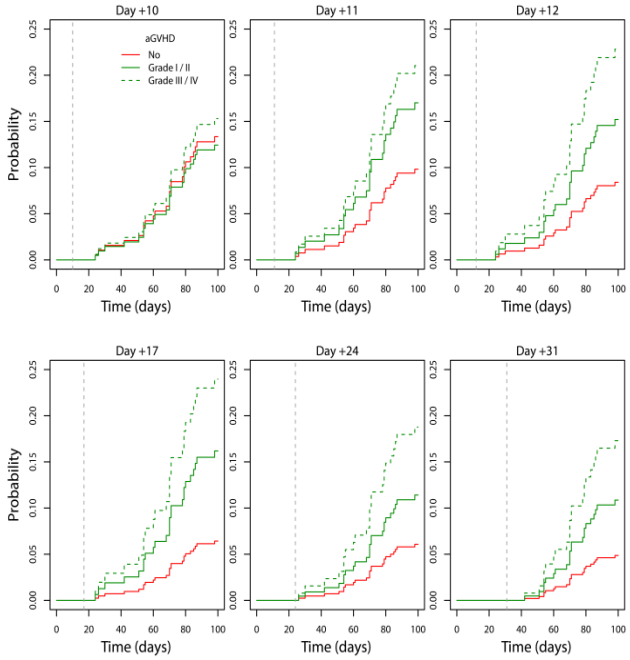

Figure 2. Estimated conditional cumulative incidence functions for NRM separated by no aGVHD, grade I or II of aGVHD, and grade III or IV of aGVHD. Predictions are for a patient with EBMT risk score 2, and are calculated at different landmark time points.

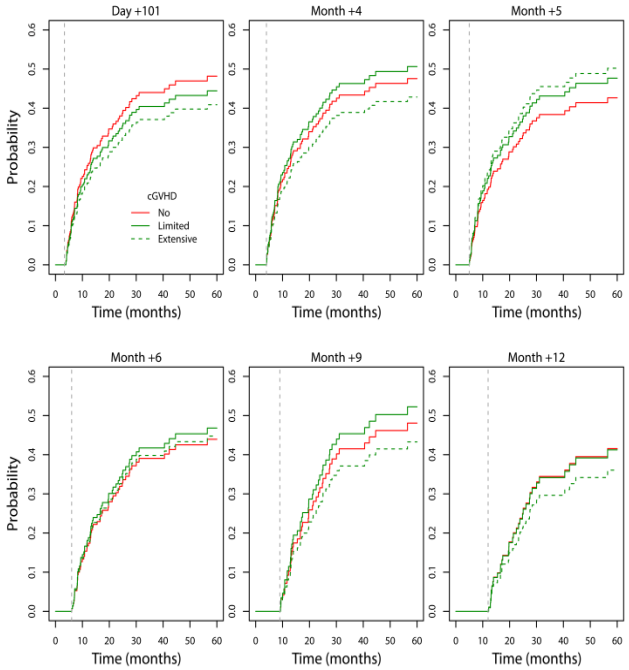

Figure 3. Estimated conditional cumulative incidence functions for relapse separated by no cGVHD, Limited and Extensive cGVHD. Predictions are for a patient with EBMT risk score 2, and are calculated at different landmark time points.

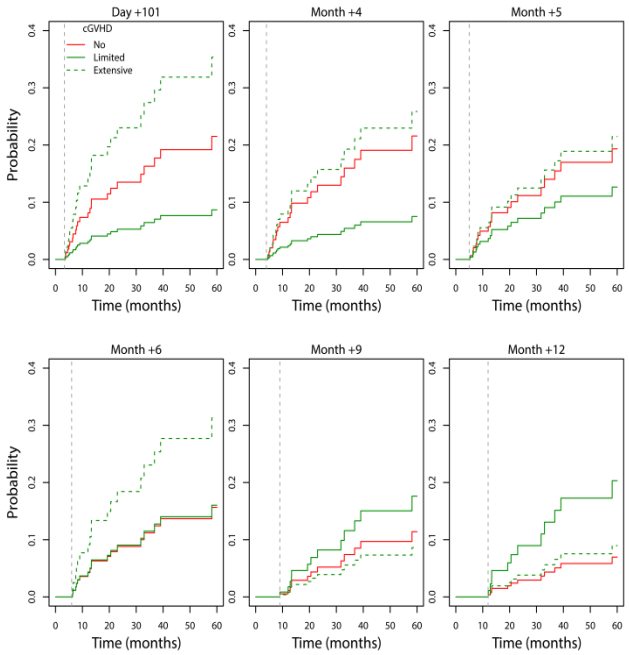

Figure 4. Estimated conditional cumulative incidence functions for NRM separated by no cGVHD, Limited and Extensive cGVHD. Predictions are for a patient with EBMT risk score 2, and are calculated at different landmark time points.

DISCUSSION

The 5-year OS in our study was very close to the results reported by Goldstone et al.[25] Also, the results for long-term NRM was similar to the NRM they reported for standard-risk patients. Patients transplanted in CR1 had better OS and lower relapse incidence. The rates of acute and chronic GVHD were as well similar to other studies that report results of HSCT with PB as the source of stem cell.[26, 27] Our findings showed that patients with higher grades of aGVHD are more at risk of early NRM and are consequently lower at risk of early relapse. For late outcomes, we found no predictive effect of cGVHD on relapse, but landmark analysis revealed that patients with limited cGVHD had lower probability of experiencing NRM however the difference between limited, extensive, and no cGVHD disappears after 6 months post-transplant. This can be due to decrease in the rates of NRM in patients with extensive and no cGVHD while this rate remains almost constant in limited cGVHD patients.

Almost all the donors and recipients in this study were CMV seropositive and most of the patients had Karnofsky performance score more than 90. High frequency of CMV seropositive donors and patients and Karnofsky score >90 made these two important factors insignificant in our study. While the status of disease is an ingredient of the EBMT risk score,[16, 17] we preferred to use the EBMT risk score for adjustment since it additionally contains age, donor to recipient gender combination, and interval time between diagnosis and transplant. This was a single-center study with a limited number of transplanted patients which lead to small number of events. This limitation resulted in not statistically significant findings however a trend was observed in some situations.

By applying landmark analysis similar to Cortese and Anderson[12] in this study, we pre-specified a small number of landmark time points. Therefore, we limited ourselves to dynamic prediction at these pre-defined points. Nicolaie et al.,[13] extended Cortese and Anderson[12] approach by building supermodels which allows dynamic prediction on all arbitrary points in a prediction interval. Using such advanced models enables us to estimate the effects more precisely and ultimately make inference more accurately.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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