



FULL-LENGTH ARTICLE

Translational Research

Advantages of peripheral blood stem cells from unrelated donors versus bone marrow transplants in outcomes of adult acute myeloid leukemia patients



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ARTICLE INFO

Article History:

Received 9 February 2022

Accepted 20 May 2022

Keywords:

acute myeloid leukemia
 peripheral blood stem cell transplantation
 unrelated donors

ABSTRACT

Background aims: In allogeneic stem cell transplantation, unrelated donors are chosen in cases where appropriate related donors are not available. Peripheral blood stem cells (PBSCs) are more often selected as a graft source than bone marrow (BM). However, the prognostic benefits of PBSCs versus BM transplants from unrelated donors have not been carefully examined in patients with acute myeloid leukemia (AML). This study compared outcomes of adult AML patients who underwent unrelated PBSC and BM transplantation, evaluating post-transplant complications, including engraftment, graft-versus-host disease (GVHD) and infections, and determined subgroups of patients who are most likely to benefit from unrelated PBSCs compared with BM transplants.

Methods: The authors analyzed 2962 adult AML patients who underwent unrelated PBSC or BM transplants between 2011 and 2018 (221 PBSC and 2741 BM) using the Japanese nationwide registry database, in which graft source selection is not skewed toward PBSCs.

Results: In 49.7% of patients, disease status at transplantation was first complete remission (CR1). In 57.1% of cases, HLA-matched donors were selected. Myeloablative conditioning was performed in 75.1% of cases, and anti-thymocyte globulin (ATG) was added to conditioning in 10.5%. Multivariate analyses showed a trend toward favorable non-relapse mortality (NRM) in PBSC recipients compared with BM recipients (hazard ratio

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<https://doi.org/10.1016/j.jcyt.2022.05.009>

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[HR], 0.731, $P = 0.096$), whereas overall survival (OS) (HR, 0.959, $P = 0.230$) and disease-free survival (DFS) (HR, 0.868, $P = 0.221$) were comparable between PBSC and BM recipients. Although the rate of chronic GVHD (cGVHD) was significantly higher in PBSC patients (HR, 1.367, $P = 0.016$), NRM was not increased, mainly as a result of significantly reduced risk of bacterial infections (HR, 0.618, $P = 0.010$), reflecting more prompt engraftments in PBSC recipients. Subgroup analyses revealed that PBSC transplantation was advantageous in patients transplanted at CR1 and in those without ATG use. PBSC recipients experienced significantly better OS and/or DFS compared with BM recipients in this patient group.

Conclusions: The authors' results confirmed the overall safety of unrelated PBSC transplantation for adult AML patients and suggested an advantage of PBSCs, especially for those in CR1. Further optimization of the prophylactic strategy for cGVHD is required to improve the overall outcome in transplantation from unrelated PBSC donors.

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Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) can be a curative treatment for patients with hematological malignancies, including acute leukemia and malignant lymphoma [1]. Unrelated donors are chosen when appropriate related donors are not available [2]. Currently, according to reports from the Center for International Blood and Marrow Transplant Research and the European Society of Blood and Marrow Transplantation, peripheral blood stem cells (PBSCs) are more often selected than bone marrow (BM) as a graft source in such cases [3–5]. Such a trend toward PBSCs in graft source selection is mainly due to less invasive procedures and more flexible harvest schedules for donors of PBSCs compared with BM [6,7].

Thus, PBSCs are more often selected as a “donor-friendly” graft source in cases of unrelated allo-HSCT, but this selection preference should be revisited from the viewpoint of post-transplant outcomes in recipients [8]. Although the multicenter randomized trial from the Blood and Marrow Transplant Clinical Trials Network indicated non-significant differences in survival, non-relapse mortality (NRM) and relapse between PBSCs and BM in the whole cohort of patients with various hematological malignancies [4], such prognostic similarities between the two sources of graft could differ depending on the underlying disease [9], and further information is required on the superiority or inferiority of PBSCs over BM based on the underlying disease. Acute myeloid leukemia (AML) should be analyzed with priority because this is the most prevalent disease worldwide with an indication for unrelated HSCT [5,10]. As previous observations have suggested a higher risk of chronic graft-versus-host disease (cGVHD) in unrelated PBSC versus BM recipients, we are now taking more intensive measures to prevent cGVHD as well as acute GVHD (aGVHD) and to treat it earlier than before. In addition, the advent of novel targeted therapeutics for GVHD [11,12] as well as novel antimicrobials [13] can further reduce the incidence of GVHD and serious infections. Such changes in clinical practice can potentially modify transplantation outcomes.

Thus, the impact of using unrelated PBSCs versus BM as a graft source on patient outcomes should be updated. Moreover, the severity of adverse events can vary widely depending on patient-specific characteristics, such as disease status, conditioning regimens and HLA type. It is time to evaluate whether there are specific subgroups of patients who can benefit from PBSC or BM transplants in clinical practice.

Therefore, the authors performed a retrospective cohort study to (i) compare outcomes of adult patients with AML who underwent unrelated PBSC and BM transplantation; (ii) evaluate post-transplant complications, including engraftment, GVHD and infections; and (iii) identify subgroups of patients who are most likely to benefit from unrelated PBSC compared with BM transplantation. In this study, the authors used the Japanese nationwide transplant registry. In Japan, the number of unrelated donor PBSC transplants is still low [14] but has gradually increased since 2010, when the Japan Marrow Donor Program started facilitating PBSC transplantation from unrelated donors [15]; thus, the authors were able to make legitimate

comparisons between PBSC and BM recipients in real-world cohorts. Such comparisons are almost impossible outside the framework of clinical trials in US and European cohorts because the standard sources of unrelated donors are PBSC grafts [3,5], and BM is selected in only a minor proportion of cases. The authors' findings provide valuable insights into the donor selection algorithm (PBSCs versus BM) in unrelated allo-HSCT for adult AML patients and should contribute to improvements in transplantation outcomes.

Methods

Patients

Data on adult patients (aged ≥ 16 years) with AML who had undergone their first allogeneic PBSC or BM transplant from unrelated donors between 2011 and 2018 were identified through the Transplant Registry Unified Management Program sponsored by the Japanese Society for Transplantation and Cellular Therapy [16,17]. Patients without survival data or with HLA mismatches at three or more loci were excluded. The study was planned by the Adult AML Working Group of the Japanese Society for Transplantation and Cellular Therapy, approved by the data management committees of the Transplant Registry Unified Management Program and the institutional review board of Kyoto University Hospital and conducted in accordance with the Declaration of Helsinki.

Study endpoints and definitions

The primary endpoint was overall survival (OS) after transplantation. Death, regardless of cause, was considered an event. Secondary endpoints were disease-free survival (DFS); cumulative incidence of relapse; NRM; neutrophil and platelet engraftment; aGVHD; cGVHD; GVHD relapse-free survival (GRFS); viral, bacterial and fungal infection; and infection-related mortality. DFS was defined as survival without disease progression or relapse. aGVHD and cGVHD were assessed according to standard criteria [18,19]. GRFS was defined as survival without death, relapse, development of grade III–IV aGVHD or development of cGVHD that required systemic treatment [20]. Neutrophil and platelet engraftment was defined as the first three consecutive measures with a neutrophil count $\geq 0.5 \times 10^9/L$ and a platelet count $\geq 50 \times 10^9/L$ without platelet transfusion after transplantation. Viral infection included infections with cytomegalovirus; Epstein–Barr virus, including Epstein–Barr virus post-transplant lymphoproliferative disorder; and human herpesvirus 6. Bacterial infection included any bacterial infection, excluding febrile neutropenia without proven infection. Fungal infection included candidemia; proven, probable or possible aspergillosis with previously reported criteria [21]; and other proven fungal infections. Infection-related mortality was defined as death from infection as the primary cause of death. Cytogenetic risk was classified in accordance with criteria specified by the National Comprehensive Cancer Network guidelines, which have been described in detail elsewhere [22]. Conditioning

intensity was defined according to operational definitions of the National Marrow Donor Program/Center for International Blood and Marrow Transplant Research [23]. HLA matching was assessed using allele data for the HLA-A, -B, -C and -DRB1 loci [24]. HLA mismatch was defined in the GVHD vector when recipient alleles were not shared by the donor and was defined in the host-versus-graft direction when donor alleles were not shared by the recipient.

Propensity score matching

Propensity score was calculated to evaluate the intention to use PBSCs. Propensity score matching analysis accounted for patient age at the time of transplantation (<50 or ≥50 years), sex (male or female), Eastern Cooperative Oncology Group performance status (ECOG PS) (0–1 or 2–4), cytogenetic risk (favorable, intermediate, poor or unevaluable), disease status at transplantation (first complete remission [CR1], second complete remission [CR2], ≥3 complete remission [CR3] or non-complete remission [non-CR]), donor age (<40 or ≥40), donor–sex mismatch (matched, female to male or male to female), HLA mismatches (0, 1 or 2), intensity of the conditioning (myeloablative conditioning or reduced intensity conditioning), use of total body irradiation (TBI) (no or yes), GVHD prophylaxis (cyclosporin A-based or tacrolimus-based), addition of anti-thymocyte globulin (ATG) to conditioning (no or yes) and year of transplantation (2011–2014 or 2015–2018). Matching (1:1) was performed using the nearest neighbor matching method with a caliper width fixed at 0.2 standard deviations of the propensity score.

Statistical analysis

Categorical variables and continuous variables were compared between groups with Fisher exact test and two-tailed unpaired Student's *t*-test, respectively. The probabilities of OS and DFS were estimated according to the Kaplan–Meier method and compared among groups with the Cox proportional hazards model. Probabilities of NRM; relapse; engraftment; aGVHD; cGVHD; viral, bacterial or fungal infection; and infection-related mortality were estimated on the basis of cumulative incidence methods and compared among groups with the Fine–Gray proportional hazards model, considering death without relapse as a competing event for relapse, relapse as a competing event for NRM, death without engraftment as a competing event for neutrophil and platelet engraftment, death or relapse without GVHD as a competing event for aGVHD and cGVHD and death without infection as a competing event for infection and infection-related mortality. The following variables were considered in multivariate analyses: patient age at the time of transplantation, sex, ECOG PS, cytogenetic risk, disease status at the time of transplantation, donor age, donor–sex mismatch, HLA mismatches, intensity of conditioning, use of TBI, GVHD prophylaxis, addition of ATG to conditioning regimen and year of transplantation. All tests were two-sided, and $P < 0.05$ was considered statistically significant. All analyses were performed with Stata 17 software (StataCorp LLC, College Station, TX, USA).

Results

Patient characteristics

A total of 2962 patients were eligible for analysis. Of these, 221 underwent unrelated PBSC transplantation (PBSC group), and 2741 received unrelated BM transplantation (BM group). Patient characteristics, including transplant procedures, are shown in Table 1. Median patient age was 53 years (range, 16–69) for the PBSC group and 53 years (range, 16–76) for the BM group. ECOG PS at time of HSCT and cytogenetic risk at initial diagnosis were equivalent between the groups. Disease status at time of HSCT was CR1 in 49.7% of the whole

cohort, and no significant differences were observed according to graft source ($P = 0.248$). With regard to donors, distribution of donor age and recipient–donor–sex disparities were comparable between the PBSC and BM groups. By contrast, HLA matching showed significant differences, with HLA-matched donors selected in 70.1% of the PBSC group but in only 56.1% of the BM group ($P < 0.001$). Conditioning regimens were composed of myeloablative conditioning in 75.1% of the whole cohort (no statistical difference between PBSC and BM), and TBI was more frequently used in the BM group (45.2% versus 61.8%, $P < 0.001$). Regarding GVHD prophylaxis, PBSC patients were more likely to receive tacrolimus-based prophylaxis (95.0% versus 87.2%, $P < 0.001$) and ATG (25.3% versus 9.3%, $P < 0.001$) than were BM recipients. Median follow-up of survivors in the PBSC and BM groups was 1.6 years and 3.4 years, respectively.

PBSC recipients demonstrated a lower incidence of NRM than BM recipients

Respective 3-year OS and DFS rates were 57.5% and 51.6% in the PBSC group and 52.4% and 48.3% in the BM group (Figure 1A,B). Multivariate analyses revealed that OS (hazard ratio [HR], 0.859, $P = 0.230$) and DFS (HR, 0.868, $P = 0.221$) in the PBSC group were not inferior to those in the BM group (Table 2, Figure 1A,B; also see supplementary Table 1). Respective 3-year cumulative incidences of NRM and relapse were 17.9% and 30.6% in the PBSC group and 22.6% and 29.1% in the BM group (Figure 1C,D). Multivariate analyses revealed a trend toward a lower incidence of NRM in the PBSC group (HR, 0.731, $P = 0.096$), whereas the incidence of relapse was comparable between the PBSC and BM groups (HR, 0.978, $P = 0.872$) (Table 2, Figure 1C,D; also see supplementary Table 1). These results indicated that unrelated PBSC transplantation is at least safe for adult AML patients, with suggestions of a more favorable trend regarding NRM.

PBSC recipients demonstrated fewer infection-related complications but higher incidence of cGVHD than BM recipients

Next, the authors performed detailed analyses focusing on post-transplant engraftment and complications. The cumulative incidences of neutrophil engraftment at day 30 and platelet engraftment at day 60 were both significantly higher in the PBSC group than in the BM group (95.9% versus 93.1%, HR, 2.109, $P < 0.001$, and 84.6% versus 73.9%, HR, 1.920, $P < 0.001$), and the time between HSCT and engraftment was significantly shorter in the PBSC group (Figure 2A,B). Among patients who achieved engraftment, secondary graft failure was significantly less frequent in the PBSC group than in the BM group (0.9% versus 3.4%, $P = 0.044$), suggesting robust engraftment in the PBSC group.

With regard to GVHD, the respective cumulative incidence of grade II–IV and III–IV aGVHD at 100 days in the PBSC group was comparable to that in the BM group (31.5% versus 37.4%, HR, 0.890, $P = 0.369$, 7.4% versus 10.8%, HR, 0.875, $P = 0.586$) (Figure 2C,D; also see supplementary Table 2). By contrast, the respective cumulative incidence of cGVHD and extensive cGVHD at 2 years was significantly higher in the PBSC group than in the BM group (39.8% versus 31.4%, HR, 1.367, $P = 0.016$, 24.9% versus 18.5%, HR, 1.450, $P = 0.025$) (Figure 2E,F; also see supplementary Table 2). Three-year GRFS was comparable between the PBSC and BM groups (32.0% versus 31.3%, adjusted HR, 0.975, 95% confidence interval, 0.809–1.174, $P = 0.789$), suggesting that the higher incidence of cGVHD did not lead to decreased GRFS.

As regards infection-related complications, the cumulative incidence of bacterial infection at day 100 was significantly lower in the PBSC group than in the BM group (13.4% versus 20.4%, HR, 0.618, $P = 0.010$) (Figure 2G). The lower incidence of bacterial infection in the PBSC group accounted for the significantly lower cumulative incidence of infection-related mortality in this group (2.5% versus 7.5%,

Table 1
Patient characteristics.

	Total (N = 2962)	PBSC (N = 221)	BM (N = 2741)	P value
Patient age, years, median (range)	53 (16–76)	53 (16–69)	53 (16–76)	0.050
Patient age, years, n (%)				
<50	1252 (42.3)	83 (37.6)	1169 (42.6)	0.157
≥50	1710 (57.7)	138 (62.4)	1572 (57.4)	
Patient sex, n (%)				0.046*
Male	1752 (59.1)	145 (65.6)	1607 (58.6)	
Female	1209 (40.8)	76 (34.4)	1133 (41.3)	
ECOG PS, n (%)				0.168
0–1	2753 (92.9)	211 (95.5)	2542 (92.7)	
2–4	205 (6.9)	10 (4.5)	195 (7.1)	
Cytogenetic risk, n (%)				0.610
Favorable	351 (11.9)	20 (9.0)	331 (12.1)	
Intermediate	1833 (61.9)	143 (64.7)	1690 (61.7)	
Poor	613 (20.7)	46 (20.8)	567 (20.7)	
Unevaluable	165 (5.6)	12 (5.4)	153 (5.6)	
Disease status, n (%)				0.248
CR1	1472 (49.7)	112 (50.7)	1360 (49.6)	
CR2	495 (16.7)	34 (15.4)	461 (16.8)	
≥CR3	27 (0.9)	5 (2.3)	22 (0.8)	
Non-CR	967 (32.6)	70 (31.7)	897 (32.7)	
Donor age, years, median (range)	39 (19–55)	39 (19–55)	39 (19–55)	0.516
Donor age, years, n (%)				0.484
<40	1567 (52.9)	113 (51.1)	1454 (53.0)	
≥40	1367 (46.2)	108 (48.9)	1259 (45.9)	
Sex mismatch, n (%)				0.813
Matched	1729 (58.4)	134 (60.6)	1595 (58.2)	
Female to male	425 (14.3)	30 (13.6)	395 (14.4)	
Male to female	792 (26.7)	56 (25.3)	736 (26.9)	
HLA mismatch, ABCDE genotype, total, n (%)				< 0.001
0	1692 (57.1)	155 (70.1)	1537 (56.1)	
1	1046 (35.3)	57 (25.8)	989 (36.1)	
2	224 (7.6)	9 (4.1)	215 (7.8)	
Conditioning, n (%)				0.936
Myeloablative	2223 (75.1)	167 (75.6)	2056 (75.0)	
Reduced intensity	738 (24.9)	54 (24.4)	684 (25.0)	
TBI, n (%)				< 0.001
No	1166 (39.4)	121 (54.8)	1045 (38.1)	
Yes	1795 (60.6)	100 (45.2)	1695 (61.8)	
GVHD prophylaxis, n (%)				< 0.001
Tac-based	2600 (87.8)	210 (95.0)	2390 (87.2)	
CyA-based	309 (10.4)	8 (3.6)	301 (11.0)	
Addition of ATG to conditioning regimen, n (%)	311 (10.5)	56 (25.3)	255 (9.3)	< 0.001
Years of transplant, n (%)				< 0.001
2011–2014	1555 (52.5)	36 (16.3)	1519 (55.4)	
2015–2018	1407 (47.5)	185 (83.7)	1222 (44.6)	

CyA, cyclosporin A; Tac, tacrolimus.

HR, 0.307, $P = 0.019$) (Table 3, Figure 2H). There was no significant difference in the cumulative incidence of viral or fungal infections between the PBSC and BM groups (see supplementary Figure 1A,B). These results suggested that the reduced risk of bacterial infection, possibly reflecting the more prompt and stable engraftment in the PBSC group, resulted in the lower NRM observed in this group, whereas the higher incidence of cGVHD did not cause increased mortality after transplantation.

PBSC is clearly beneficial for patients with CR1 at transplantation and may improve DFS in patients on non-ATG regimens

To identify the subgroup of patients who clearly benefit from PBSCs rather than BM transplantation, the authors performed subgroup analyses of OS (Figure 3). Significantly favorable effects of PBSCs over BM on OS were observed in the patient subgroup with CR1 at transplantation (HR, 0.624, $P = 0.030$) and conditioning regimens without ATG (HR, 0.743, $P = 0.037$).

In patients with CR1 at transplantation, PBSCs were significantly associated with favorable 3-year OS and DFS (73.9% versus 61.7%, HR, 0.551, $P = 0.011$, 70.9% versus 57.3%, HR, 0.546, $P = 0.005$,

respectively) (Figure 4A,B) as well as marginally reduced risk of NRM (HR, 0.570, $P = 0.058$) and relapse (HR, 0.612, $P = 0.106$) compared with BM patients (Figure 4C,D). By contrast, PBSC transplantation offered no advantage to patients with CR2 or more advanced-stage disease (non-CR or ≥CR3) compared with BM transplantation (see supplementary Figure 2A–D).

The authors observed greater DFS (HR, 0.761, $P = 0.043$) in PBSC transplant recipients in comparison with BM in patients on non-ATG regimens as well as comparable NRM (HR, 0.706, $P = 0.093$), whereas the incidence of relapse was similar between the two groups (HR, 0.863, $P = 0.383$). These effects were not apparent in patients who received conditioning with ATG (Figure 4E–H; also see supplementary Figure 2E–H). This may be partially explained by the fact that adding ATG to the conditioning regimen had no beneficial effect on the risk of grade II–IV aGVHD (HR, 1.502, $P = 0.222$) and was associated with a tendency toward increased risk of relapse (HR, 1.691, $P = 0.094$) in PBSC transplantation. As a result, ATG was associated with worse OS (HR, 1.737, $P = 0.084$) and significantly worse DFS (HR, 1.773, $P = 0.042$) in PBSC recipients (see supplementary Table 3). In contrast to the PBSC group, in the BM group, ATG significantly reduced the cumulative risk of grade II–IV aGVHD (HR, 0.662,

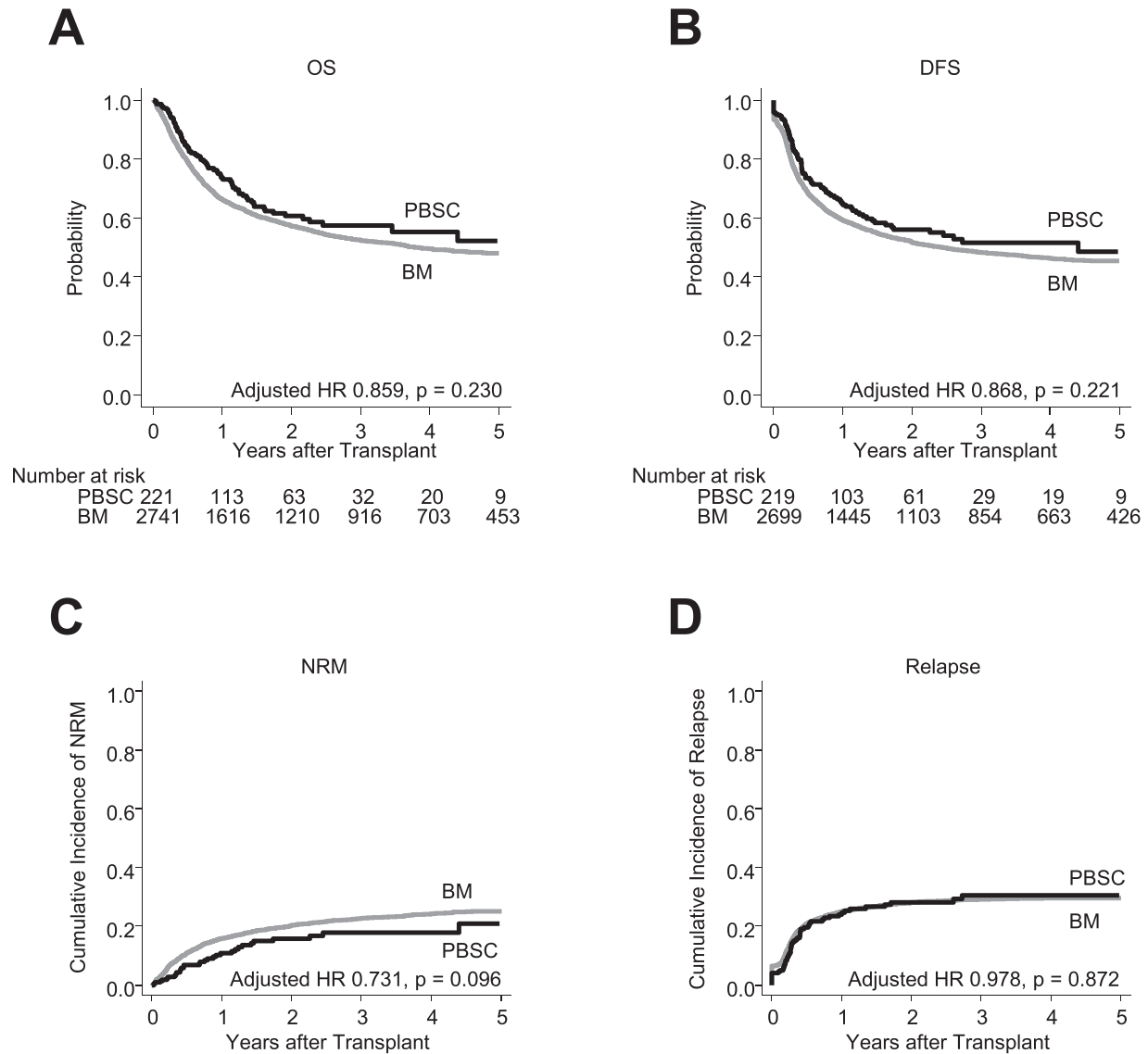


Fig. 1. Comparison of outcomes between unrelated PBSC and BM transplants in the whole cohort. (A) OS. (B) DFS. (C) Cumulative incidence of NRM. (D) Cumulative incidence of relapse. HRs and P values were calculated using the Cox proportional hazards model (A,B) and Fine–Gray tests (C,D) after being adjusted for confounding factors.

$P = 0.001$) and NRM (HR, 0.645, $P = 0.007$), which resulted in significantly better OS (HR, 0.774, $P = 0.014$) and comparable DFS (HR, 0.824, $P = 0.054$).

These results suggested that PBSCs from unrelated donors should be considered for adult AML patients in CR1 or those transplanted without ATG instead of BM. There were no patient subgroups in which PBSCs were associated with significantly worse OS than BM. Of note, HLA mismatch and conditioning intensity did not obviously interact with the graft source with regard to survival as well as risk of GVHD, NRM and relapse (Figure 3; also see supplementary Figure 3A–H)

Propensity score matching analyses confirmed the advantage of PBSCs over BM transplantation for adult AML patients

To confirm the superiority of unrelated PBSC transplantation for adult AML patients indicated by the subgroup analyses, the authors performed a propensity score matching analysis. A total of 201 PBSC recipients were pair-matched with 201 BM recipients (see supplementary Table 4). The propensity score analysis (Figure 5A–D; also see supplementary Figure 4A–H) showed a trend toward better 3-year OS (58.4% versus 51.0%, HR, 0.764, $P = 0.102$) and 3-year DFS

(55.3% versus 45.6%, HR, 0.763, $P = 0.077$) and a lower 3-year NRM rate (17.8% versus 24.8%, HR, 0.658, $P = 0.080$) in the PBSC group than in the BM group (Figure 5A–C). Three-year cumulative incidence of relapse was similar between the PBSC and BM groups (27.0% versus 29.6%, HR, 0.885, $P = 0.533$) (Figure 5D). In analysis of the propensity score-matched cohort, PBSCs in CR1 were associated with significantly better OS and DFS as well as significantly lower NRM and a marginally lower relapse rate, but not in those transplanted at more advanced stages (see supplementary Figure 4A–D). Trends for better OS and DFS as well as lower NRM and relapse rate in the PBSC group were also observed in patients transplanted without ATG, although the difference was not statistically significant (see supplementary Figure 4E–H). These results were consistent with those observed in the whole cohort, confirming the efficacy of unrelated PBSC transplantation in adult AML patients, especially those in CR1.

Discussion

Using the Japanese nationwide registry database, the present retrospective cohort study analyzed outcome differences between PBSCs from unrelated donors and BM transplantation in adult AML patients. There were three major findings. First, there was a favorable

Table 2

Multivariate analysis for OS, DFS, NRM and relapse.

		OS			DFS			NRM			Relapse		
		HR	(95% CI)	P value	HR	(95% CI)	P value	HR	(95% CI)	P value	HR	(95% CI)	P value
Graft source	PBSC versus BM	0.859	(0.670–1.101)	0.230	0.868	(0.691–1.089)	0.221	0.731	(0.505–1.058)	0.096	0.978	(0.745–1.284)	0.872
Patient age	≥50 versus <50	1.538	(1.357–1.743)	< 0.001	1.336	(1.185–1.506)	< 0.001	1.823	(1.511–2.199)	< 0.001	0.933	(0.794–1.097)	0.402
Patient sex	Female versus male	0.809	(0.681–0.960)	0.016	0.846	(0.718–0.998)	0.047	0.681	(0.520–0.893)	0.005	1.118	(0.899–1.389)	0.316
Performance status	2–4 versus 0–1	2.382	(1.995–2.843)	< 0.001	1.943	(1.631–2.314)	< 0.001	1.802	(1.338–2.427)	< 0.001	1.223	(0.958–1.561)	0.105
Cytogenetic risk	Intermediate versus favorable	1.372	(1.111–1.694)	0.003	1.329	(1.085–1.628)	0.006	1.279	(0.958–1.708)	0.095	1.257	(0.955–1.653)	0.102
	Poor versus favorable	2.295	(1.828–2.882)	< 0.001	2.259	(1.814–2.812)	< 0.001	1.130	(0.810–1.576)	0.473	2.414	(1.799–3.239)	< 0.001
	Unevaluable versus favorable	1.539	(1.128–2.100)	0.007	1.552	(1.153–2.090)	0.004	1.114	(0.706–1.757)	0.643	1.705	(1.147–2.533)	0.008
Disease status	CR2 versus CR1	0.997	(0.828–1.200)	0.974	0.991	(0.829–1.184)	0.918	0.906	(0.713–1.152)	0.420	1.055	(0.822–1.357)	0.680
	≥CR3 versus CR1	2.539	(1.507–4.278)	< 0.001	2.227	(1.345–3.689)	0.002	2.003	(1.015–3.955)	0.045	1.897	(0.896–4.015)	0.094
	Non-CR versus CR1	2.354	(2.084–2.659)	< 0.001	2.525	(2.246–2.838)	< 0.001	0.970	(0.801–1.174)	0.754	3.308	(2.826–3.872)	< 0.001
Donor age	≥40 versus <40	1.190	(1.065–1.330)	0.002	1.192	(1.071–1.326)	0.001	1.317	(1.117–1.552)	0.001	0.996	(0.862–1.151)	0.955
Sex mismatch	Female to male versus matched	1.031	(0.881–1.207)	0.701	1.023	(0.879–1.192)	0.765	1.008	(0.800–1.271)	0.946	1.060	(0.866–1.298)	0.571
	Male to female versus matched	1.086	(0.899–1.312)	0.391	1.044	(0.871–1.251)	0.642	1.359	(1.014–1.820)	0.040	0.815	(0.640–1.037)	0.096
HLA mismatch	1 versus 0	1.128	(1.001–1.272)	0.049	1.113	(0.992–1.248)	0.068	1.414	(1.189–1.680)	< 0.001	0.855	(0.730–1.002)	0.052
	2 versus 0	1.380	(1.133–1.681)	0.001	1.404	(1.162–1.696)	< 0.001	1.733	(1.288–2.330)	< 0.001	0.985	(0.757–1.282)	0.912
Conditioning	RIC versus MAC	0.997	(0.872–1.139)	0.965	1.083	(0.953–1.230)	0.221	1.032	(0.848–1.257)	0.753	1.112	(0.931–1.328)	0.241
TBI	Yes versus no	1.083	(0.964–1.217)	0.180	1.063	(0.951–1.189)	0.281	1.012	(0.852–1.201)	0.896	1.082	(0.930–1.260)	0.307
GVHD prophylaxis	Tac-based versus CyA-based	0.723	(0.610–0.857)	< 0.001	0.803	(0.680–0.947)	0.009	0.742	(0.578–0.952)	0.019	1.010	(0.794–1.285)	0.934
ATG	Yes versus no	0.837	(0.692–1.012)	0.066	0.902	(0.752–1.081)	0.264	0.655	(0.484–0.886)	0.006	1.212	(0.961–1.528)	0.104
Years of transplant	2015–2018 versus 2011–2014	1.042	(0.926–1.172)	0.499	1.048	(0.937–1.173)	0.413	0.997	(0.843–1.179)	0.969	0.978	(0.840–1.137)	0.769

CI, confidence interval; CyA, cyclosporin A; MAC, myeloablative conditioning; RIC, reduced intensity conditioning; Tac, tacrolimus.

NRM as well as non-inferior OS and DFS in PBSC recipients compared with BM recipients. Second, more rapid engraftment resulted in significantly lower mortality caused by bacterial infection despite a higher incidence of cGVHD with PBSCs. Third, PBSCs were associated with significantly better OS and DFS compared with BM in patients transplanted in CR1, suggesting an advantage of PBSCs over BM for these patient subgroups.

Importantly, the authors found that OS, DFS, NRM and relapse in Japanese patients after unrelated transplantation with PBSCs were not inferior to those after unrelated transplantation with BM. These results are compatible with previous reports from US and European cohorts [4,8,25], but fair real-world comparisons are guaranteed in this study using a Japanese cohort because the prevalence of PBSCs is still low [14]. In the US and Europe, PBSCs are the standard selection, and BM is selected only in special clinical situations, including donor health issues [26]; thus, such a comparison between PBSCs and BM is no longer possible.

The favorable outcomes of PBSCs compared with BM in unrelated HSCT observed in this study contrast with significantly inferior outcomes for PBSCs relative to BM in related HSCT in a Japanese cohort [27]. This discrepancy may be partly explained by the biased donor selection in the related HSCT setting, as PBSC grafts are more often used for patients with high-risk HSCT in donor coordination.

Cryopreservation-available PBSC grafts from related donors are often selected for patients with chemorefractory disease or those with severe infection [27,28].

Regarding engraftment, the authors' study demonstrates that there is an advantage provided by faster neutrophil recovery that results in reduced risk of bacterial infection in unrelated PBSC transplantation, which is consistent with previous reports [29]. Moreover, the authors found that the decrease in bacterial infections actually led to a significant reduction in infection-related death (Figure 2H); thus, an advantage in engraftment is one of the reasons for superior OS with lower NRM in PBSCs compared with BM. Indeed, the effect of PBSCs in lowering the odds ratio of NRM was more prominent in the early phase—where infection-related death accounts for the majority of NRM—than the later phase after transplantation (odds ratio, 0.368 at day 100 and 0.630 at 2 years). Furthermore, the authors speculate that bacterial infection in the early days after allo-HSCT has a significant impact on the post-transplant prognosis that goes beyond the infection itself, as severe infections along with concurrent cytokine storms can enhance various inflammation-related complications, including hemophagocytic syndrome, engraftment failure, thrombotic microangiopathy, sinusoidal obstruction syndrome and aGVHD [30–33].

With regard to adverse events with long-term follow-up, the authors' study confirmed the significantly higher incidence of cGVHD

in the PBSC cohort versus the BM cohort, and this result was compatible with previous reports from US and European cohorts [4,9,34]. In the Japanese cohort, the incidence of both aGVHD and cGVHD was lower compared with Western cohorts—probably due to less diverse ethnicity in Japan [35]—but the difference between PBSCs and BM with respect to cGVHD was recapitulated in the authors' cohort. Although there was a higher incidence of cGVHD among PBSC

recipients in this study, reduction in OS or DFS was not observed compared with BM recipients. The effects of cGVHD on quality of life should be further evaluated because long-term follow-up of a randomized clinical trial has shown that unrelated PBSCs result in a higher burden of cGVHD symptoms than BM [36].

The third major finding of the authors' study derived from the subgroup analyses was that PBSCs were associated with

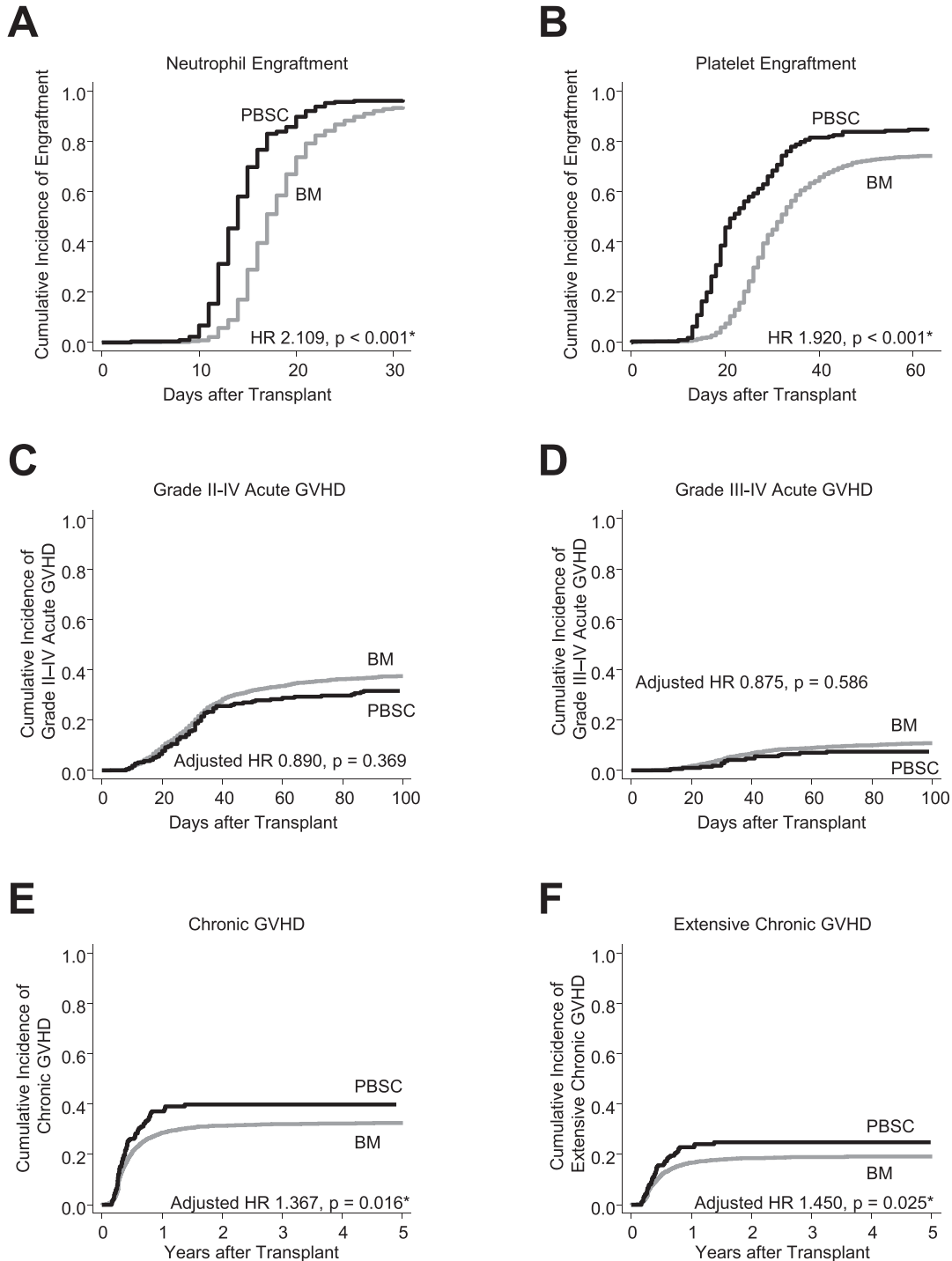


Fig. 2. Comparison of engraftment and post-transplant complications between unrelated PBSC and BM transplants in the whole cohort. (A) Cumulative incidence of neutrophil engraftment. (B) Cumulative incidence of platelet engraftment. (C) Cumulative incidence of grade II–IV aGVHD. (D) Cumulative incidence of grade III–IV aGVHD. (E) Cumulative incidence of cGVHD. (F) Cumulative incidence of extensive cGVHD. (G) Cumulative incidence of bacterial infection. (H) Cumulative incidence of infection-related mortality. HRs and P values were calculated using Fine–Gray tests (A–H) and adjusted for confounding factors (C–F). $^*P < 0.05$.

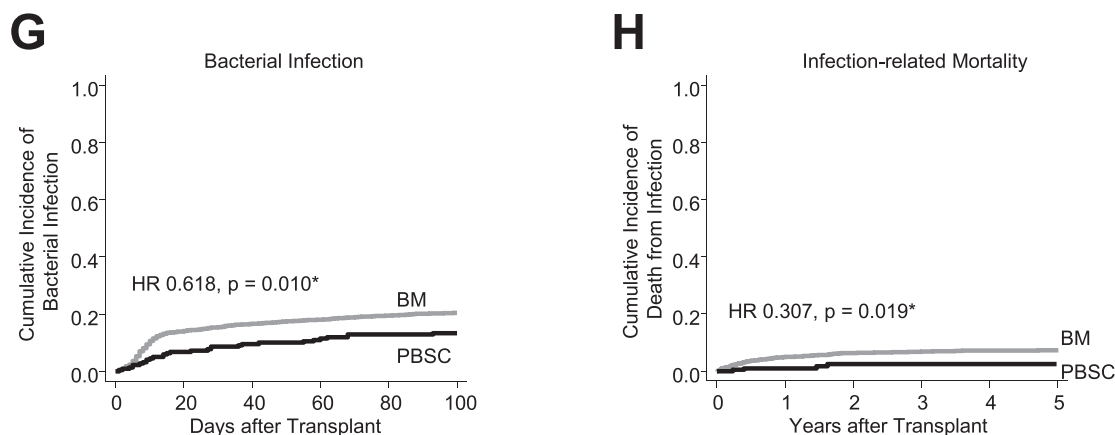


Fig. 2. Continued.

statistically better OS and DFS as well as reduced relapse compared with BM in patients transplanted at CR1, but not at more advanced stages (CR2 or later). The significantly lower risk of relapse in CR1 patients may reflect the presence of stronger graft-versus-leukemia (GVL) effects in PBSC versus BM transplants [37]. GVL effects are generally stronger with PBSCs than BM because of the relatively higher number of infused donor-derived cytotoxic T cells at transplantation. Such enhanced GVL effects can reduce the incidence of relapse most effectively in patient subgroups in which the incidence of post-transplant relapse is relatively low [38,39]. By contrast, it is difficult to observe GVL effects when HSCT is performed in patients with advanced-stage disease without remission and/or with more unfavorable conditions after long-term, repetitive, intensive chemotherapy as well as infectious episodes [40]. However, the authors were still able to observe tendencies for improved outcomes with PBSCs in those transplanted at CR2, although not in those at \geq CR3 or non-CR.

In addition, positive effects of PBSCs were observed only in subgroups without the use of ATG. Here the addition of ATG was associated with a reduced risk of aGVHD in BM recipients (see supplementary Table 3), and this observation was compatible with previous reports [41,42]. Administration of ATG with PBSCs can reduce both aGVHD and cGVHD [43–46], but at the same time, it can also induce severe infections and post-transplant lymphoproliferative disorders and increase the incidence of relapse by reducing GVL effects [43,44,47]. As a result, overall, ATG does not always improve NRM or survival [43,45,48,49] and can even reduce OS [50]. The authors' study suggests that these negative impacts of ATG can be observed more in PBSC patients than in BM patients. Differences in the effects of ATG on cGVHD between previous randomized studies and this study were at least partly due to differences in the types of ATG preparations administered as well as the doses and ethnicities involved. In addition, this study included various transplantation protocols with different indications for and administration schedules of ATG in different centers. Although among PBSC recipients the proportion of patients who received ATG was higher in recipients transplanted from HLA-mismatched donors than in those transplanted from HLA-matched donors, ATG use did not improve OS in either the HLA-matched or -mismatched group (see supplementary Figure 5; see supplementary Table 1), suggesting that the negative effects of ATG observed in the PBSC group may not be attributable solely to the HLA disparity. Given that a larger proportion of PBSC recipients in the authors' cohort underwent transplantation with ATG than BM recipients (Table 1; also see supplementary Table 5), wider use of ATG in PBSC recipients may offset the benefits of ATG. Indeed, a previous

study reported that absolute lymphocyte count before administration of ATG can affect the incidence of cGVHD and relapse after unrelated HSCT from PBSC donors [51]. Therefore, more refined indications as well as optimal ATG administration protocols for GVHD prophylaxis in unrelated PBSC transplantation should be determined in future studies.

None of the patient subgroups were related to the graft source in the authors' study. It is especially notable that HLA status (matched versus mismatched) and conditioning regimen (myeloablative versus reduced intensity) did not interact with the graft source with respect to outcomes, which is in agreement with previous reports [52,53]. Thus, the authors' data support the use of unrelated PBSC grafts for adult AML patients irrespective of HLA status and conditioning regimen.

Although the strengths of the study include its restriction to a single disease (AML) and detailed patient subgroup analyses using real-world data in which graft source selection is not skewed toward PBSCs, limitations of the study should be acknowledged. First, this was a retrospective multicenter registry study, and various protocols were used in different centers. Therefore, pre-transplant patient characteristics could not be completely adjusted between the PBSC and BM groups even though the authors utilized multivariate and subgroup analyses along with propensity score matching. Second, the effects of dose and branch of ATG used or of minimal residual disease on transplantation outcomes were not evaluated because of lack of information. Third, given the relatively short follow-up period of survivors in this study, further study of the long-term effects of PBSCs is required. Fourth, since ethnicity affects the incidence and severity of GVHD [54], the authors' conclusions based on a Japanese cohort should be validated in other ethnic groups. Fifth, grading of cGVHD in this study was performed using conventional criteria [18] because of frequent missing values with regard to National Institutes of Health criteria [55].

Conclusions

Outcomes after unrelated HSCT from PBSC donors for adult patients with AML indicate a trend toward favorable NRM as well as OS and DFS, which is comparable to that of BM recipients. Although the rate of cGVHD was significantly higher with PBSCs, NRM was not increased, primarily because of the reduced risk of bacterial infection following the more robust engraftment in PBSC recipients. These tendencies were prominent in patient subgroups of HSCT at CR1, suggesting that PBSCs are the preferred source in these situations. The authors did not find any subgroup of patients for which BM

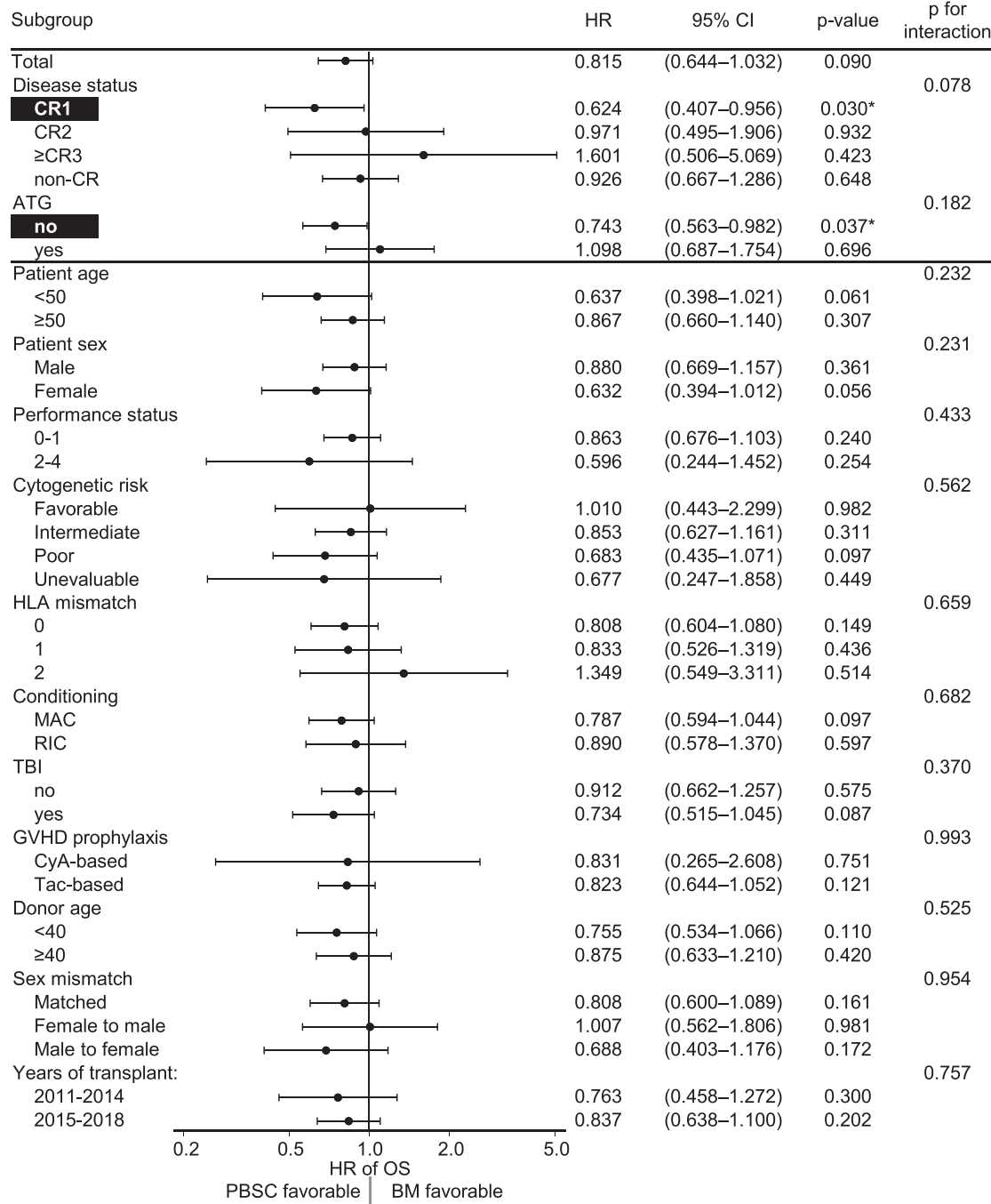


Fig. 3. Subgroup analyses of OS with respect to patient characteristics. OS is compared in each subgroup regarding patient characteristics. HRs of OS in the PBSC group are shown in comparison with the BM group. HR < 1 indicates favorable OS in the PBSC group. Black dots = HRs. Black bars = 95% CI. *P < 0.05. CI, confidence interval.

transplants are advantageous. Therefore, the authors' study supports the recent preferred donor selection of PBSCs in unrelated allo-HSCT in AML. Further optimization of the prophylactic strategy for cGVHD is required to improve outcomes after allo-HSCT from PBSC donors.

Funding

This work was supported in part by Program for the Development of Next-Generation Leading Scientists with Global Insight (L-INSIGHT) sponsored by the Ministry of Education, Culture, Sports, Science and Technology to YA.

Author Contributions

Conception and design of the study: TJ, YAr, TK and MY. Acquisition of data: TJ, YAr, TK, MY, ND, TF, YO, YKatayama, YKanda, KF, KM, ST, MS, TA, MO, TI and YAtsuta. Analysis and interpretation of data: TJ, YA, TK, SM, SH, YI, JK and MY. Drafting or revising the manuscript: TJ and YAr. All authors have approved the final article.

Declaration of Competing Interest

The authors have no commercial, proprietary or financial interest in the products or companies described in this article.

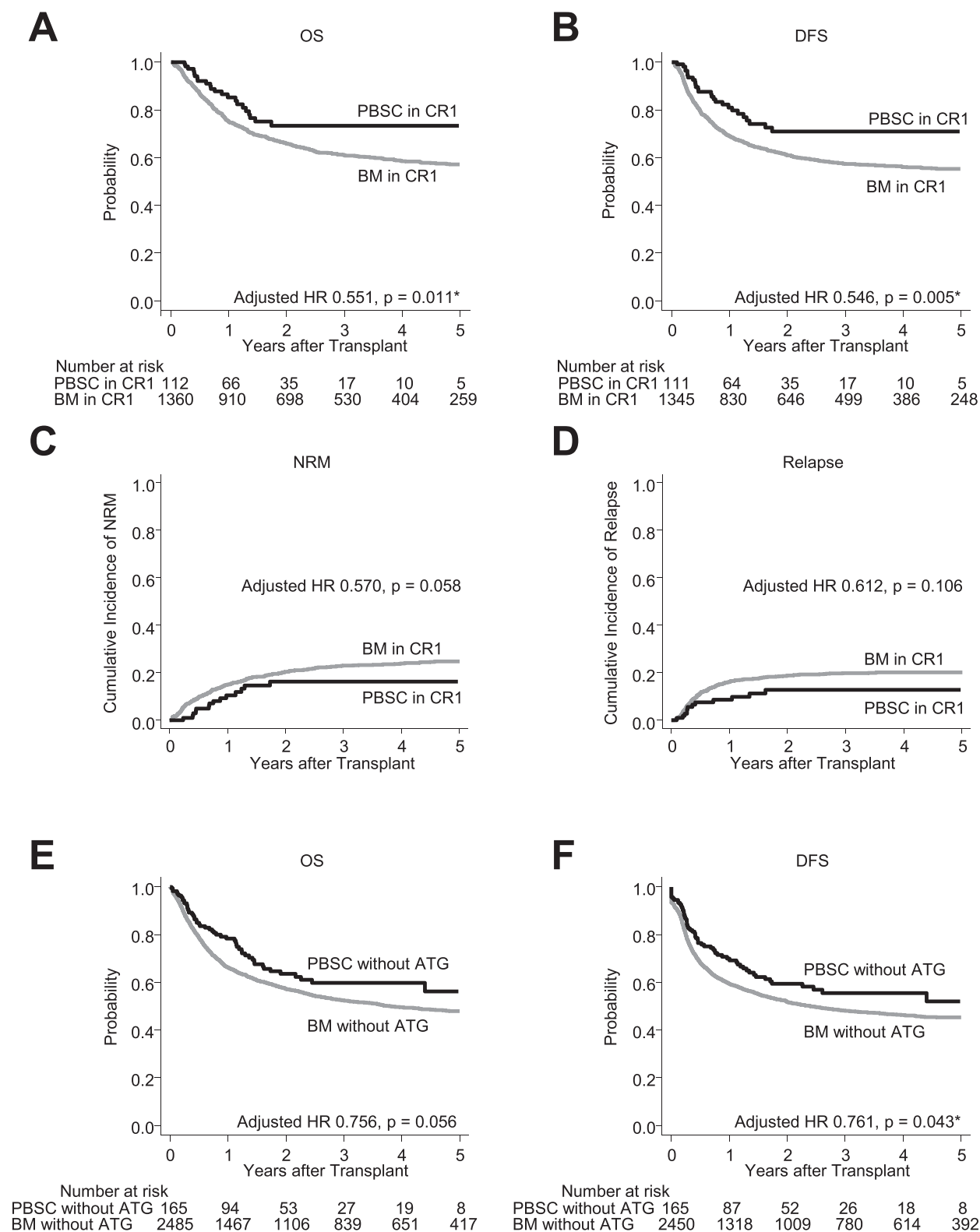


Fig. 4. Beneficial effects of PBSCs in the CR1 and non-ATG regimen subgroups. (A) OS in the CR1 subgroup. (B) DFS in the CR1 subgroup. (C) Cumulative incidence of NRM in the CR1 subgroup. (D) Cumulative incidence of relapse in the CR1 subgroup. (E) OS in the non-ATG regimen subgroup. (F) DFS in the non-ATG regimen subgroup. (G) Cumulative incidence of NRM in the non-ATG regimen subgroup. (H) Cumulative incidence of relapse in the non-ATG regimen subgroup. HRs and P values were calculated using the Cox proportional hazards model (A,B,E,F) and Fine–Gray tests (C,D,G,H) after being adjusted for confounding factors. $^*P < 0.05$.

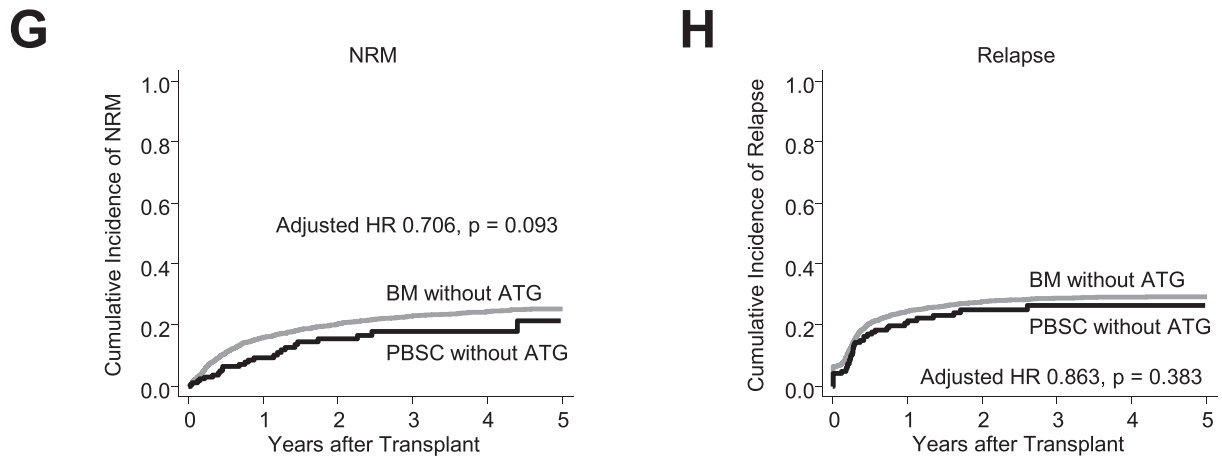


Fig. 4. Continued.

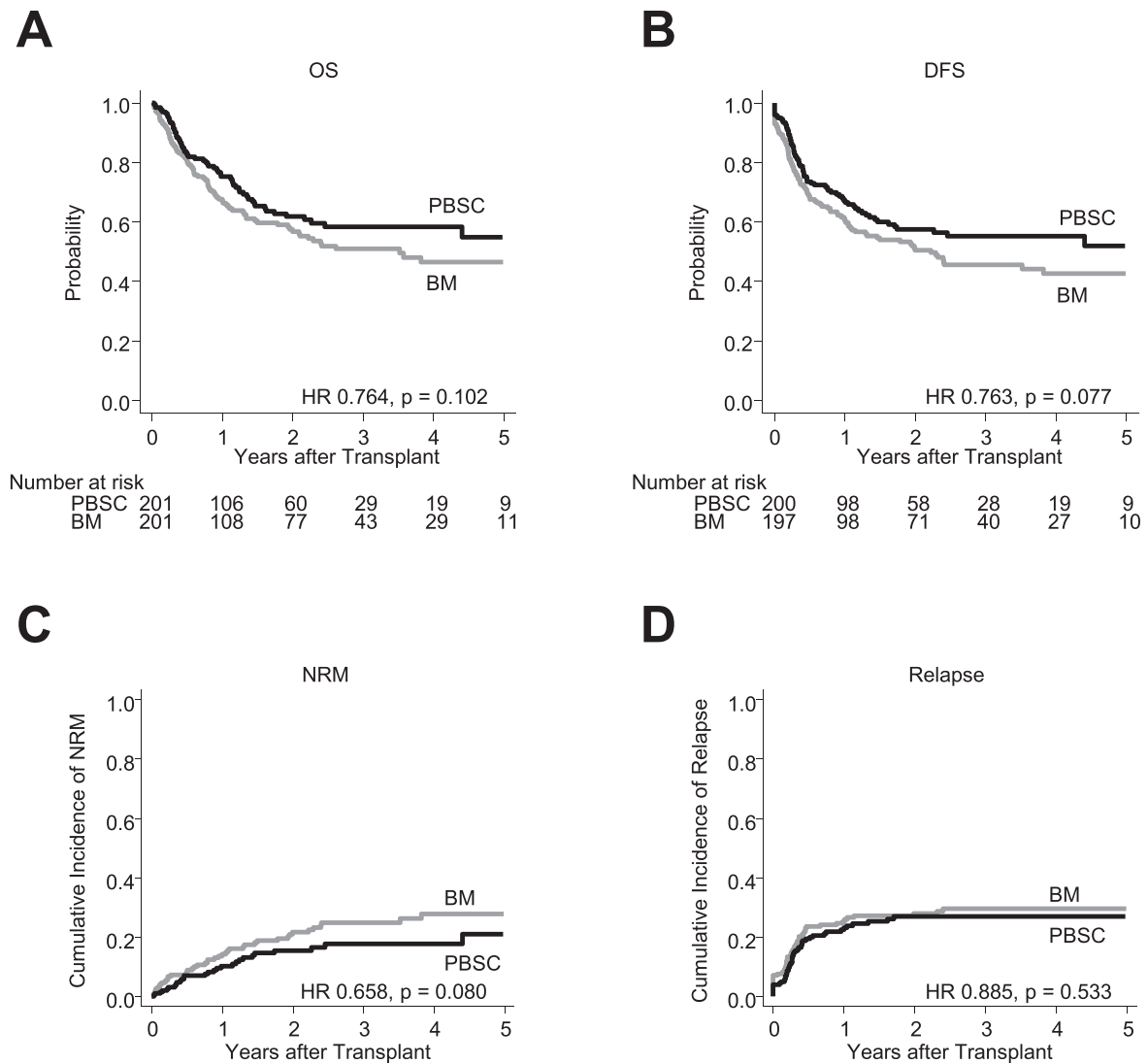


Fig. 5. Propensity score matching analyses for transplant outcomes. (A) OS. (B) DFS. (C) Cumulative incidence of NRM. (D) Cumulative incidence of relapse. HRs and P values were calculated using the Cox proportional hazards model (A,B) and Fine–Gray tests (C,D).

Table 3
Comparison of causes of mortality in the PBSC and BM groups.

	Total			CR1			≥CR2/non-CR		
	PBSC (N = 221)	BM (N = 2741)	P value	PBSC (N = 112)	BM (N = 1360)	P value	PBSC (N = 109)	BM (N = 1380)	P value
Infection, n (%)	4 (1.8)	180 (6.6)	0.002	2 (1.8)	69 (5.1)	0.165	2 (1.8)	111 (8.0)	0.014
Primary disease, n (%)	42 (19.0)	594 (21.7)	0.395	10 (8.9)	188 (13.8)	0.193	32 (29.4)	406 (29.4)	1.000
Graft failure, n (%)	1 (0.5)	13 (0.5)	1.000	0 (0.0)	6 (0.4)	1.000	1 (0.9)	7 (0.5)	0.456
GVHD, n (%)	7 (3.2)	91 (3.3)	1.000	1 (0.9)	46 (3.4)	0.255	6 (5.5)	45 (3.3)	0.264
Interstitial pneumonia/ARDS, n (%)	5 (2.3)	80 (2.9)	1.000	2 (1.8)	43 (3.2)	0.574	3 (2.8)	37 (2.7)	0.466
Organ failure/toxicity, n (%)	10 (4.5)	220 (8.0)	0.067	5 (4.5)	97 (7.1)	0.338	5 (4.6)	123 (8.9)	0.154
Secondary malignancy, n (%)	1 (0.5)	12 (0.4)	1.000	1 (0.9)	2 (0.1)	0.211	0 (0.0)	10 (0.7)	1.000
Other, n (%)	3 (1.4)	78 (2.9)	0.280	1 (0.9)	47 (3.5)	0.259	2 (1.8)	31 (2.3)	1.000
Total	73 (33.0)	1268 (46.3)		22 (19.6)	498 (36.6)		51 (46.8)	770 (55.8)	

ARDS, acute respiratory distress syndrome.

Acknowledgments

The authors thank all physicians and data managers at the centers who contributed valuable data on transplantation to the Japanese Society for Transplantation and Cellular Therapy.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:[10.1016/j.jcyt.2022.05.009](https://doi.org/10.1016/j.jcyt.2022.05.009).

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