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GVHD after HLA-matched sibling BMT or PBSCT: Comparison of North American Caucasian and Japanese Populations

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There is no conflict to disclose regarding this paper.

Authorship
Junya Kanda, Ruta Brazauskas, Zhen-Huan Hu, Yachiyo Kuwatsuka, Yoshiko Atsuta, Wael Saber designed the study, analyzed data and wrote the manuscript.
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Abstract

The risk of acute graft-versus-host disease (GVHD) after HLA-matched sibling bone marrow (BM) transplantation is lower in Japanese than in Caucasian patients. However, race may have differential effect on GVHD dependent on the graft source. North American Caucasian and Japanese patients receiving their first allogeneic BM or peripheral blood stem cell (PBSC) transplantations from an HLA-matched sibling for leukemia were eligible. BM was used in 13% and 53% of Caucasian and Japanese patients, respectively. In multivariate analysis, the interaction term between race and graft source was not significant in any of the models, indicating that graft source does not affect the impact of race on outcomes. The risk of grades III–IV acute GVHD was significantly lower in Japanese than in Caucasian patients (hazard ratio (HR) 0.74, 95% confidence interval (CI) 0.57–0.96), which resulted in lower risk of non-relapse mortality in Japanese patients (HR 0.69, 95% CI 0.54–0.89). The risk of relapse was also lower in this group. Lower risk of non-relapse mortality and relapse resulted in lower overall mortality rates among Japanese patients. In conclusion, irrespective of graft source, the risk of severe acute GVHD is lower in Japanese patients, which results in lower risk of non-relapse mortality.

Keywords

graft-versus-host disease; bone marrow transplantation; peripheral blood stem cell transplantation; race

INTRODUCTION

Several studies have demonstrated lower acute graft-versus-host disease (GVHD) risks after human leukocyte antigen (HLA)-matched sibling bone marrow transplantation (BMT) among Japanese, a genetically homogeneous population, compared to Caucasian and other races.[1,2] The lower incidence of acute GVHD was likely due to the relative homogeneity of minor histocompatibility antigens among Japanese.[3,4] Understanding outcome differences among races is particularly important for interpretation of transplant study findings and application of these results to clinical practice. In recent years, despite evidence of slightly increased risk of GVHD, peripheral blood stem cells (PBSC) have been more frequently used than bone marrow (BM) as stem cell grafts because of earlier neutrophil and platelet engraftment, perceived better overall survival in advanced or high-risk diseases,[5] and easier collection procedure. The effect of race may differ according to stem cell sources, because the number and subpopulations of T and other immune cells responsible for GVHD differ significantly between BM and PBSC.[6,7] To our knowledge, no other reports have assessed outcome differences between races after HLA-matched sibling PBSC transplantation (PBSCT).

Several groups in Europe and the U.S. have conducted randomized controlled trials comparing HLA-matched sibling BMT and PBSCT.[8–11] Based on these randomized studies, the Stem Cell Trialists' Collaborative Group conducted an individual-patient data meta-analysis using combined data from 1,111 adult patients.[5] The incidence of grades III–IV acute GVHD was 26% and 21% in the HLA-matched sibling PBSCT and BMT groups, respectively, with an odds ratio of 1.39 (95% confidence interval [CI], 1.03–1.88). Regarding matched unrelated donor transplantation, Anasetti et al. recently compared outcomes of unrelated donor BMT and PBSCT in a large multicenter randomized trial.[12] They reported a similar incidence of acute GVHD among BMT and PBSCT recipients. Nagafuji et al. retrospectively evaluated outcomes after HLA-matched sibling BMT and PBSCT in Japan using Japanese national registry data.[13] In this study, the incidence of grades III–IV acute GVHD was 14% and 5% in the HLA-matched sibling PBSCT and BMT, respectively, with a hazards ratio of 2.23 (95% CI, 1.04–4.78). These reports suggest that the incidence of severe acute GVHD was very low after HLA-matched sibling BMT in the Japanese population and the risk ratio of severe acute GVHD in PBSCT vs. BMT was much larger in Japanese than in Caucasian and other populations (2.23 vs. 1.39). In this context, we hypothesized that the lower incidence of acute GVHD in Japanese compared to Caucasian populations observed in HLA-matched sibling BMT will not be detectable in HLA-matched sibling PBSCT, and that there is an interaction between race and use of BM or PBSC. Furthermore, we hypothesized that this difference in severe acute GVHD rates between the races will affect other transplant outcomes and choice of BM or PBSC in HLA-matched sibling transplantation. Therefore, we accessed the large registry data of the Center for International Blood and Marrow Transplant Research (CIBMTR) and the Japan Society of Hematopoietic Cell Transplantation (JSHCT) to compare transplant outcomes between Japanese and Caucasian patients who received BMT or PBSCT from an HLA-matched sibling.

METHODS

Data Collection

Data were obtained from the CIBMTR and the Transplant Registry Unified Management Program (TRUMP) of JSHCT for U.S. and Japanese transplants, respectively.[14] The CIBMTR is a combined research program of the Medical College of Wisconsin and the National Marrow Donor Program. The CIBMTR comprises a voluntary network of more than 500 transplantation centers worldwide, which contribute detailed data on consecutive allogeneic and autologous hematopoietic cell transplantation to a centralized statistical center. Observational studies conducted by the CIBMTR are performed in compliance with all applicable U.S. federal regulations pertaining to the protection of human research participants. Protected health information used in the performance of such research is collected and maintained in the CIBMTR capacity as a public health authority under the Health Insurance Portability and Accountability Act Privacy Rule. Additional details regarding the data source are described elsewhere.[15] JSHCT developed the TRUMP to enable transplant centers to manage patient information with emphases on convenience to centers, safety of patient information, and quality of data management. TRUMP unifies data of 4 Japanese registries; JSHCT, Japanese Society of Pediatric Hematology, Japan Marrow Donor Program, and Japan Cord Blood Bank Network. Adult related allogeneic transplantations performed in Japan are registered through JSHCT.[14] Registration of the JSHCT does not require patient consent because clinical information is anonymized. The study was approved by the Institutional Review Board of the National Marrow Donor Program, Medical College of Wisconsin, Saitama Medical Center, Jichi Medical University, and the Data Management Committees of the JSHCT.

Inclusion criteria and data preparation

North American Caucasian and Japanese patients who received their first allogeneic BMT or PBSCT from an HLA-matched sibling for acute myelogenous leukemia (AML) and acute lymphoblastic leukemia (ALL) in first and second complete remission or chronic myelogenous leukemia (CML) in complete remission or chronic or accelerated phase between 2000 and 2011 were eligible. Patients were 18–59 years of age, received a myeloablative conditioning regimen, and used cyclosporine or tacrolimus-based GVHD prophylaxis. Patients with use of *in vivo* or *ex vivo* T cell depletion methods were excluded. AML or ALL in first complete remission and CML in first chronic phase or complete remission were defined as early risk disease. AML or ALL in the second complete remission and CML in the second or higher chronic phase or accelerated phase were defined as intermediate risk disease. Eastern Cooperative Oncology Group performance statuses of 0 and 1 or more were converted to Karnofsky performance status (KPS) 90–100 and <90, respectively, for patients in the Japanese dataset lacking KPS scores, following a conversion formula used in the CIBMTR. In the CIBMTR registration forms, race is categorized into “White or Caucasian”, “Black or African American”, “American Indian or Alaska Native”, “Asian”, and “Native Hawaiian or other Pacific Islander”. North American Caucasian includes Caucasians who live in the U.S., Canada, and Mexico.

Endpoints

Outcomes assessed include acute GVHD, chronic GVHD, relapse, non-relapse mortality, leukemia-free survival, and overall survival. Acute and chronic GVHDs were diagnosed and graded using the traditional criteria.[16,17] Non-relapse mortality was defined as death without relapse. Leukemia-free survival was defined as being alive in remission. For overall survival, death from any cause was the event.

Statistical analysis

Patient-, disease-, and transplant-related factors were compared between groups classified by race. Cohorts were compared using Chi-square and Kruskal-Wallis tests for categorical variables and continuous variables, respectively. Cumulative incidences for GVHD, relapse, and non-relapse mortality were calculated using the cumulative incidence function to account for competing risks.[18] Competing events were death without relapse for relapse, relapse for non-relapse mortality, and death without GVHD for acute and chronic GVHD. Gray's test was employed to evaluate the overall differences among cumulative incidence functions.[19] Leukemia-free and overall survival rates were estimated using the Kaplan-Meier estimator. The log-rank test was used to compare survival experience among different groups. Ninety-five percentage CIs for true survival probabilities were calculated based on arcsine-square root transformation. The impact of race and stem cell source on outcomes of interest was evaluated using the Cox proportional hazards model. The assumption of proportional hazards for each covariate in the Cox model was tested using time-dependent covariates. When the test indicated differential effects over time (non-proportional hazards), models were constructed to break the post-transplant time course into two periods. The maximized partial likelihood method was used to determine the most appropriate breakpoint. The proportionality assumptions were then further tested. A stepwise selection procedure was used to identify covariates associated with outcomes. The main effects of this study - race (North American Caucasian vs. Japanese) and graft source (BM vs. PBSC) - were included in all steps of model building. Other variables considered included recipient age group, recipient sex, KPS, disease status prior to the transplantation, donor age, donor-recipient cytomegalovirus (CMV) status, donor-recipient sex match, donor-recipient ABO blood group match, conditioning regimen, GVHD prophylaxis, and year of transplantation. Covariates that reached a significance level of 0.05 were included in the final models. An interaction test was used to determine whether the effects of graft source on transplant outcomes were different between the two groups. If the interaction was statistically significant, the main effects were combined into one main effect variable (graft source by race) in the final models. Otherwise, graft source and race were included as two independent main effects in the final models. Any potential interactions between main effect term and variables in the final model were evaluated. SAS 9.3 (SAS Inc., Cary, NC) statistical software was used for all analyses.

RESULTS

Patient characteristics

Table 1 shows patient, donor, and transplant characteristics. BM was used in 13% and 53% of the Caucasian and Japanese patients, respectively. Japanese patients were more likely to

be young, have better KPS scores, have early stages of ALL, have both donor and recipient CMV seropositivity, receive transplants from ABO mismatched donors, receive a cyclophosphamide + TBI regimen, receive cyclosporine-based prophylaxis, and receive a transplant after 2006. Majority of North American Caucasian is American and only 3% is Canadian.

Interaction between race and graft source

An interaction test was used to determine whether the effects of graft source on transplant outcomes were different between the two populations. In multivariate analysis, the interaction term between race and graft source was not significant in any of the models for all outcomes analyzed, which indicated that the impact of race on outcomes did not differ according to graft source (Supplemental Table 1). Therefore, graft source and race were treated as two independent main effects analyzing all outcomes.

Acute and chronic GVHD

The unadjusted cumulative incidence of grades II–IV acute GVHD at 100 days post transplantation was 31% (95% CI, 29%–34%) and 31% (95% CI, 28%–33%) in Caucasian and Japanese patients, respectively (Gray's test, P=0.11); the incidence for grades III–IV acute GVHD post transplantation was 14% (95% CI, 12%–16%) and 8% (95% CI, 7%–10%) in Caucasian and Japanese patients, respectively (Gray's test, P<0.001). In multivariate analysis, the risk of grades II–IV acute GVHD was comparable between both groups (hazard ratio [HR] 1.04, 95% CI 0.87–1.24, P=0.677), whereas the risk of grades III–IV acute GVHD was significantly lower in Japanese patients compared to Caucasians (HR 0.75, 95% CI 0.57–0.99, P=0.042) (Table 2). The risk of chronic GVHD was significantly lower in Japanese compared to Caucasian patients (within 12 months after transplantation, HR 0.85, 95% CI 0.73–0.99, P = 0.037; 12 months or more after transplantation, HR 0.33, 95% CI 0.21–0.51, P < 0.001). The unadjusted cumulative incidences of GVHD stratified by stem cell sources are shown in Supplemental Table 2. Adjusted cumulative incidence curves are shown in Figure 1.

Relapse and non-relapse mortality

The unadjusted cumulative incidence of relapse 3 years post transplantation was 33% (95% CI, 30%–35%) and 25% (95% CI, 23%–28%) in Caucasian and Japanese patients, respectively (Gray's test, P<0.001); the incidence of non-relapse mortality post transplantation was 18% (95% CI, 16%–20%) and 13% (95% CI, 11%–15%), respectively (Gray's test, P<0.001). In multivariate analysis, the risks of relapse and non-relapse mortality were significantly lower in Japanese than in Caucasians patients (relapse; HR 0.73, 95% CI 0.61–0.87, P<0.001, non-relapse mortality; HR 0.72, 95% CI 0.55–0.93, P=0.012, Table 3). The adjusted cumulative incidence curves are shown in Figure 2.

Disease-free and overall survival

The unadjusted probability of disease-free survival 3 years post transplantation was 49% (95% CI, 46%–52%) and 62% (95% CI, 59%–65%) in Caucasian and Japanese patients, respectively (log-rank test, P<0.001), and 57% (95% CI, 54%–60%) and 68% (95% CI,

65%–71%) for overall survival post transplantation, respectively (log-rank test, P<0.001). In multivariate analysis, the risks of death or relapse and overall mortality were significantly lower in Japanese than Caucasian patients (death or relapse; HR 0.78, 95% CI 0.68–0.89, P<0.001, overall mortality; HR 0.72, 95% CI 0.60–0.85, P<0.001, Table 3). Adjusted survival curves are shown in Figure 3.

DISCUSSION

Contrary to our initial hypothesis, the impact of race on acute GVHD did not differ according to BM or PBSC graft. Irrespective of graft source, the risk of severe acute GVHD was lower in Japanese patients. Although the main determinant of GVHD occurrence is the major histocompatibility antigen,[20] occurrence of GVHD in transplantation from an HLA-identical sibling indicates that non-HLA gene polymorphisms play an important role in GVHD.[21] Candidate gene studies have shown that various gene polymorphisms in recipients and donors are associated with GVHD.[21] Furthermore, the genome-wide association study confirms that some gene polymorphisms such as *IL-2*, *IL-6*, *CTLA4*, *HPSE*, and *MTHFR* are responsible for GVHD.[22] Such polymorphisms could be responsible for racial differences in GVHD occurrence. The relative homogeneity of minor histocompatibility antigens among Japanese individuals may also explain the reduced GVHD incidence in this population. Differences in frequencies of HLA antigens or haplotypes between the two populations may also contribute to differences in GVHD incidence.[2] Specific haplotypes have been associated with risk of acute GVHD.[23] The strength of T cell activation caused by minor histocompatibility antigens may differ by haplotype and major histocompatibility complex. Notably, our study showed that differences between the two populations were not affected by use of PBSC, which contains larger T cell populations and smaller non-hematopoietic populations than BM.

Unmeasured factors such as socioeconomic, environmental, or practice differences may also be responsible for outcome differences after allogeneic transplantation in the two populations. Analysis of unrelated myeloablative transplantation using the CIBMTR data indicated that lower income is associated with higher rates of non-relapse and overall mortality,[24] highlighting the importance of socioeconomic factors on transplant outcomes. Health insurance systems also differ; health insurance is privately purchased insurance or social welfare insurance in the U.S., while Japan offers universal health insurance coverage. This difference could affect access to medical care and medicine availability, including recently approved or unapproved treatments. The difficulty of adjusting for these factors limits the interpretation of our findings. Comparison of transplant outcomes of Japanese populations living outside Japan to those living in Japan could help evaluate these effects, although such an analysis is unlikely to be feasible due to the small sample size. Missing or insufficient data is also needs to be considered in interpreting the result. Missing data in CMV serostatus in the Japanese populations is not negligible and may have influenced the findings.

The lower risk of non-relapse mortality in the Japanese patients compared to the Caucasian patients partly reflects the lower incidence of grades III–IV acute GVHD among the Japanese patients. Interestingly, even lower risk of relapse was also observed in the

Japanese. This lower risk was previously noted in unrelated BMT and PBSCT.[25] Racial differences in leukemic cell susceptibility to chemotherapeutic agents may play a role in relapse. Yang et al. showed that genetic characteristics associated with Native American ancestry affect the risk of ALL relapse.[26] Furthermore, a particular SNP associated with drug resistance *in vitro* is also highly associated with relapse.[26] Genetic differences related to relapse between the two populations is worthy of further evaluation in future studies. Another possibility is differences in graft-versus-leukemia effects. Unlike previous findings in cohorts receiving transplantations between 1990 and 1999,[2] we did not observe any difference in the risk of grades II–IV acute GVHD between the two cohorts receiving transplantations between 2000 and 2011. This may be partly because Japanese physicians tended to weaken or taper GVHD prophylaxis earlier than before, expecting to enhance graft-versus-leukemia effects, since the GVHD incidence was very low in an HLA-matched sibling BMT among Japanese patients.[1] Alternatively, GVHD prophylaxis might have been intensified in the decade for Caucasian patients. Although cyclosporine has still been mainly used as GVHD prophylaxis for matched sibling transplantation in Japanese patients, tacrolimus-based GVHD prophylaxis has replaced this in Caucasian patients. Although the type of GVHD prophylaxis did not affect acute GVHD in the present study, such a change of practice may decrease the incidence of acute GVHD and the associated graft-versus-leukemia effects in Caucasian patients. The graft-versus-leukemia effects need to be interpreted according to each disease. In the present study, there was no interaction between race or stem cell source and disease in the multivariate analysis for relapse, which suggested that the impact of race on relapse was independent of disease type. Finally, although we included only early and intermediate disease status, i.e. AML and ALL in 1st or 2nd complete remission and CML in complete remission, or chronic or accelerated phase, lack of information on the cytogenetic and molecular risks in each disease may limit the interpretation of this study.

Contrary to the BMT and PBSCT findings, there was no difference in acute GVHD incidence or overall mortality after pediatric unrelated cord blood transplantation between Japanese and U.S. Caucasian patients.[27] In addition to qualitative and quantitative differences in the composition of BM, PBSC, and unrelated cord blood grafts, this may be partly because advantages associated with shared minor histocompatibility antigens in the more homogenous Japanese population may be weakened in unrelated cord blood transplantation with multiple major histocompatibility antigen mismatches.

In conclusion, irrespective of graft source, the risk of severe acute GVHD in this study was lower in Japanese patients, which resulted in a lower risk of non-relapse mortality. The difference in the incidence of grades III–IV acute GVHD may have been due to racial differences in non-HLA gene polymorphisms and minor histocompatibility antigens presented by specific major histocompatibility antigens. However, this could also be affected by socioeconomic or environmental factors or differences between practices. Although this study cannot separately evaluate genetic and non-genetic effects, it highlights the importance of considering racial differences not only in HLA-matched sibling BMT but also in PBSCT, particularly when interpreting and applying findings from different racial populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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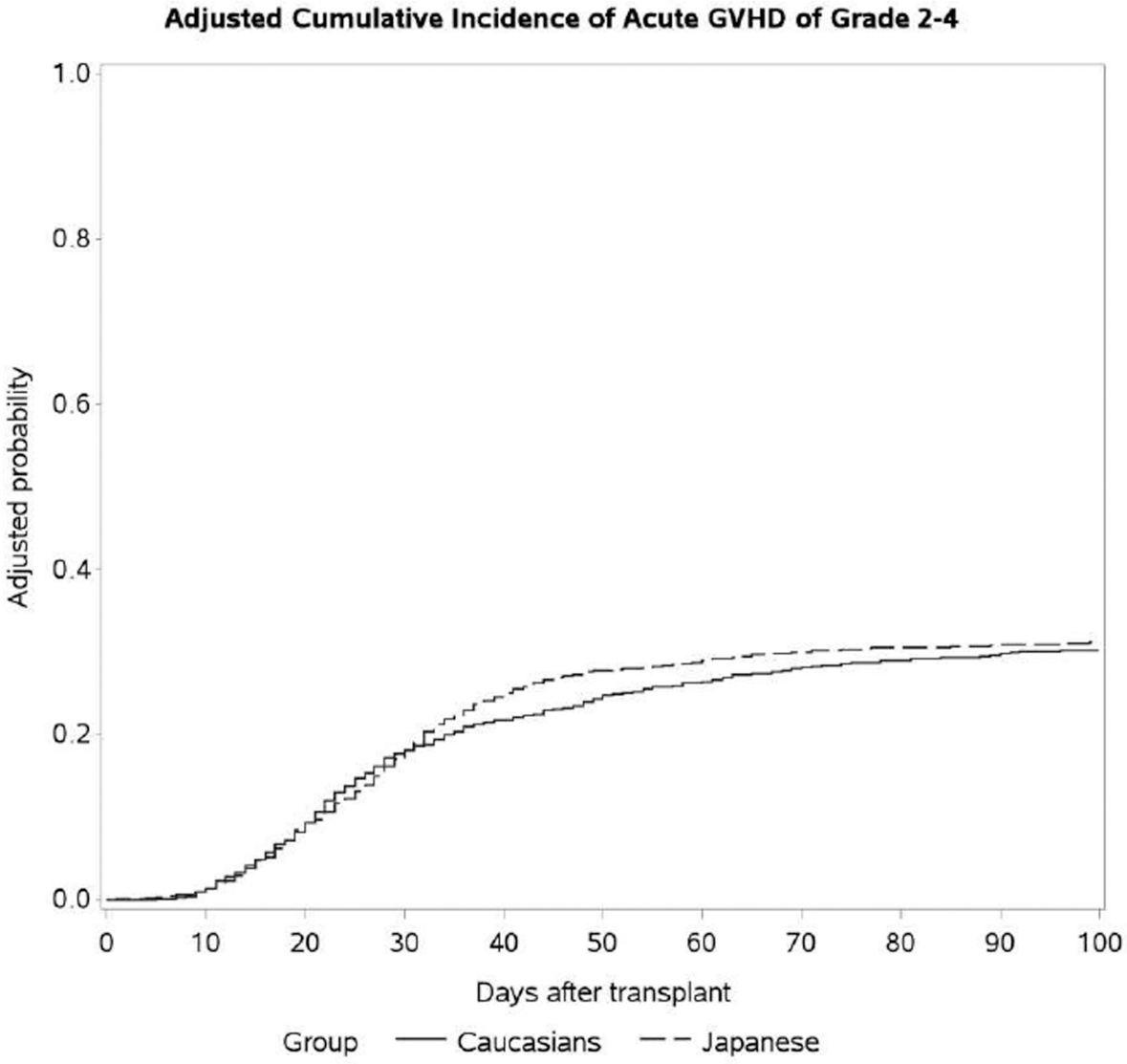
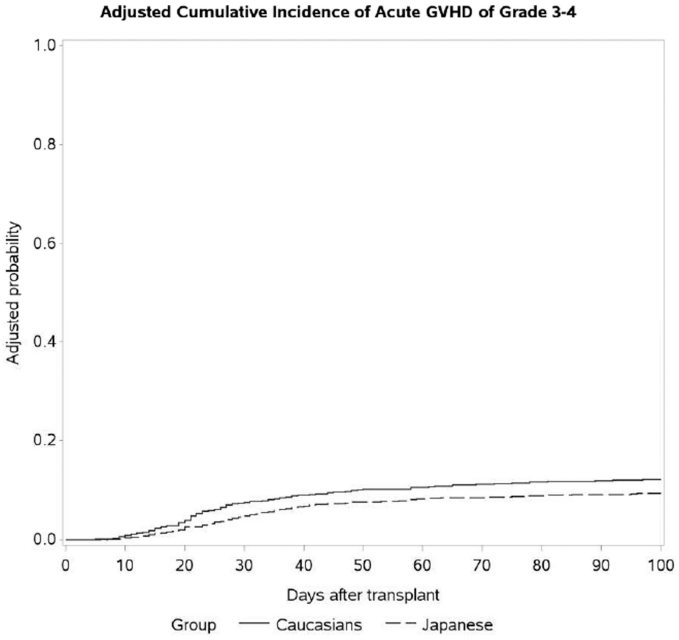
Highlights

- The impact of race on transplant outcomes was independent of graft source.
- The risk of severe acute GVHD was lower in Japanese than in Caucasian patients.
- Lower risk of acute GVHD resulted in lower risk of non-relapse mortality in Japanese.
- The risk of relapse was lower in Japanese than in Caucasian patients.
- Overall survival was higher in Japanese than in Caucasian patients.

(A)



(B)



(C)

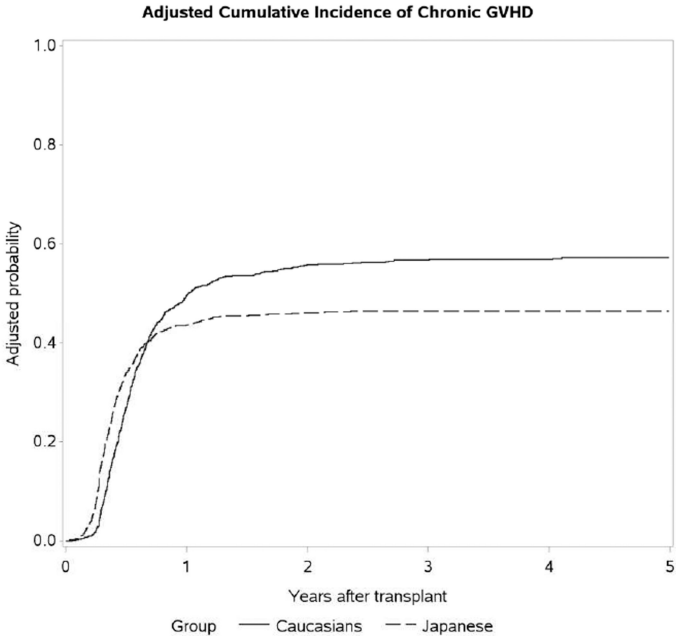
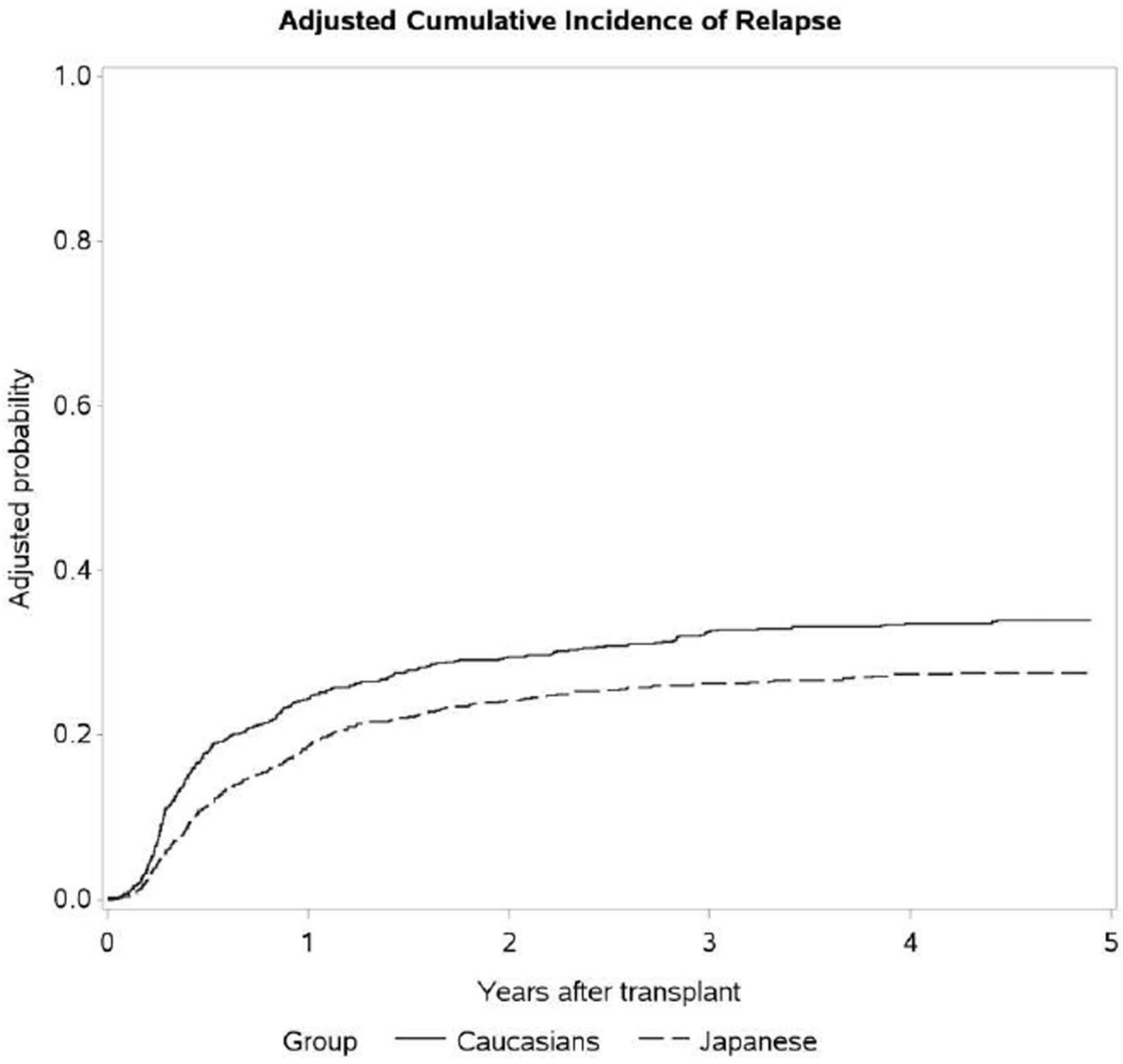


Figure 1.

Adjusted cumulative incidence of grades II–IV (A) or III–IV acute GVHD (B) and chronic GVHD (C)

(A)



(B)

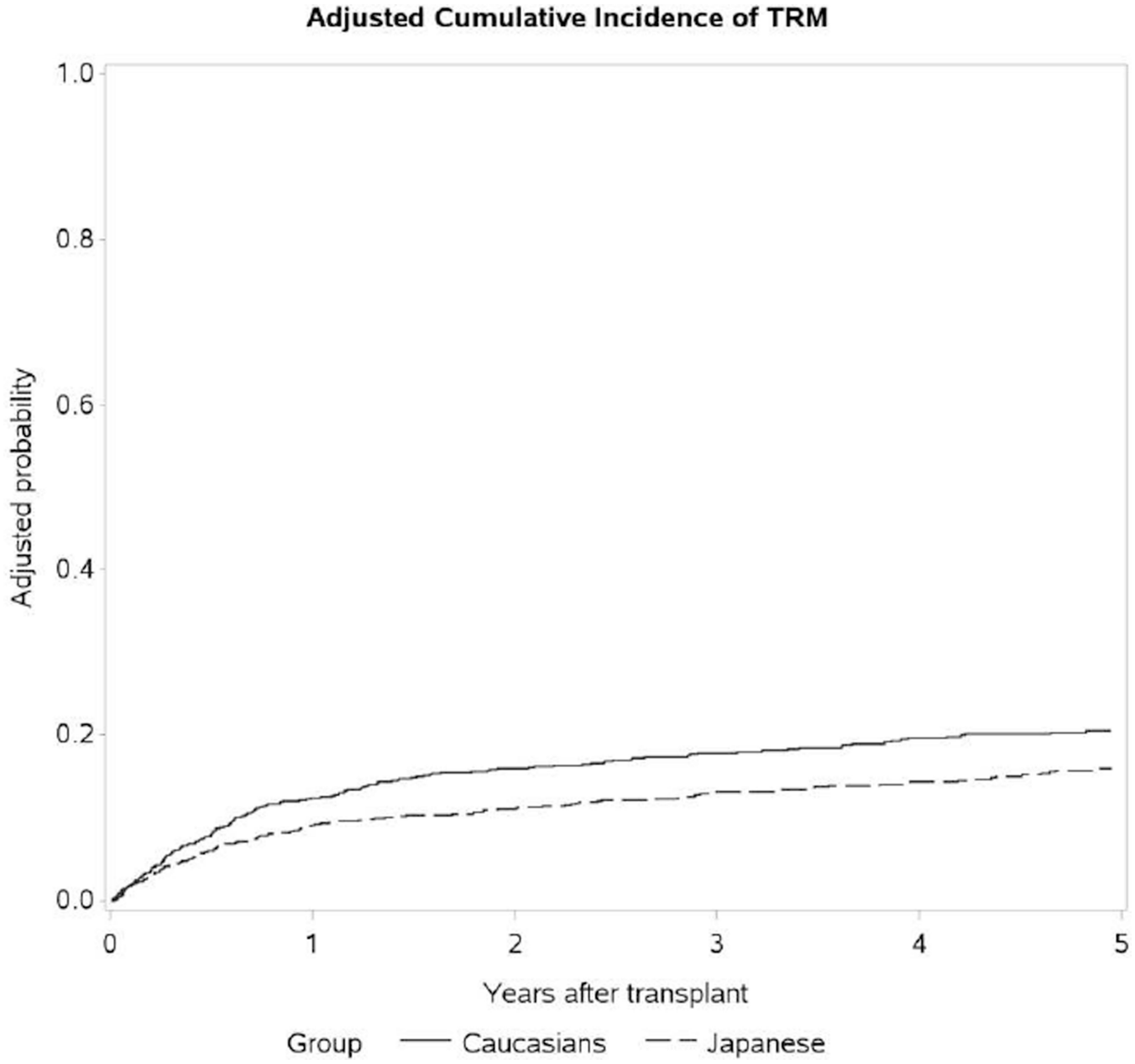
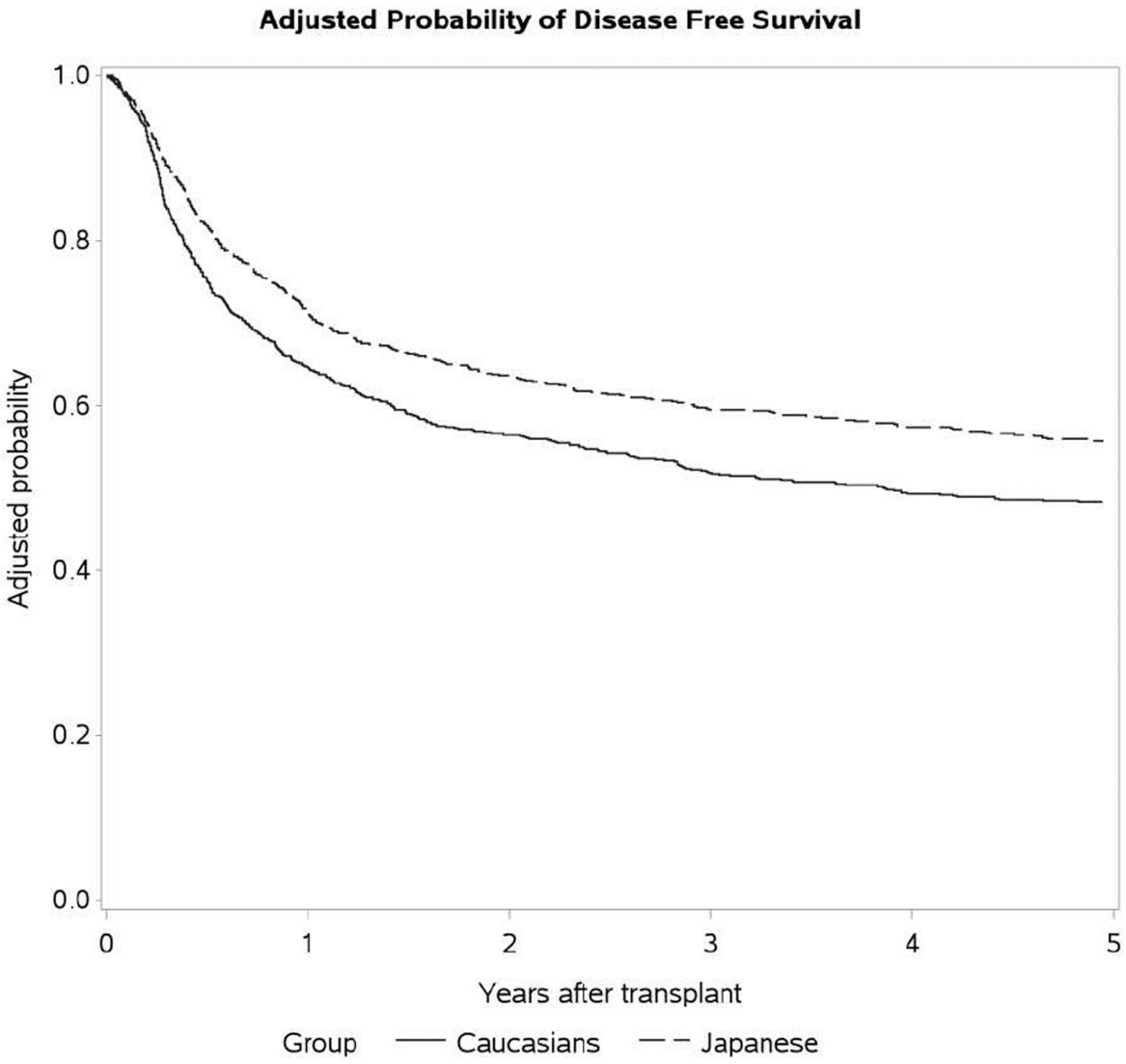


Figure 2.
Adjusted cumulative incidence of relapse (A) and non-relapse mortality (B)

(A)



(B)

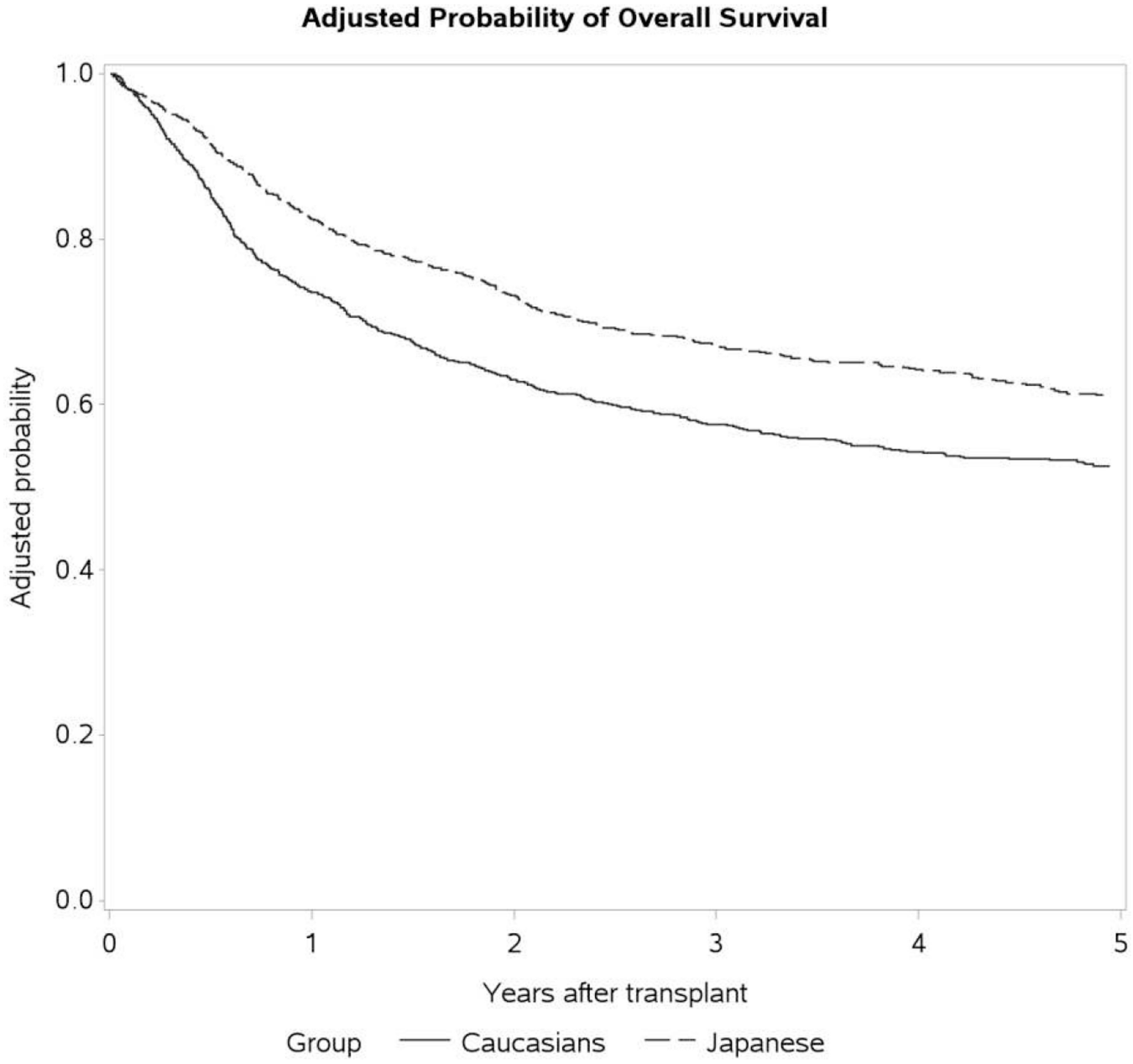


Figure 3.
Adjusted probability of disease-free (A) and overall survival (B)

Table 1

Patient-, donor-, and transplant-characteristics

Variable	NA Caucasian (n = 1300)	Japanese (n = 1352)	P-value
Median recipient age at transplant (range), years	45 (18–59)	38 (18–59)	<0.001
Recipient age at transplant, years			<0.001
18–29	229 (18)	342 (25)	
30–39	230 (18)	414 (31)	
40–49	417 (32)	354 (26)	
50–59	424 (33)	242 (18)	
Recipient sex			0.82
Male	729 (56)	764 (57)	
Female	571 (44)	588 (43)	
Karnofsky score			<0.001
90–100%	872 (67)	1138 (84)	
< 90%	380 (29)	208 (15)	
Missing	48 (4)	6 (<1)	
Stem cell source			<0.001
Bone marrow	165 (13)	717 (53)	
Peripheral blood	1135 (87)	635 (47)	
Disease risk prior to transplant			
AML			0.26
Early	565 (43)	506 (37)	
Intermediate	174 (13)	179 (13)	
ALL			<0.001
Early	238 (18)	472 (35)	
Intermediate	68 (5)	57 (4)	
CML			0.31
Early	179 (14)	90 (7)	
Intermediate	76 (6)	48 (4)	
Donor age, median	44 (8–75)	38 (11–67)	<0.001
Donor-recipient CMV status			<0.001
+/+	384 (30)	654 (48)	
+/−	159 (12)	110 (8)	
−/+	334 (26)	108 (8)	
−/−	390 (30)	95 (7)	
Missing	33 (3)	385 (28)	
Donor-recipient sex match			0.02
Male-Male	421 (32)	413 (31)	
Male-Female	311 (24)	310 (23)	
Female-Male	308 (24)	346 (26)	
Female-Female	260 (20)	273 (20)	
Missing	0	10 (<1)	

Variable	NA Caucasian (n = 1300)	Japanese (n = 1352)	P-value
Donor-recipient ABO match			<0.001
Match	854 (66)	750 (55)	
Minor mismatch	197 (15)	211 (16)	
Major mismatch	176 (14)	202 (15)	
Bidirectional mismatch	48 (4)	86 (6)	
Missing	25 (2)	103 (8)	
Conditioning regimen			<0.001
Cy + TBI	566 (44)	931 (69)	
Other TBI regimen	132 (10)	98 (7)	
Bu + Cy +/− other	466 (36)	258 (19)	
Other non TBI regimen	136 (10)	65 (5)	
GVHD prophylaxis			<0.001
TAC + MTX	642 (49)	84 (6)	
Other TAC based prophylaxis	238 (18)	7 (<1)	
CSA + MTX	343 (26)	1197 (89)	
Other CSA based prophylaxis	77 (6)	64 (5)	
Year of transplant			0.013
2000–2005	498 (38)	455 (34)	
2006–2011	802 (62)	897 (66)	
Country			
United States	1262 (97)	0	
Canada	38 (3)	0	
Japan	0	1352 (100)	
Median follow-up of survivors (range), months	52 (3–149)	49 (1–151)	

Abbreviations: AML, acute myelogenous leukemia; ALL, acute lymphoblastic leukemia; CML, chronic myelogenous leukemia; CMV, cytomegalovirus; Cy, cyclophosphamide; TBI, total body irradiation; Bu, busulfan; TAC, tacrolimus; MTX, methotrexate; CSA, cyclosporine.

Table 2

Multivariate analyses of grades II–IV or III–IV acute GVHD and chronic GVHD

		Number	HR	P value
Grades II–IV acute GVHD*				
Race	Caucasian	1298	1.00	Reference
	Japanese	1343	1.04 (0.87–1.24)	0.677
Graft	BM	876	1.00	Reference
	PBSC	1765	1.20 (1.02–1.42)	0.029
Grades III–IV acute GVHD†				
Race	Caucasian	1299	1.00	Reference
	Japanese	1342	0.75 (0.57–0.99)	0.042
Graft	BM	877	1.00	Reference
	PBSC	1764	1.57 (1.16–2.14)	0.004
Chronic GVHD††				
Race	Caucasian	1267	1.00	Reference
	Japanese (< 12 mos after HCT)	1324	0.85 (0.73–0.99)	0.037
	Japanese (≥ 12 mos after HCT)		0.33 (0.21–0.51)	<0.001
Graft	BM	866	1.00	Reference
	PBSC	1725	1.66 (1.45–1.91)	<0.001

BM, bone marrow; PBSC, peripheral blood stem cell; mos, months; HCT, hematopoietic cell transplantation

*Other significant variables used for adjustment were donor age and CMV match.

†Other significant variables used for adjustment were donor age and disease.

††Other significant variables used for adjustment were sex match, GVHD prophylaxis and year of transplant.

Table 3

Multivariate analyses of relapse, non-relapse mortality, death or relapse, and overall mortality

		Number	HR	P value
Relapse*				
Race	Caucasian	1281	1.00	Reference
	Japanese	1313	0.73 (0.61–0.87)	<0.001
Graft	BM	861	1.00	Reference
	PBSC	1733	1.00 (0.84–1.19)	0.999
Non-relapse mortality**				
Race	Caucasian	1281	1.00	Reference
	Japanese	1323	0.72 (0.55–0.93)	0.012
Graft	BM	862	1.00	Reference
	PBSC	1742	1.35 (1.07–1.71)	0.012
Death or relapse†				
Race	Caucasian	1281	1.00	Reference
	Japanese	1323	0.78 (0.68–0.89)	<0.001
Graft	BM	862	1.00	Reference
	PBSC	1742	1.09 (0.94–1.25)	0.253
Overall mortality††				
Race	Caucasian	1300	1.00	Reference
	Japanese	1352	0.72 (0.60–0.85)	<0.001
Graft	BM	882	1.00	Reference
	PBSC	1770	1.18 (1.01–1.37)	0.038

BM, bone marrow; PBSC, peripheral blood stem cell

*Other significant variables used for adjustment were ABO match, conditioning, disease, sex match, and KPS.

**Other significant variables used for adjustment were recipient age, conditioning, sex match, GVHD prophylaxis, KPS, year of transplant, and disease.

†Other significant variables used for adjustment were recipient age, disease, KPS, and recipient sex.

††Other significant variables used for adjustment were recipient age, conditioning, disease, GVHD prophylaxis, KPS, recipient sex, and year of transplant.