The impact of GVHD on outcomes after adult single cord blood transplantation in European and Japanese populations

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Abstract

The impact of GVHD and graft-versus-leukemia effect in unrelated cord blood transplantation (UCBT) is controversial. In the Eurocord/ALWP EBMT and JSTCT/JDCHCT collaborative study, we evaluated the impact of GVHD on UCBT outcomes in Japanese and European registries. A total of 3,690 adult patients with acute leukemia who received their first single UCBT were included. A multivariate analysis of overall survival (OS) revealed a positive impact of grade II acute GVHD compared with grade 0-I GVHD, in the Japanese cohort (hazard ratio (HR), 0.81; P = 0.001), and an adverse impact in the European cohort (HR, 1.37; P = 0.007). A negative impact of grade III-IV acute GVHD on OS was observed regardless of registries. In the analysis of relapse, a positive impact of grade II acute GVHD compared with grade 0-I GVHD was observed only in the Japanese cohort, regardless of disease risk. The positive impact of limited chronic GVHD on OS was observed only in the Japanese cohort. In conclusion, a positive impact of mild GVHD after single UCBT was observed only in the Japanese cohort. This could explain the ethnic difference in UCBT outcomes and might contribute to the preference usage of UCBT in Japan.

KEYWORDS: single cord blood transplantation; adult; HLA mismatch; international transplant registries; graft-versus-host disease; graft-versus-leukemia effect

INTRODUCTION

The umbilical cord blood is an established alternative source for those who cannot find an HLA-matched sibling or unrelated donors.[1-13] The risk of acute graft-versus-host disease (GVHD) after unrelated cord blood transplantation (UCBT) is comparable to that after HLA-matched unrelated bone marrow transplantation (BMT) or peripheral blood stem cell transplantation (PBSCT). Furthermore, the risk of chronic GVHD after UCBT is comparable or even lower than that after unrelated BMT or PBSCT.[7,14,15]

The clinical practice for UCBT in Japan and Europe are different, which creates a barrier for the mutual understanding and application of clinical results between these populations. The acceptable cut-off level of total nucleated cells (TNCs) in single cord blood unit selection is different among Japan and Europe (Japan, ≥ 2.0 × 10^7/kg, Europe ≥ 2.5 or 3.0 × 10^7/kg).[5,16] A double UCBT is not allowed in Japan except for one clinical trial of a double UCBT[17], while the use of double UCBT is fairly common in the adult setting in Europe. HLA mismatches in UCBT is counted based on allele level for HLA-DRB1 in Western countries, whereas antigen level for HLA-DRB1 in Japan.

Despite these differences, we have reported that prognostic factors after single UCBT were shared between the two registries in the collaborative study between Eurocord/the Acute Leukaemia Working Party of European Society for Blood and Marrow Transplantation (ALWP-EBMT) and the Japanese Society for Transplantation and Cellular Therapy/Japanese Data Center for Hematopoietic Cell Transplantation (JSTCT/JDCHCT).[18] Only one substantial difference in prognostic factors between the two populations was demonstrated, which was the impact of HLA on outcomes. The impact of HLA on relapse and non-relapse mortality (NRM) was seen only in

Japanese populations. Considering the different impact of HLA on UCBT outcomes, we hypothesised that the impact of GVHD could differ between Japanese and European populations. In the present Eurocord/ALWP EBMT and JSTCT/JDCHCT collaborative study, we evaluated the impact of GVHD on transplant outcomes for adult patients with acute myelogenous leukaemia (AML) or acute lymphoblastic leukemia (ALL) in Japanese and European registries.

METHODS

Data collection

Data were obtained from the Eurocord/EBMT Registries and the Transplant Registry Unified Management Program of JSTCT/JDCHCT. Written informed consent for research was provided from all participants. The study was conducted according to the Declaration of Helsinki and was approved by the Institutional Review Board of the EBMT, Eurocord, and the Data Management Committees of the JSTCT/JDCHCT, and Kyoto University.

Inclusion and exclusion criteria

Patients aged between 18 and 75 years with AML or ALL who underwent their first allogeneic single UCBT from 2000 to 2014 were eligible for the study (3,764 and 1,033 patients of the JSTCT/JDCHCT and Eurocord/ALWP-EBMT registries). Patients who received manipulated, double or UCB combined with other cell sources and patients with secondary leukemia were excluded (n = 6). Those without information on GVHD (n = 66) or relapse (n = 58) were also excluded. Finally, patients failing to achieve neutrophil engraftment or experiencing graft failure within the first 100 days after UCBT, with or without autologous recovery, were excluded to compare the effect of GVHD on outcomes (793 out of 3679 (22%) for Japanese cohort and 183 out of 988 (19%) for European cohort). As a result, 2,886 and 804 patients of the JSTCT/JDCHCT and Eurocord/ALWP-EBMT registries, respectively, were included.

Definitions

Overall survival (OS) was defined as the time from transplantation to the date of last follow-up or death. Leukemia-free survival (LFS) was defined as the time from transplantation to the date of death, relapse, or last follow-up whichever occurred first. Relapse was defined based on the morphological and clinical evidence of

disease activity, and NRM was defined as the time to date of death without relapse. Acute and chronic GVHD were diagnosed and graded by the physicians who performed transplantation at each center using traditional criteria.[19,20]

The intensity of the conditioning regimen was classified based on the report by the Center for International Blood and Marrow Transplant Research.[21] HLA typing was classified based on low-resolution typing for HLA-A and HLA-B loci and high-resolution for HLA-DRB1 locus according to the European cord blood historical selection criteria.

Endpoints

The primary endpoint was to evaluate the impact of acute GVHD on OS in the Eurocord/ALWP of EBMT and JSTCT/JDCHCT registries. The secondary endpoints were the impact of acute and chronic GVHD on LFS, relapse, NRM as well as the effect of chronic GVHD on OS.

Statistical analysis

The Cox proportional-hazards model was used to evaluate the impact of GVHD on OS, LFS, relapse and NRM. The occurrence of acute and chronic GVHD was treated as a time-dependent covariate. In the analysis of acute GVHD, patients were assigned to the ‘no or grade I acute GVHD group’ at the time of transplantation and then transferred to the ‘grade II acute GVHD group’ or the ‘grade III–IV acute GVHD group’ at the onset of acute GVHD. The analysis of chronic GVHD were performed for patients who were alive without relapse at least 100 days after transplantation. Patients were assigned to the ‘no chronic GVHD group’ at the time of transplantation and then transferred to the ‘limited chronic GVHD group’ or the ‘extensive chronic GVHD group’ at the onset of chronic GVHD. The prior history of acute GVHD (no or grade I, grade II or grade III–IV acute GVHD) at day 100 were included in the analysis of chronic GVHD. The impact of GVHD on survival, relapse, and NRM was

graphically illustrated by Simon–Makuch plots.[20]

Variables considered included patient sex, patient age, disease, refined disease risk index (rDRI), transplant year, center experience, TNC of UCB, HLA matching, ABO blood type matching, use of total body irradiation, and conditioning regimen.[22] TNCs were categorized into two groups according to the guidelines and published studies in Europe (cut-off, 3.0 x 10^7/kg) and Japan (2.5 x 10^7/kg).[8,9,23-2516] Center experience was categorized according to the number of UCBT included during the period of observation in each cohort (1-4, 5-9, 10-19, ≥20). Missing data were considered as a separate category if a variable had ≥5% missing values. Since ATG was rarely used in Japanese cohort, it was included only in the European cohort. In addition to the clinically important variables mentioned above, other variables that remained significant after a backward stepwise selection with a variable retention criterion of $P < 0.05$ in each dataset were included in adjusted multivariate models.

P-values were two-sided and results under <0.05 were considered significant. All statistical analyses were performed using Stata version 13 (Stata Corp., College Station, TX).

RESULTS

Patient characteristics

Characteristics of patient, donor, and transplantation were shown in **Table 1**. The median follow-up of survivors was 48 (range, 1-195) and 45 (range, 1-183) months in the JSTCT/JDCHCT and Eurocord/ALWP-EBMT registries, respectively. The Japanese cohorts are older than the European cohorts (median age, 50 vs 38 years). Patients with higher rDRI were more frequently included in the Japanese cohort than the European cohort. UCBs with three or more HLA mismatches were more frequently used in the Japanese cohort (23%) than in the European cohort (3%). Median TNC counts were higher in European cohort (3.51×10^7/kg) than the Japanese cohort (2.58×10^7/kg). ATG was used in only 2% of the Japanese cohort. Combination of calcineurin inhibitor and methotrexate was frequently used as GVHD prophylaxis in the Japanese cohort. UCB grafts were obtained from 11 Japanese public banks for the JSTCT/JDCHCT cohort and from at least 65 international public banks for the Eurocord/ALWP-EBMT cohort. Data were provided by 206 JSTCT/JDCHCT centers in Japan and 135 EBMT centers in 25 countries.

Effect of acute GVHD on OS and LFS

The grades II-IV and III-IV acute GVHD occurred in 1286 (45%) and 402 (14%) in the Japanese population, and in 246 (31%) and 94 (12%) in the European cohort. The median day of onset of grades II–IV acute GVHD after transplantation in the Japanese and European cohort was 31 (range 1-411) and 28 (range 4-123), respectively.

The effect of acute GVHD on OS and LFS was illustrated with reference to three categories: grade 0–I, II, and III–IV acute GVHD in either Japanese or European cohort (**Figure 1**). A multivariate analysis of OS that treated acute GVHD as a

time-dependent covariate revealed that a positive impact of grade II acute GVHD compared with grade 0-I GVHD was observed in the Japanese cohort (hazard ratio (HR), 0.81; 95% confidence interval (CI), 0.72–0.92; P=0.001), whereas the adverse impact was observed in the European cohort (HR, 1.37; 95% CI, 1.09–1.73; P=0.007; **Table 2**). The positive impact of grade II acute GVHD in Japanese cohort was more apparent in the high-risk groups. Positive impact of grade II acute GVHD was consistently observed regardless of diagnosis or condition intensity in Japanese cohort, whereas adverse impact of grade II acute GVHD was observed regardless of diagnosis, condition intensity, or use of ATG in European cohort (**supplemental table 1**). The analysis also showed an adverse impact of grade III-IV acute GVHD on OS compared with grade 0-I GVHD regardless of registries (Japanese, HR, 1.81; 95% CI, 1.57–2.08; P<0.001; European, HR, 2.14; 95% CI, 1.62–2.84; P<0.001).

In the analysis of LFS, similar results were obtained (**Table 2**)

Effect of acute GVHD on relapse and NRM

The effect of acute GVHD on relapse and NRM was illustrated in **Supplemental Figure 1**. A multivariate analysis of relapse showed that a positive impact of grade II acute GVHD compared with grade 0-I acute GVHD was observed in the Japanese cohort (HR, 0.81; 95% CI, 0.69–0.95; P=0.010), but not in the European cohort (HR, 0.94; 95% CI, 0.68–1.31; P=0.718; **Table 3**). The positive impact of grade II acute GVHD seemed to be consistent regardless of disease risk. A positive impact of grade III-IV acute GVHD compared with grade 0-I GVHD was observed regardless of registries, although it did not reach statistical significance in the European cohort.

A multivariate analysis of NRM showed that an adverse impact of grade III-IV acute GVHD compared with grade 0-I GVHD was consistently observed in the Japanese cohort (HR, 2.97; 95% CI, 2.47–3.56; P<0.001) and in the European cohort (HR, 3.91; 95% CI, 2.77-5.51; P<0.001; **Table 3**). Interestingly, the positive impact of grade

II acute GVHD was observed in Japanese cohort (HR, 0.82; 95% CI, 0.67–0.99; P=0.037), whereas the adverse impact was observed in European cohort (HR, 1.76; 95% CI, 1.29–2.40; P<0.001). Causes of NRM are shown in **Table 4**. GVHD and infection among patients with grade II acute GVHD was more frequently observed as a cause of death in European cohort than in Japanese cohort.

Effect of chronic GVHD on OS and LFS

Any or extensive chronic GVHD occurred in the 792 (36%) and 330 (15%) in the Japanese cohort and 235 (35%) and 95 (14%) in the European cohort. The median day of onset of chronic GVHD after transplantation in the Japanese and European cohort was 108 (range 45-2275) and 146 (range 66-1109) days, respectively.

The effect of chronic GVHD on OS and LFS was illustrated in **Figure 2**. The positive impact of limited chronic GVHD on OS and LFS was observed only in the Japanese cohort (OS, HR, 0.51; 95% CI, 0.42-0.63; P<0.001; LFS, HR, 0.59; 95% CI, 0.48-0.71; P<0.001), but not in the European cohort (OS, HR, 0.87; 95% CI, 0.64-1.19; P=0.391; LFS, HR, 1.06; 95% CI, 0.79-1.44; P=0.697, **Table 5**).
The adverse impact of extensive chronic GVHD was observed only in the European cohort, but not in the Japanese cohort (**Table 5**).

Effect of chronic GVHD on relapse and NRM

The effect of chronic GVHD on relapse and NRM was illustrated in **Supplemental Figure 2**. The positive impact of limited chronic GVHD on relapse was observed only in the Japanese cohort (HR, 0.75; 95% CI, 0.59–0.94; P=0.013), but not in the European cohort (HR, 1.03; 95% CI, 0.70–1.51; P=0.896).

The adverse impact of extensive chronic GVHD on NRM was only observed in the European cohort (HR, 3.25; 95% CI, 2.24–4.71; P<0.001). Interestingly, the positive

impact of limited chronic GVHD on NRM was observed in the Japanese cohort (HR, 0.38; 95% CI, 0.26–0.53; P<0.001).

Discussion

In the present study, we demonstrated that a positive impact of grade II acute GVHD on OS and LFS was observed in the Japanese cohort, but an adverse impact in the European cohort. The positive impact of grade II acute GVHD in the Japanese cohort was more apparent in the high-risk groups. Further, a positive impact of grade II acute GVHD on relapse was observed in the Japanese cohort, but not in the European cohort. Similarly, a positive impact of limited chronic GVHD on OS and LFS was observed in the Japanese cohort. These divergent results potentially reflect the ethnic difference in UCBT outcomes and may contribute to the increased preference of UCBT in Japan in comparison to Western countries.

A greater impact of grade II acute GVHD for patients with acute leukemia was observed only in Japanese populations, which is in agreement with a previous study.[26-29] A positive impact of acute GVHD, not only on relapse but also on NRM, was observed. This was partly due to a better response to corticosteroids for acute GVHD in the Japanese population, leading to the separation of GVHD and a graft-versus-leukemia effect, and improved immune recovery for those who experienced grade II acute GVHD without long-term steroid usage.[30] Similar with the findings in the analysis of acute GVHD, the positive impact of limited chronic GVHD on OS, LFS, relapse and NRM was observed only in the Japanese cohort. These differences in the impact of GVHD on transplant outcomes may be partly due to differences in ethnicity. A low incidence of grade II-IV acute GVHD in the Japanese populations compared with Caucasian populations was shown in related BMT and PBSCT.[31,32] Furthermore, this was confirmed in unrelated BMT.[33] Specific haplotypes have been associated with a greater risk of acute GVHD in Japan.[34,35] T-cell activation caused by minor histocompatibility antigens/tumor associated antigens may differ by haplotype and major histocompatibility complex. These might have led

to improved survival in Japanese populations.

Another potential reason underlying the differences in GVHD and outcomes could be differences in GVHD prophylaxis. ATG was more frequently used in the European populations, whereas it was used in only 2% of the Japanese cohort. Previous studies have reported that the use of ATG in UCBT was associated with an increased risk of overall mortality and NRM, infectious complications and related deaths, and delayed immune reconstitution.[23,36-39] Moreover, a recent study reported that better T-cell reconstitution at GVHD onset is associated with lower mortality.[40] Therefore, delayed T-cell reconstitution after the use of ATG could have affected the impact of acute GVHD on mortality. Although the incidence of acute GVHD was comparable between the Japanese and the European populations, treatment with corticosteroids may increase the risk of transplant-related complications for those who have developed acute GVHD even after the use of ATG prophylaxis in the European cohort. Actually, grade III-IV acute GVHD was more detrimental effect on mortality in the ATG cohort, although the use of ATG did not significantly change the impact of grade II acute GVHD. Importantly, ATG use in European centers and Japan was very distinct, with two-thirds of patients from the European cohort receiving ATG in comparison to a negligible use in the Japanese cohort. Therefore, we could not exclude that some of different results observed might be attributed, in part, to differences in ATG usage between Japan and Europe. Further, the impact of acute GVHD did not change according to diagnosis and conditioning intensity in either Japanese or European cohort.

Of note, a no detrimental impact of acute GVHD on survival was reported in American cohort, however the potential impact of grade II acute GVHD was not separately analyzed.[28,41] As we have previously reported, UCB grafts were obtained from 11 Japanese public banks for the JSTCT/JDCHCT cohort, whereas they were obtained

from at least 65 international public banks for the Eurocord/ALWP-EBMT cohort. Further UCBT data in Eurocord were obtained from 25 countries. The potentially different management of cord blood collection and clinical practices including patient management and GVHD grading in various countries might have an effect on the outcome.

Several limitations should be noted. First, there are unmeasured biases in the two studies. Differences in clinical practices and insurance systems could affect transplant outcomes and should be considered for interpretation. Second, there are a variety of different patients/transplant backgrounds, although we have shown that the data from the two registries shared similar prognostic factors on transplant outcomes, except for HLA mismatches, and tried to adjust the main effect by the confounding factors. Lastly, in this study, acute and chronic GVHD were diagnosed on the basis of traditional criteria. Therefore, it is not possible to differentiate persistent or recurrent acute GVHD or late-onset acute GVHD from classical or overlap chronic GVHD. This may bias the association between acute and chronic GVHD.

In summary, a positive impact of grade II acute GVHD after single UCBT on OS and leukemia-free survival was observed only in the Japanese cohort. Grade III-IV acute GVHD should be avoided regardless of the registry. Limited chronic GVHD after single UCBT on OS and leukemia-free survival was also observed only in the Japanese cohort. Extensive chronic GVHD had an adverse effect only in the European cohort. Mild GVHD, i.e. grade II acute GVHD, and limited chronic GVHD was beneficial in the Japanese cohort. This could reflect ethnic differences in UCBT outcomes and might contribute to the preference of UCBT in Japan.

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Author contributions

JK, YA, and EG designed the research, and organized the project. JK performed the statistical analysis; JK wrote the first draft and all other authors interpreted the data, critically reviewed the draft, and approved the final version for publication.

Conflict of interests

None of the authors has a relevant conflict of interest to this article.

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Figure legend

Figure 1 Impact of acute GVHD on overall survival and leukemia-free survival

Impact of acute GVHD (aGVHD) on overall survival and leukemia-free survival in Japanese (A, C) and European cohort (B, D) was graphically illustrated by Simon–Makuch plots.

Figure 2 Impact of chronic GVHD on overall survival and leukemia-free survival

Effect of chronic GVHD (cGVHD) on overall survival and leukemia-free survival in Japanese (A, C) and European cohort (B, D) was graphically illustrated by Simon–Makuch plots.

Table 1 Patient, donor, and transplant characteristics

Variables		Japanese cohort (n = 2,886)		European cohort (n = 804)	
Recipient age (years)	Median (range)	50 (18-75)		38 (18-70)	
Recipient sex	Female	1,291	45%	408	51%
	Male	1,594	55%	392	49%
	Missing	1	0%	4	0%
Recipient weight (kg)	Median (range)	55 (29.1-155.6)		65 (35-120)	
Recipient height (cm)	Median (range)	163 (137-190.5)		168 (149-200)	
Disease	AML	2,127	74%	534	66%
	ALL	759	26%	270	34%
Refined DRI	Low	118	4%	34	4%
	Intermediate	1,206	42%	487	61%
	High	1,190	41%	201	25%
	Very high	367	13%	42	5%
	Missing	5	0%	40	5%
Total nucleated cells at collection (x10^7/kg)	Median (range)	2.58 (1.02-8.54)		3.51 (1.40-9.50)	
Number of HLA mismatch	0	119	4%	32	4%
	1	438	15%	210	26%
	2	1,455	50%	431	54%
	3-5	665	23%	28	3%
	Missing	209	7%	103	13%
ABO compatibility	Match	992	34%	232	29%
	Mismatch	1,885	65%	361	45%
	Missing	9	0%	211	26%
Sex compatibility	Match	1,056	37%	400	50%

	Female to male	665	23%	190	24%
	Male to female	543	19%	183	23%
	Missing	622	22%	31	4%
Conditioning intensity	Myeloablative	1,922	67%	598	74%
	Reduced-intensity	961	33%	194	24%
	Missing	3	0%	12	1%
Dose of TBI (Gy)	0	410	14%	385	48%
	1-8	1,066	37%	144	18%
	9-14	1,404	49%	184	23%
	Missing	6	0%	91	11%
Use of ATG	No	2,831	98%	220	27%
	Yes	55	2%	527	66%
	Missing	0	0%	57	7%
GVHD prophylaxis	CI+MTX+-steroid	1,720	60%	39	5%
	CI+MMF+-steroid	653	23%	356	44%
	CI+steroid	14	0%	277	34%
	CI only	469	16%	67	8%
	Others/missing	30	1%	65	8%
Year of transplantation	2000-2004	368	13%	85	11%
	2005-2009	907	31%	385	48%
	2010-2014	1,611	56%	334	42%
Number of UCBTs	20- CBTs	2,122	74%	442	55%
per center	10-19 CBTs	527	18%	141	18%
	5-9 CBTs	171	6%	125	16%
	1-4 CBTs	66	2%	96	12%

Abbreviation: DRI, disease risk index; TBI, total body irradiation; GVHD, graft-versus-host disease; AML, acute myelogenous leukemia; ALL, acute lymphoblastic leukemia; CI, calcineurin inhibitor; MMF, mycophenolate mofetil; MTX, methotrexate; CBT, cord blood transplantation

Table 2 Impact of acute GVHD grade on overall survival and leukemia-free survival

Variable	Japanese cohort			European cohort		
	HR	95% CI	P value	HR	95% CI	P value
Overall survival*						
Grade 0-I	1.00		reference	1.00		reference
Grade II	0.81	(0.72 - 0.92)	0.001	1.37	(1.09 - 1.73)	0.007
Grade III-IV	1.81	(1.57 - 2.08)	<0.001	2.14	(1.62 - 2.84)	<0.001
Standard risk						
Grade 0-I	1.00		reference	1.00		reference
Grade II	0.92	(0.74 - 1.15)	0.460	1.32	(0.97 - 1.79)	0.075
Grade III-IV	2.89	(2.27 - 3.68)	<0.001	2.70	(1.87 - 3.87)	<0.001
High risk						
Grade 0-I	1.00		reference	1.00		reference
Grade II	0.76	(0.66 - 0.88)	<0.001	1.26	(0.85 - 1.87)	0.256
Grade III-IV	1.46	(1.23 - 1.73)	<0.001	1.52	(0.95 - 2.43)	0.084
Leukemia-free survival†						
Grade 0-I	1.00		reference	1.00		reference
Grade II	0.83	(0.73 - 0.94)	0.003	1.27	(1.01 - 1.59)	0.041
Grade III-IV	1.68	(1.45 - 1.93)	<0.001	1.82	(1.38 - 2.39)	<0.001
Standard risk						
Grade 0-I	1.00		reference	1.00		reference
Grade II	0.86	(0.70 - 1.07)	0.176	1.23	(0.91 - 1.66)	0.173
Grade III-IV	2.47	(1.96 - 3.13)	<0.001	2.33	(1.63 - 3.32)	<0.001
High risk						
Grade 0-I	1.00		reference	1.00		reference
Grade II	0.80	(0.69 - 0.94)	0.005	1.10	(0.74 - 1.62)	0.639

Grade III-IV	1.40	(	1.17	-	1.68	)	<0.001	1.25	(	0.79	-	2.00	)	0.342

Abbreviations: GVHD, graft-versus-host disease; HR, hazard ratio; CI, confidence interval.
*HRs were adjusted by TNC, HLA compatibility, center experience, recipient age, year of transplantation, refined disease risk index, sex incompatibility, and use of anti-thymocyte globulin (only in European cohort).
†HRs were adjusted by TNC, HLA compatibility, center experience, recipient age, year of transplantation, refined disease risk index, sex incompatibility, and use of anti-thymocyte globulin (only in European cohort).

Table 3 Impact of acute GVHD grade on relapse and non-relapse mortality

Variable	Japanese cohort			European cohort		
	HR	95% CI	P value	HR	95% CI	P value
Relapse*						
Grade 0-I	1.00		reference	1.00		reference
Grade II	0.81	(0.69 - 0.95)	0.010	0.94	(0.68 - 1.31)	0.718
Grade III-IV	0.75	(0.58 - 0.97)	0.026	0.67	(0.41 - 1.10)	0.110
Standard risk						
Grade 0-I	1.00		reference	1.00		reference
Grade II	0.74	(0.55 - 1.01)	0.061	0.88	(0.55 - 1.41)	0.598
Grade III-IV	0.77	(0.46 - 1.30)	0.334	0.45	(0.18 - 1.12)	0.087
High risk						
Grade 0-I	1.00		reference	1.00		reference
Grade II	0.85	(0.70 - 1.03)	0.098	0.78	(0.46 - 1.32)	0.348
Grade III-IV	0.77	(0.57 - 1.03)	0.075	0.82	(0.44 - 1.55)	0.549
Non-relapse mortality†						
Grade 0-I	1.00		reference	1.00		reference
Grade II	0.82	(0.67 - 0.99)	0.037	1.76	(1.29 - 2.40)	<0.001
Grade III-IV	2.97	(2.47 - 3.56)	<0.001	3.91	(2.77 - 5.51)	<0.001
Standard risk						
Grade 0-I	1.00		reference	1.00		reference
Grade II	0.98	(0.73 - 1.32)	0.899	1.62	(1.10 - 2.39)	0.015
Grade III-IV	4.27	(3.22 - 5.66)	<0.001	4.84	(3.20 - 7.34)	<0.001
High risk						
Grade 0-I	1.00		reference	1.00		reference
Grade II	0.70	(0.54 - 0.90)	0.005	1.87	(1.05 - 3.33)	0.033

Grade III-IV	2.32	(	1.83	-	2.95	)	<0.001	2.24	(	1.16	-	4.32	)	0.017

Abbreviations: GVHD, graft-versus-host disease; HR, hazard ratio; CI, confidence interval.
*HRs were adjusted by TNC, HLA compatibility, center experience, age, refined disease risk index, and use of anti-thymocyte globulin (only in European cohort).
†HRs were adjusted by TNC, HLA compatibility, center experience, recipient age, refined disease risk index, sex incompatibility, year of transplantation, and use of anti-thymocyte globulin (only in European cohort).

Table 4 Causes of death for non-relapse mortality

Japanese cohort

Cause of death	Grade 0-I aGVHD (n = 1600)		Grade II aGVHD (n = 884)		Grade III-IV aGVHD (n = 402)	
GVHD	10	3%	12	7%	57	29%
Idiopathic pneumonia	38	11%	11	7%	9	5%
Infection	91	26%	55	34%	65	33%
Organ failure	50	14%	23	14%	14	7%
Hemorrhage	20	6%	7	4%	10	5%
VOD	11	3%	4	2%	2	1%
Others	79	23%	26	16%	36	18%
Missing	52	15%	23	14%	6	3%
Total	351	100%	161	100%	199	100%

European cohort

Cause of death	Grade 0-I aGVHD (n = 558)		Grade II aGVHD (n = 152)		Grade III-IV aGVHD (n = 94)	
GVHD	21	14%	12	20%	31	60%
Idiopathic pneumonia	4	3%	3	5%	0	0%
Infection	70	48%	33	56%	14	27%
Organ failure	9	6%	2	3%	2	4%
Hemorrhage	9	6%	0	0%	0	0%
VOD	2	1%	0	0%	1	2%
Others	21	14%	5	8%	4	8%

Missing	10	7%	4	7%	0	0%
Total	146	100%	59	100%	52	100%

Abbreviations: aGVHD, acute graft-versus-host disease

Table 5 Impact of chronic GVHD on overall survival, leukemia-free survival, relapse, and non-relapse mortality

	Japanese cohort				European cohort			
	HR	95% CI		P value	HR	95% CI		P value
Overall survival*								
No cGVHD	1.00			reference	1.00			reference
Limited cGVHD	0.51	(0.42 - 0.63)		<0.001	0.87	(0.64 - 1.19)		0.391
Extensive cGVHD	0.90	(0.75 - 1.09)		0.285	1.89	(1.42 - 2.52)		<0.001
Leukemia-free survival†								
No cGVHD	1.00			reference	1.00			reference
Limited cGVHD	0.59	(0.48 - 0.71)		<0.001	1.06	(0.79 - 1.44)		0.697
Extensive cGVHD	0.94	(0.78 - 1.12)		0.480	1.85	(1.37 - 2.49)		<0.001
Relapse**								
No cGVHD	1.00			reference	1.00			reference
Limited cGVHD	0.75	(0.59 - 0.94)		0.013	1.03	(0.70 - 1.51)		0.896
Extensive cGVHD	0.81	(0.63 - 1.06)		0.123	0.77	(0.44 - 1.34)		0.352
Non-relapse mortality††								
No cGVHD	1.00			reference				
Limited cGVHD	0.38	(0.26 - 0.53)		<0.001	1.14	(0.72 - 1.81)		0.567
Extensive cGVHD	1.08	(0.83 - 1.40)		0.551	3.25	(2.24 - 4.71)		<0.001

Abbreviations: cGVHD, chronic graft-versus-host disease; HR, hazard ratio; CI, confidence interval.

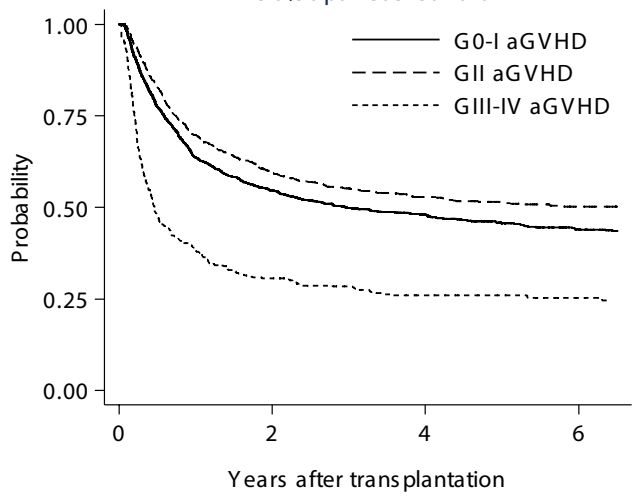
*HRs were adjusted by TNC, HLA compatibility, center experience, recipient age, year of transplantation, refined disease risk index, sex incompatibility, and use of anti-thymocyte globulin (only in European cohort).

†HRs were adjusted by TNC, HLA compatibility, center experience, recipient age, year of transplantation, refined disease risk index, sex incompatibility, and use of anti-thymocyte globulin (only in European cohort).

**HRs were adjusted by TNC, HLA compatibility, center experience, age, refined disease risk index, and use of anti-thymocyte globulin (only in European cohort).

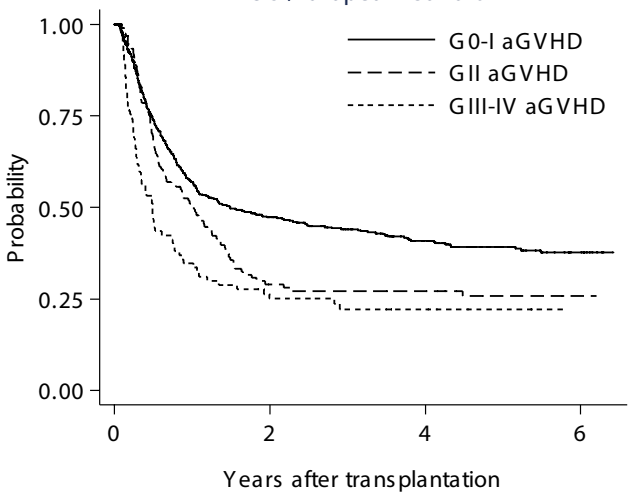
Figure 1

(A)



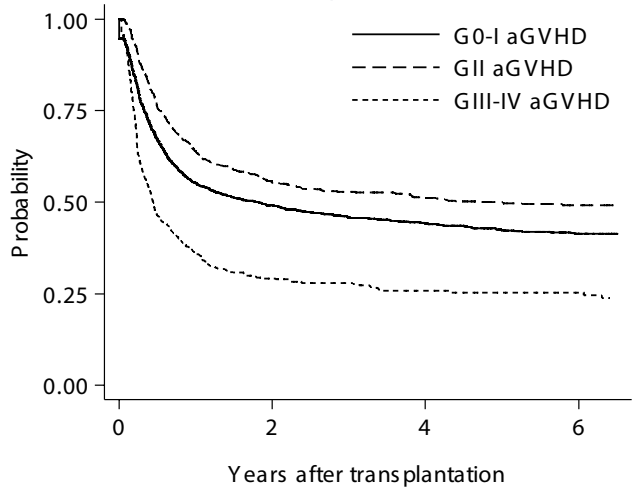
Number at risk				
G0-I aGVHD	2886	728	407	220
GII aGVHD	0	457	294	173
GIII-IV aGVHD	0	117	62	39

(B)



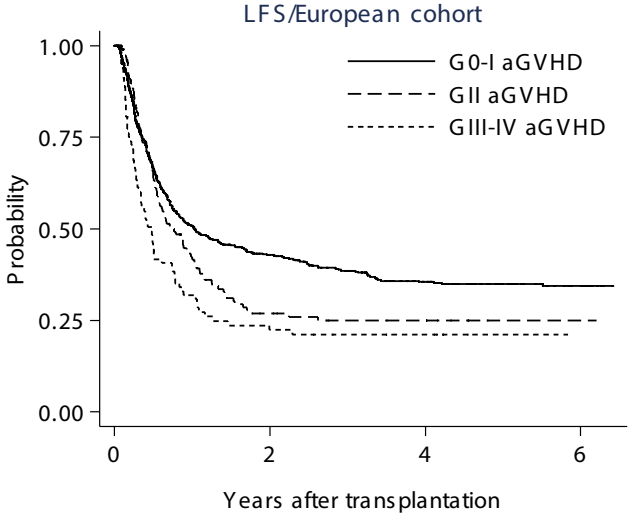
Number at risk				
G0-I aGVHD	804	204	128	71
GII aGVHD	0	33	26	10
GIII-IV aGVHD	0	20	13	5

(C)



Number at risk				
G0-I aGVHD	2886	651	372	204
GII aGVHD	0	410	273	160
GIII-IV aGVHD	0	107	59	36

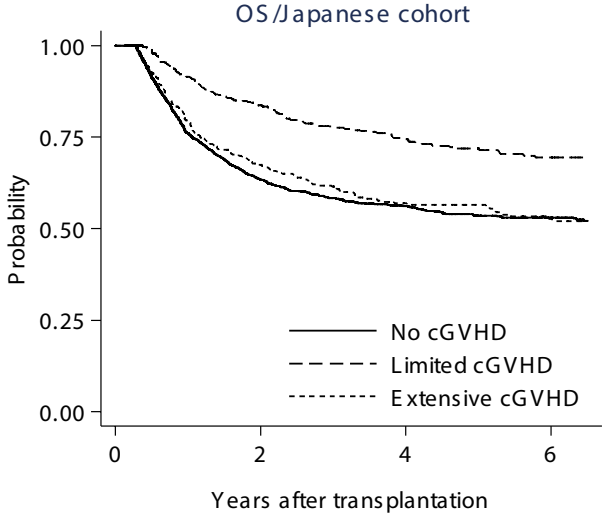
(D)



Number at risk				
G0-I aGVHD	804	184	114	65
GII aGVHD	0	30	23	10
GIII-IV aGVHD	0	18	12	4

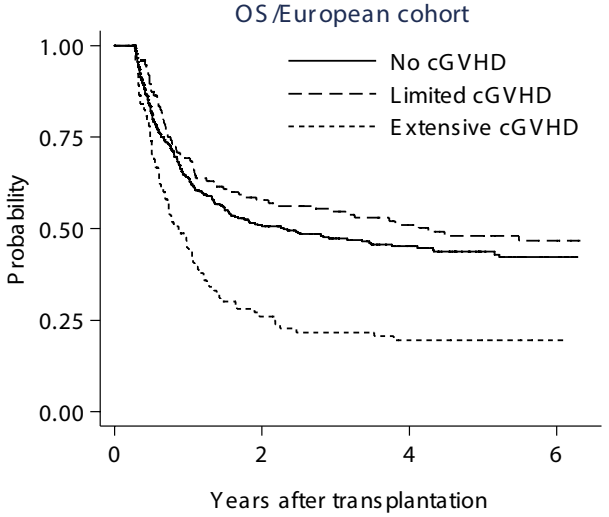
Figure 2

(A)



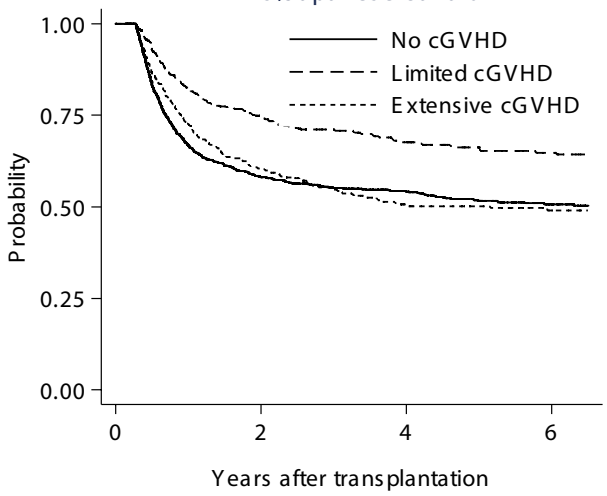
Number at risk				
No cGVHD	2182	723	384	212
Limited cGVHD	0	337	221	126
Extensive cGVHD	0	213	137	82

(B)



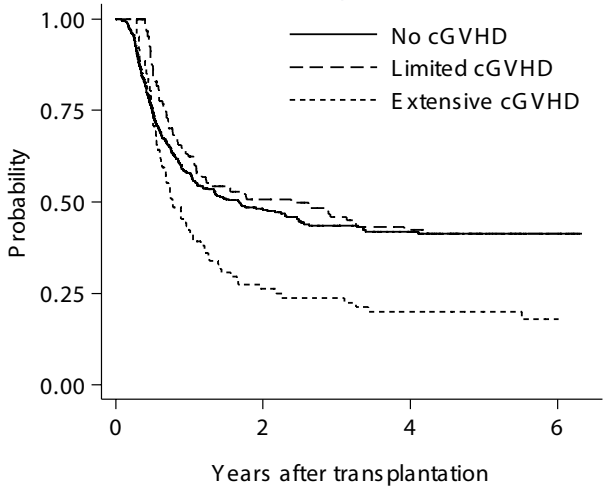
Number at risk				
No cGVHD	680	156	97	44
Limited cGVHD	0	76	54	33
Extensive cGVHD	0	25	16	9

(C)



Number at risk				
No cGVHD	2182	653	366	199
Limited cGVHD	0	305	203	119
Extensive cGVHD	0	197	124	74

(D)



Number at risk				
No cGVHD	680	143	90	42
Limited cGVHD	0	66	45	30
Extensive cGVHD	0	23	14	7

Supplemental Figure legend

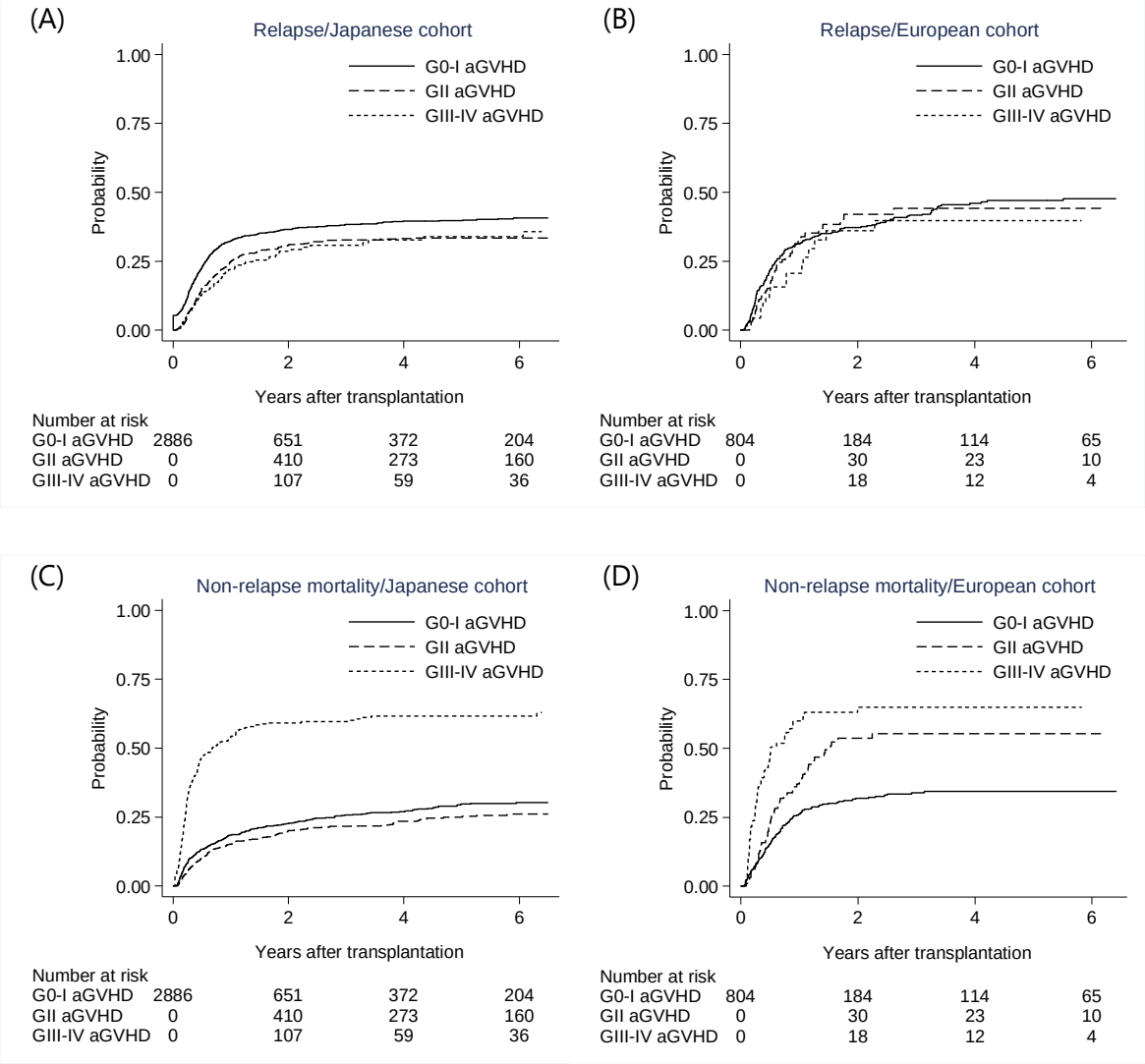
Supplemental Figure 1 Impact of acute GVHD on relapse and non-relapse mortality

Impact of acute GVHD (aGVHD) on relapse and non-relapse mortality in Japanese (A, C) and European cohort (B, D) was graphically illustrated by Simon–Makuch plots.

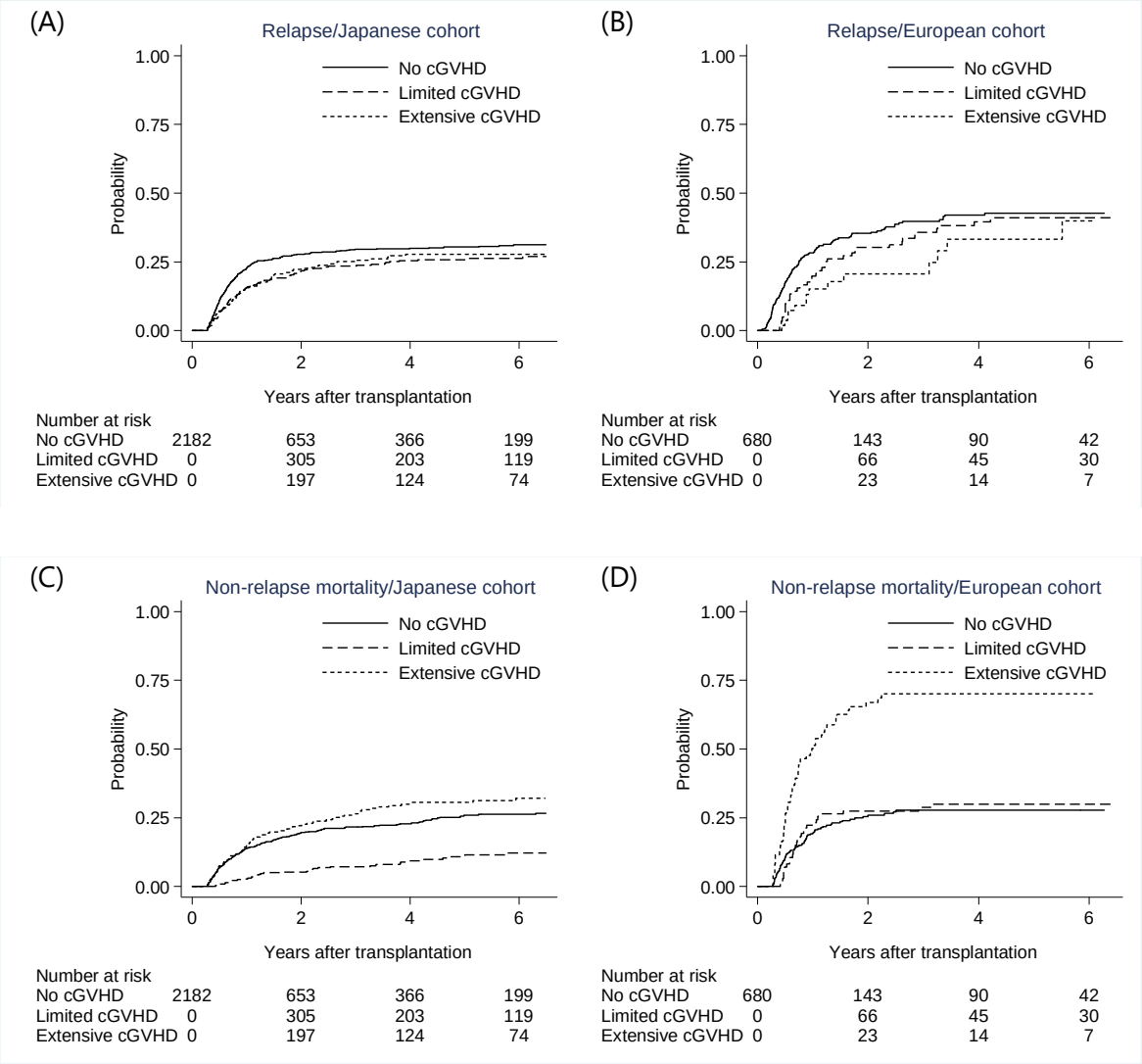
Supplemental Figure 2 Impact of chronic GVHD on relapse and non-relapse mortality

Impact of chronic GVHD (cGVHD) on relapse and non-relapse mortality in Japanese (A, C) and European cohort (B, D) was graphically illustrated by Simon–Makuch plots.

Supplemental Figure 1



Supplemental Figure 2



Supplemental Table 1

Impact of acute GVHD grade on overall mortality stratified by diagnosis, conditioning intensity, and use of ATG

Variable	Japanese cohort			European cohort		
	HR	95% CI	P value	HR	95% CI	P value
Total cohort						
Grade 0-I aGVHD	1.00		reference	1.00		reference
Grade II aGVHD	0.81	(0.72 - 0.92)	0.001	1.37	(1.09 - 1.73)	0.007
Grade III-IV aGVHD	1.81	(1.57 - 2.08)	<0.001	2.14	(1.62 - 2.84)	<0.001
Diagnosis						
AML						
Grade 0-I aGVHD	1.00		reference	1.00		reference
Grade II aGVHD	0.82	(0.72 - 0.94)	0.006	1.17	(0.87 - 1.56)	0.294
Grade III-IV aGVHD	1.69	(1.44 - 1.99)	<0.001	2.70	(1.33 - 2.76)	<0.001
ALL						
Grade 0-I aGVHD	1.00		reference	1.00		reference
Grade II aGVHD	0.80	(0.62 - 1.03)	0.087	1.78	(1.17 - 2.70)	0.007
Grade III-IV aGVHD	2.35	(1.76 - 3.12)	<0.001	2.54	(1.59 - 4.03)	<0.001
Conditioning intensity						
MAC						
Grade 0-I aGVHD	1.00		reference	1.00		reference
Grade II aGVHD	0.79	(0.68 - 0.92)	0.002	1.34	(1.01 - 1.79)	0.045
Grade III-IV aGVHD	1.53	(1.28 - 1.84)	<0.001	2.63	(1.90 - 3.64)	<0.001
RIC						
Grade 0-I aGVHD	1.00		reference	1.00		reference
Grade II aGVHD	0.83	(0.67 - 1.03)	0.086	1.76	(1.10 - 2.81)	0.017
Grade III-IV aGVHD	2.20	(1.76 - 2.76)	<0.001	1.49	(0.82 - 2.71)	0.196
Use of ATG						
Non-ATG						
Grade 0-I aGVHD				1.00		reference
Grade II aGVHD				1.82	(1.14 - 2.89)	0.012
Grade III-IV aGVHD				1.05	(0.62 - 1.80)	0.844
ATG						
Grade 0-I aGVHD				1.00		reference
Grade II aGVHD				1.28	(0.95 - 1.72)	0.105
Grade III-IV aGVHD				3.71	(2.63 - 5.24)	<0.001