Age-related differences in donor selection priorities for allogeneic hematopoietic transplantation

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Abstract

Patient age might influence donor selection priorities in allogeneic hematopoietic stem cell transplantation (allo-HCT), due to the differences in donor age, organ function, and resistance to graft-*versus*-host disease between younger and older patients. We compared the transplant outcomes between patients aged <50 years and those aged ≥50 years who received transplants from human leukocyte antigen (HLA)-matched related donors (M-RD, N=4,106), HLA one-antigen-mismatched related donors (1MM-RD, N=592), HLA two or three-antigen-mismatched related donors (23MM-RD, N=882), HLA-matched unrelated donors (M-UD, N=3,927), HLA one-locus-mismatched unrelated donors (1MM-UD, N=2,474), or unrelated cord blood units (U-CB, N=5,867). To assess the impact of donor age, the M-UD and 1MM-UD groups were further subclassified into younger (M-UD-Y, 1MM-UD-Y: donor age <50 years) and older (M-UD-O, 1MM-UD-O: donor age ≥50 years) donor subgroups. Among patients aged ≥50 years, overall survival in the M-UD-Y group was significantly superior to that in the M-RD group (hazard ratio=0.87, *P*=0.0039), whereas the M-UD-O group showed no advantage (hazard ratio=1.08, *P*=0.48). In this age group, 1MM-RD, 23MM-RD, and U-CB were associated with significantly inferior overall survival, while neither 1MM-UD-Y nor 1MM-UD-O was. NRM was significantly lower in the M-UD-Y group than in the M-UD-O group among patients aged ≥50 years, without increasing relapse risk. For patients aged <50 years, overall survival in the M-UD-Y and M-UD-O groups was comparable to that in the M-RD group, but 23MM-RD, 1MM-UD-Y, and U-CB were associated with inferior overall survival. Therefore, donor selection priorities in allo-HCT might differ according to recipient age. A younger M-UD might be preferred for patients aged ≥50 years.

Introduction

The selection of an appropriate donor is crucial for the success of allogeneic hematopoietic stem cell transplantation (allo-HCT). Generally, a human leukocyte antigen (HLA)-matched related donor and an HLA-matched unrelated donor are considered the first and second preferred donors, respectively, in allo-HCT due to the comparable transplant outcomes in both groups.[1-3] When these donors are unavailable, the best alternative donor should be considered.[4,5] Although alternative donors, or third preferred donors, including an HLA-haploidentical donor, an unrelated donor with one allele/antigen mismatch, or an unrelated cord blood unit, are considered, the most suitable alternative donor remains unclear. Recently, the use of antithymocyte globulin and post-transplant cyclophosphamide for graft-*versus*-host disease (GvHD) prophylaxis and the measurement of HLA antibodies to reduce the risk of graft failure have improved transplant outcomes with alternative donors.[3,5-10] In addition, despite the increasing number of allo-HCT procedures performed in older patients, data on suitable donor selection for older patients are limited.[11]

We hypothesize that patient age might influence donor selection priority in allo-HCT, as related donor age, organ function, and resistance to GvHD or infection differ between younger and older patients. Therefore, this nationwide, large-scale retrospective study aimed to investigate the donor selection priorities in allo-HCT based on patient age.

Methods

Patients

Clinical data of patients were obtained from the Transplant Registry Unified Management Program (TRUMP),[12-14] which includes information on allo-HCT performed in Japan. Patients considered eligible for inclusion in this study were: (i) aged ≥16 years; (ii) diagnosed with acute myeloid leukemia, acute lymphoblastic leukemia, chronic myeloid leukemia, or myelodysplastic syndrome; (iii) underwent an initial allo-HCT between 2007 and 2017; and (iv) had suitable donors (related donors with HLA-A, -B, and -DR antigen match [M-RD], one antigen mismatch in the graft-*versus*-host direction [1MM-RD], or two or three antigen mismatches in the graft-*versus*-host direction [23MM-RD]; unrelated donors with HLA-A, -B, -C, and -DRB1 allele match [M-UD] or one allele/antigen mismatch in the graft-*versus*-host direction [1MM-UD]; or unrelated cord blood [U-CB] units). A total of 17,848 patients fulfilled these selection criteria, and 4,106, 592, 882, 3,927, 2,427, and 5,867 patients who received allo-HCT from M-RD, 1MM-RD, 23MM-RD, M-UD, 1MM-UD, and U-CB, respectively, were included in this study.

This study was initiated by the Donor/Source Working Group of the Japanese Society for Transplantation and Cellular Therapy and approved by the data management committees of TRUMP and the Institutional Review Board of Jichi Medical University Saitama Medical Center. The data of this study are not publicly available due to ethical restrictions that their divulgation would exceed the scope of the recipient/donor consent for research use in the registry.

Endpoints and definitions

The primary endpoint was overall survival (OS) after allo-HCT. The secondary endpoints were disease-free survival (DFS), GvHD-free, relapse-free survival (GRFS), and the cumulative incidence rates of acute and chronic GvHD, relapse, and non-relapse mortality (NRM) in the entire cohort and in patients aged <50 years and ≥50 years. The age cutoff of 50 years was chosen based on previously published studies, as well as the distribution and outcomes observed in our cohort, which supported the appropriateness of this threshold (*Online Supplementary Figure S1*). Acute and chronic GvHD were graded according to previously published criteria.[15,16] The incidence of chronic GvHD was evaluated in patients who survived for at least 100 days. DFS was defined as survival without disease progression or relapse, while NRM was defined as death without relapse. GRFS was defined as survival without grade 3-4 acute GvHD, chronic GvHD requiring systemic treatment, relapse, or death from any cause.[17] The conditioning regimen was classified as either myeloablative or reduced-intensity according to the operational definitions of the National Marrow Donor Program/Center for International Blood and Marrow Transplant Research.[18] Acute leukemia in first or second remission, chronic myeloid leukemia in the first or second chronic phase, and myelodysplastic syndrome were defined as standard-risk diseases, while others were defined as high-risk diseases.

Statistical analysis

Categorical variables were compared among groups using the χ^2-test or Fisher exact test, while continuous variables were compared using the Kruskal-Wallis test. The probability rates of OS and DFS were estimated using the Kaplan-Meier method and compared among groups with the log-rank test. The probability rates of acute and chronic GvHD, relapse, and NRM were estimated using the cumulative incidence method and compared among groups with the Gray test, considering death or relapse without GvHD as competing events for acute and chronic GvHD, death without relapse as a competing event for relapse, and relapse as a competing event for NRM.[19,20] Multivariate analyses of OS and DFS were performed using the Cox proportional hazards model, while multivariate analyses of acute and chronic GvHD, relapse, and NRM were performed using the Fine-Gray regression model.[21] The following variables were considered: patient age at transplantation (<50 years or ≥50 years), donor type (M-RD, 1MM-RD, 23MM-RD, M-UD, 1MM-UD, or U-CB), patient sex (male or female), disease type (acute myeloid leukemia, acute lymphoblastic leukemia, myelodysplastic syndrome, or chronic myeloid leukemia), disease risk (standard or high risk),

Eastern Cooperative Oncology Group Performance Status (ECOG PS) (0-1 or 2-4), conditioning regimen (myeloablative or reduced-intensity), use of *in vivo* T-cell depletion (yes or no), and year of transplantation (2007-2012 or 2013-2017). A *P* value of <0.05 was considered statistically significant. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University),[22] which is a graphical user interface for R (The R Foundation for Statistical Computing, version 3.0.2, Vienna, Austria).

Results

Patient characteristics

The characteristics of the patients in each group are summarized in Table 1. The median ages at the time of allo-HCT were 45.5 years (range, 16-74) in the M-RD group, 49.5 years (range, 16-76) in the 1MM-RD group, 50 years (range, 16-80) in the 23MM-RD group, 51 years (range, 16-77) in the M-UD group, 50 years (range, 16-74) in the 1MM-UD group, and 55 years (range, 16-85) in the U-CB group (*P*<0.001). Patients in the M-RD group had the lowest median age among all groups, while those in the U-CB group had the highest median age. The incidence of high-risk diseases was highest in the 23MM-RD group (59.6%), followed by the U-CB group (43.0%) and the 1MM-RD group (42.2%). In the other groups, the incidence was approximately one-quarter. *In vivo* T-cell depletion was most commonly used in the 23MM-RD group (50.9%), followed by the 1MM-RD group (34.3%) and the 1MM-MUD group (13.7%), while only 2%-4% of patients

Table 1. Patient characteristics.

Variable	M-RD N=4,106	1MM-RD N=592	23MM-RD N=882	M-UD N=3,927	1MM-UD N=2,474	U-CB N=5,867	*P*
Age, years, median (range)	45.5 (16-74)	49.5 (16-76)	50 (16-80)	51 (16-77)	50 (16-74)	55 (16-85)	<0.001
Recipient sex, N (%)							
Female	1,682 (41.0)	220 (37.2)	331 (37.5)	1,608 (41.0)	980 (39.6)	2,439 (41.6)	0.072
Male	2,424 (59.0)	372 (62.8)	551 (62.5)	2,317 (59.0)	1,494 (60.4)	3,426 (58.4)	
Disease, N (%)							
Acute myelogenous leukemia	2,272 (55.3)	369 (62.3)	572 (64.9)	2,064 (52.6)	1,288 (52.1)	3,700 (63.1)	<0.001
Acute lymphoblastic leukemia	1,060 (25.8)	115 (19.4)	186 (21.1)	931 (23.7)	594 (24.0)	1,094 (18.6)	
Myelodysplastic syndrome	630 (15.3)	89 (15.0)	92 (10.4)	797 (20.3)	494 (20.0)	881 (15.0)	
Chronic myeloid leukemia	144 (3.5)	19 (3.2)	32 (3.6)	135 (3.4)	98 (4.0)	192 (3.3)	
Disease risk, N (%)*							
Standard risk	3,023 (73.7)	342 (57.8)	356 (40.4)	3,005 (76.6)	1,873 (75.7)	3,335 (57.0)	<0.001
High risk	1,081 (26.3)	250 (42.2)	526 (59.6)	918 (23.4)	600 (24.3)	2,521 (43.0)	
ECOG PS, N (%)							
0-1	3,790 (92.4)	515 (87.0)	748 (85.1)	3,681 (93.9)	2,286 (92.5)	5,072 (86.8)	<0.001
2-4	310 (7.6)	77 (13.0)	131 (14.9)	239 (6.1)	186 (7.5)	770 (13.2)	
Conditioning regimen, N (%)							
Myeloablative	3,162 (77.1)	380 (64.3)	313 (35.5)	2,870 (73.2)	1,792 (72.5)	3,799 (64.9)	<0.001
Reduced-intensity	941 (22.9)	211 (35.7)	568 (64.5)	1,052 (26.8)	680 (27.5)	2,059 (35.1)	
GvHD prophylaxis, N (%)							
CSA with MTX	3,046 (74.2)	91 (15.4)	44 (5.0)	517 (13.2)	226 (9.1)	1,321 (22.6)	<0.001
CSA without MTX	216 (5.3)	23 (3.9)	33 (3.7)	18 (0.5)	6 (0.2)	290 (5.0)	
TAC with MTX	674 (16.4)	330 (55.7)	162 (18.4)	3,128 (79.7)	2,090 (84.5)	2,116 (36.1)	
TAC without MTX	90 (2.2)	133 (22.5)	617 (70.0)	198 (5.0)	104 (4.2)	2,060 (35.2)	
Others/None	79 (1.9)	15 (2.5)	26 (3.0)	63 (1.6)	47 (1.9)	69 (1.2)	
In vivo T-cell depletion, N (%)							
Yes	112 (2.7)	203 (34.3)	449 (50.9)	158 (4.0)	338 (13.7)	178 (3.0)	<0.001
No	3,994 (97.3)	389 (65.7)	433 (49.1)	3,769 (96.0)	2,136 (86.3)	5,689 (97.0)	
Year of transplantation, N (%)							
2007-2012	2,280 (55.5)	322 (54.4)	259 (29.4)	1,780 (45.3)	1,127 (45.6)	2,705 (46.1)	<0.001
2013-2017	1,826 (44.5)	270 (45.6)	623 (70.6)	2,147 (54.7)	1,347 (54.4)	3,162 (53.9)	

*Acute leukemia in first or second remission, chronic myeloid leukemia in first or second chronic phase, and myelodysplastic syndrome were defined as standard-risk diseases, while others were defined as high-risk diseases. M-RD: related donors with HLA-A, -B, and -DR antigen match; 1MM-RD: related donors with one antigen mismatch in the graft-*versus*-host direction; 23MM-RD: related donors with two or three antigen mismatches in the graft-*versus*-host direction; M-UD: unrelated donors with HLA-A, -B, -C, and -DRB1 allele match; 1MM-UD: unrelated donors with one allele/antigen mismatch in the graft-*versus*-host direction; U-CB: unrelated cord blood units; ECOG PS: Eastern Cooperative Oncology Group performance status; CSA: cyclosporine; MTX: methotrexate: TAC: tacrolimus.

in the remaining groups utilized this method. Notably, the 23MM-RD group more frequently received reduced-intensity regimens than myeloablative regimens, and the number of transplants performed after 2013 was significantly higher than those performed before 2013.

Survival outcomes and relapse

Figure 1 illustrates the adjusted probability rates of OS, DFS, GRFS, NRM, and relapse by donor source groups. The adjusted probability rates of OS at 3 years were 52.7% (95% confidence interval [95% CI]: 51.0%-54.5%) in the M-RD group, 47.6% (95% CI: 43.4%-52.2%) in the 1MM-RD group, 40.2% (95% CI: 36.3%-44.4%) in the 23MM-RD group, 55.4% (95% CI: 53.7%-57.2%) in the M-UD group, 50.7% (95% CI: 48.5%-52.9%) in the 1MM-UD group, and 50.2% (95% CI: 48.8%-51.7%) in the U-CB group (Figure 1A). The results of the multivariate analysis of OS, NRM, and relapse are summarized in *Online Supplementary Table S1*.

Acute and chronic graft-*versus*-host disease

In the multivariate analysis, the risk of grade 3-4 acute GvHD was significantly higher in the 1MM-RD (hazard ratio [HR]=1.59, 95% CI: 1.26-2.00, *P*=0.00011), 23MM-RD (HR=1.74, 95% CI: 1.42-2.12, *P*<0.0001), and 1MM-UD (HR=1.34, 95% CI: 1.14-1.58, *P*=0.00038) groups compared with the M-RD group. No significant differences were observed in the M-UD and U-CBT groups compared with the M-RD group (*Online Supplementary Table S3*). Conversely, the risk of extensive chronic GvHD was significantly lower in the 23MM-RD (HR=0.66, 95% CI: 0.53-0.82, *P*=0.00020), M-UD (HR=0.82, 95% CI: 0.73-0.92, *P*=0.00038), 1MM-UD (HR=0.87, 95% CI: 0.76-0.99, *P*=0.033), and U-CB donor (HR=0.43, 95% CI: 0.38-0.49, *P*<0.0001) groups compared with the M-RD group (*Online Supplementary Table S2*).

Transplant outcomes based on patient and donor age

An interaction test revealed the difference in the effect of M-UD on OS and NRM between patients aged <50 years and those aged ≥50 years (HR=0.88, 95% CI: 0.76-1.00, *P*=0.055, and HR=0.78, 95% CI: 0.63-0.96, *P*=0.019, respectively) (*Online Supplementary Table S3*). Subsequently, we compared the transplant outcomes across different donor sources, by age group (<50 years and ≥50 years). In addition, we classified the M-UD and 1MM-UD groups according to donor age (M-UD-Y: donor age <50 years; M-UD-O: donor age ≥50 years; 1MM-UD-Y: donor age <50 years; 1MM-UD-O: donor age ≥50 years). For patients aged ≥50 years, the mean ages of the donors (standard deviation [SD]) were 54.1 (SD=8.6) years for M-RD, 36.3 (SD=7.3) years for M-UD-Y, 52.2 (SD=2.4) years for M-UD-O, 37.0 (SD=7.4) years for 1MM-UD-Y, and 51.9 (SD=2.8) years for 1MM-UD-O. For patients aged <50 years, the mean ages of the donors were 35.8 (SD=10.8) years for M-RD, 36.3 (SD=7.5) years for M-UD-Y, 51.9 (SD=1.7) years for M-UD-O, 36.4 (SD=7.4) years for 1MM-UD-Y, and 51.8 (SD=1.6) years for 1MM-UD-O. An interaction test revealed a difference in the effect of M-UD-Y on OS between patients aged <50 years and those aged ≥50 years (HR=0.86, 95% CI: 0.75-0.99, *P*=0.035), but no difference was found in the effect of M-UD-O on OS between these age groups (HR=1.08, 95% CI: 0.74-1.56, *P*=0.70) (*Online Supplementary Table S4*).

For patients aged ≥50 years, the OS in the M-UD-Y group was superior to that in the M-RD group (HR=0.87, 95% CI: 0.80-0.96, *P*=0.0039), while no significant difference was observed in OS between the M-UD-O and M-RD groups (HR=1.08, 95% CI: 0.87-1.35, *P*=0.48). In addition, the 23MM-RD, 1MM-RD, and U-CB groups were identified as significant independent adverse factors for OS (HR=1.44, 95% CI: 1.25-1.67, *P*<0.0001 for 23MM-RD; HR=1.31, 95% CI: 1.11-1.53, *P*=0.0010 for 1MM-RD; and HR=1.17, 95% CI: 1.08-1.27, *P*<0.0001 for U-CB). In contrast, neither the 1MM-UD-Y group nor the 1MM-UD-O group was significantly associated with inferior OS (HR=1.07, 95% CI: 0.96-1.18, *P*=0.23 for 1MM-UD-Y; HR=1.18, 95% CI: 0.88-1.57, *P*=0.26 for 1MM-UD-O) in this age group (Table 2).

For patients aged <50 years, the OS in the M-UD-Y and M-UD-O groups was comparable to that in the M-RD group (HR=1.02, 95% CI: 0.92-1.13, *P*=0.73 and HR=1.04, 95% CI: 0.77-1.40, *P*=0.82). In contrast, the 23MM-RD, 1MM-UD-Y, and U-CB groups were identified as significant independent adverse factors for OS (HR=1.44, 95% CI: 1.22-1.70, *P*<0.0001 for 23MM-RD; HR=1.17, 95% CI: 1.04-1.32, *P*=0.0070 for 1MM-UD-Y; and HR=1.20, 95% CI: 1.10-1.31, *P*<0.0001 for U-CB). Additionally, the 1MM-RD and 1MM-UD-O groups tended to be associated with inferior OS, although these differences did not reach statistical significance (HR=1.18, 95% CI: 0.98-1.42, *P*=0.074 for 1MM-RD; HR=1.17, 95% CI: 0.85-1.60, *P*=0.35 for 1MM-UD-O) (Table 2).

In the multivariate analysis of NRM accounting for M-UD age, for patients aged ≥50 years, the risk of NRM in the M-UD-Y group was comparable to that in the M-RD group (HR=1.04, 95% CI: 0.91-1.19, *P*=0.55), but the risk of NRM in the M-UD-O group was significantly higher than that in the M-RD group (HR=1.44, 95% CI: 1.08-1.92, *P*=0.013). Recipients of grafts from the other donor groups also had a statistically significantly higher NRM than those transplanted from the M-RD group (Table 2). For patients aged <50 years, the risk of NRM in the M-UD-Y and M-UD-O groups was higher than that in the M-RD group (HR=1.36, 95% CI: 1.15-1.60, *P*=0.00027 and HR=1.62, 95% CI: 1.07-2.45, *P*=0.021, respectively). Similarly, recipients of transplants from the other donor groups also showed higher NRM compared to those receiving transplants from the M-RD (Table 2).

In the multivariate analysis of relapse, the risk of relapse in the M-UD-Y and M-UD-O groups, as well as in the other donor groups, was significantly lower than that in the M-RD group, regardless of patient age (Table 2).

The probability rates of adjusted OS at 3 years for patients aged <50 years were 63.5% (95% CI: 61.5%-65.7%) in the M-RD group, 58.8% (95% CI: 53.2%-65.1%) in the 1MM-RD group,

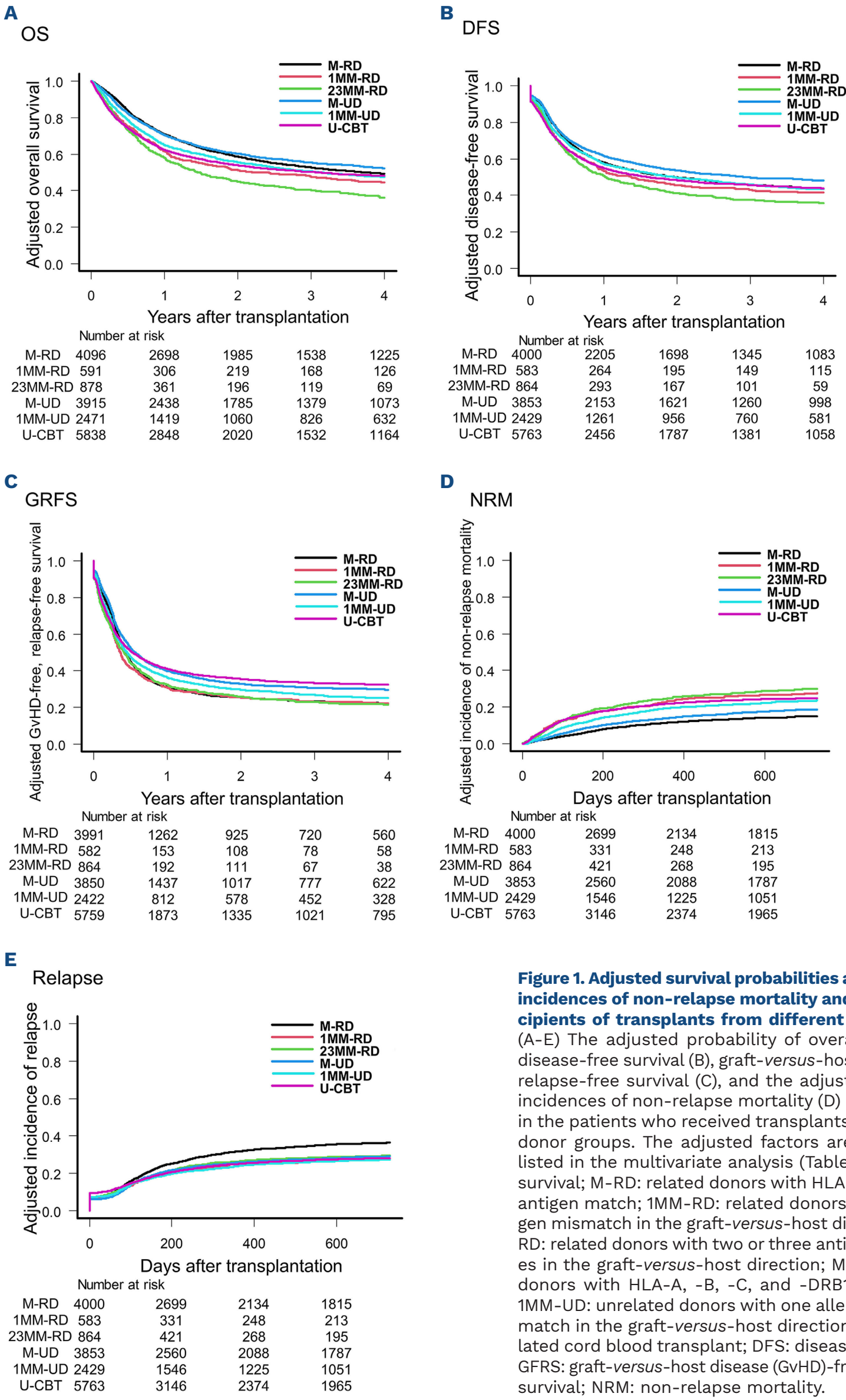


Figure 1. Adjusted survival probabilities and cumulative incidences of non-relapse mortality and relapse in recipients of transplants from different donor groups. (A-E) The adjusted probability of overall survival (A), disease-free survival (B), graft-*versus*-host disease-free, relapse-free survival (C), and the adjusted cumulative incidences of non-relapse mortality (D) and relapse (E) in the patients who received transplants from different donor groups. The adjusted factors are the variables listed in the multivariate analysis (Table 2). OS: overall survival; M-RD: related donors with HLA-A, -B, and -DR antigen match; 1MM-RD: related donors with one antigen mismatch in the graft-*versus*-host direction; 23MM-RD: related donors with two or three antigen mismatches in the graft-*versus*-host direction; M-UD: unrelated donors with HLA-A, -B, -C, and -DRB1 allele match; 1MM-UD: unrelated donors with one allele/antigen mismatch in the graft-*versus*-host direction; U-CBT: unrelated cord blood transplant; DFS: disease-free survival; GFRS: graft-*versus*-host disease (GvHD)-free, relapse-free survival; NRM: non-relapse mortality.

53.5% (95% CI: 48.2%-59.3%) in the 23MM-RD group, 63.7% (95% CI: 61.2%-66.4%) in the M-UD-Y group, 61.2% (95% CI: 52.6%-71.2%) in the M-UD-O group, 58.7% (95% CI: 55.5%-62.0%) in the 1MM-UD-Y group, 62.5% (95% CI: 53.3%-73.3%) in the 1MM-UD-O group, and 60.0% (95% CI: 57.9%-62.2%) in the U-CB group (Figure 2A). Conversely, the probability rates of adjusted OS at 3 years for patients aged ≥50 years were 41.7% (95% CI: 39.1%-44.5%) in the M-RD group, 38.3% (95% CI: 32.7%-44.8%) in the 1MM-RD group, 29.4% (95% CI: 24.4%-35.4%) in the 23MM-RD group, 47.9% (95% CI: 45.4%-50.5%) in the M-UD-Y group, 38.1% (95% CI: 3.3%-47.9%) in the M-UD-O group, 42.4% (95% CI: 39.3%-45.8%) in the 1MM-UD-Y group, 42.3% (95% CI: 32.3%-55.3%) in the 1MM-UD-O group, and 40.3% (95% CI: 38.6%-42.2%) in the U-CB group (Figure 2B). The cumulative incidence of each donor source, stratified by patient age (<50 and ≥50 years), is shown in Figure 3.

Donor selection algorithm based on patient age

Based on the results of multivariate and subgroup analyses, we developed a donor selection algorithm stratified by patient age, as illustrated in Figure 4. Patients were categorized into two groups: those aged <50 years and those aged ≥50 years. Among patients aged ≥50 years, the M-UD-Y group was prioritized over the M-RD group, highlighting the beneficial impact of donor youth in this age group. Similarly, within the 1MM-UD category, the 1MM-UD-Y group was preferred over the 1MM-UD-O group. In contrast, among patients aged <50 years, the impact of donor age was relatively limited; therefore, the M-UD-Y and M-UD-O groups, as well as the 1MM-UD-Y and 1MM-UD-O groups, were placed at the same priority level. As a point of consideration, it is worth noting that in the MRD setting, patients aged ≥50 years who received grafts from younger sibling donors also showed favorable outcomes comparable to those in the M-UD-Y group (*Online Supplementary Figure S2*).

Discussion

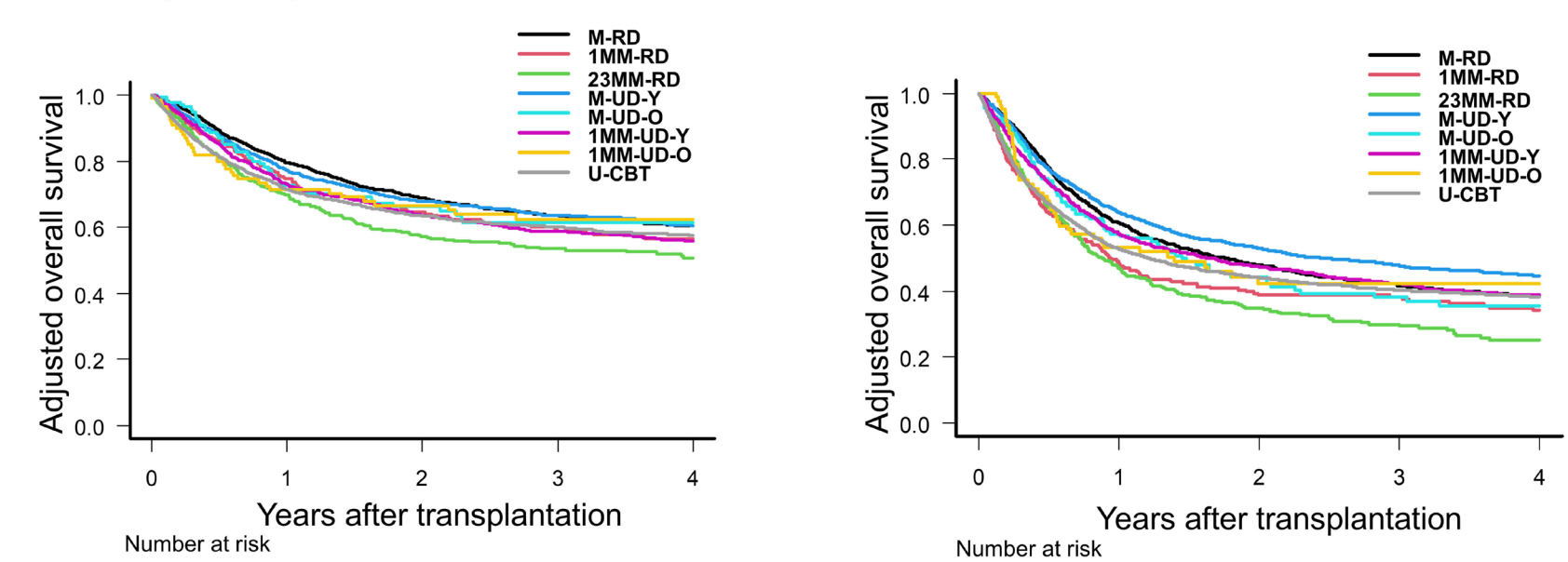
In this study, we conducted a large-scale retrospective analysis to examine the donor selection priorities for allo-HCT based on patient age. OS did not differ significantly between the M-RD and M-UD groups, but the M-RD group showed superior outcomes compared with other groups. We further stratified patients by age (<50 and ≥50 years) and analyzed the outcomes based on the age of M-UD. In patients aged ≥50 years, the OS in the M-UD-Y group was superior to that in the M-RD group, while no significant difference was found in OS between the M-UD-O and M-RD groups. In patients aged <50 years, the OS in the M-UD-Y and M-UD-O groups was comparable to that in the M-RD

Table 2. Results of multivariate analyses of overall survival, non-relapse mortality, and relapse in patients, classified by patient age group (<50 years and ≥50 years)

Recipient age/ donor group	OS*		NRM*		Relapse*	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Age <50 years						
M-RD	1.00	Reference	1.00	Reference	1.00	Reference
1MM-RD	1.18 (0.98-1.42)	0.074	1.84 (1.39-2.43)	<0.0001	0.72 (0.57-0.90)	0.0050
23MM-RD	1.44 (1.22-1.70)	<0.0001	2.24 (1.75-2.87)	<0.0001	0.75 (0.61-0.93)	0.0083
M-UD-Y	1.02 (0.92-1.13)	0.73	1.36 (1.15-1.60)	0.00027	0.73 (0.63-0.84)	<0.0001
M-UD-O	1.04 (0.77-1.40)	0.82	1.62 (1.07-2.45)	0.021	0.57 (0.36-0.89)	0.013
1MM-UD-Y	1.17 (1.04-1.32)	0.0070	1.75 (1.47-2.09)	<0.0001	0.80 (0.71-0.90)	0.00028
1MM-UD-O	1.17 (0.85-1.60)	0.35	2.22 (1.48-3.31)	0.00011	0.68 (0.46-0.99)	0.045
U-CB	1.20 (1.10-1.31)	<0.0001	1.71 (1.47-1.98)	<0.0001	0.80 (0.72-0.89)	<0.0001
Age ≥50 years						
M-RD	1.00	Reference	1.00	Reference	1.00	Reference
1MM-RD	1.31 (1.11-1.53)	0.0010	1.76 (1.42-2.20)	<0.0001	0.71 (0.57-0.89)	0.0024
23MM-RD	1.44 (1.25-1.67)	<0.0001	1.70 (1.39-2.09)	<0.0001	0.80 (0.66-0.97)	0.025
M-UD-Y	0.87 (0.80-0.96)	0.0039	1.04 (0.91-1.19)	0.550	0.76 (0.68-0.85)	<0.0001
M-UD-O	1.08 (0.87-1.35)	0.48	1.44 (1.08-1.92)	0.013	0.63 (0.46-0.87)	0.0051
1MM-UD-Y	1.07 (0.96-1.18)	0.23	1.43 (1.24-1.65)	<0.0001	0.72 (0.62-0.82)	<0.0001
1MM-UD-O	1.18 (0.88-1.57)	0.26	1.59 (1.10-2.32)	0.014	0.76 (0.49-1.16)	0.200
U-CB	1.17 (1.08-1.27)	<0.0001	1.53 (1.37-1.72)	<0.0001	0.73 (0.66-0.81)	<0.0001

*Adjusted for other significant variables including recipient sex, disease, disease risk, Eastern Cooperative Oncology Group performance status, conditioning regimen, use of *in vivo* T-cell depletion, and year of transplantation. OS: overall survival; NRM: non-relapse mortality; HR: hazard ratio; 95% CI: 95% confidence interval; M-RD: related donors with HLA-A, -B, and -DR antigen match; 1MM-RD: related donors with one antigen mismatch in the graft-*versus*-host direction; 23MM-RD: related donors with two or three antigen mismatches in the graft-*versus*-host direction; M-UD-Y: unrelated donors with HLA-A, -B, -C, and -DRB1 allele match <50 years old; M-UD-O: unrelated donors with HLA-A, -B, -C, and -DRB1 allele match ≥50 years old; 1MM-UD-Y: unrelated donors with one allele/antigen mismatch in the graft-*versus*-host direction <50 years old; 1MM-UD-O: unrelated donors with one allele/antigen mismatch in the graft-*versus*-host direction ≥50 years old; U-CB: unrelated cord blood units.

group. This discrepancy is likely attributed to the reduction in the NRM risk when younger M-UD are selected for patients aged ≥50 years, while maintaining a lower recurrence rate. In other words, older M-RD no longer provide the advantage of lower NRM risk compared with younger M-UD. Importantly, although selecting a younger M-RD is generally not feasible in older patients, our subanalysis suggests that in the M-RD setting, patients aged ≥50 years who received transplants from younger M-RD achieved outcomes comparable to those with younger M-UD. Therefore, when such a donor is available, selecting a younger M-RD may be considered a reasonable option. These findings suggest that the donor selection priorities in allo-HCT may vary according to patient age, with young M-UD potentially being the first preferred donor for patients aged ≥50 years. With the widespread use of reduced-intensity conditioning regimens and advancements in GvHD prophylaxis and supportive care, such as antimicrobial agents, the proportion of older allo-HCT patients has been increasing.[11] Inevitably, sibling donors for these patients are likely to be older and may have some comorbidities. The Center for International Blood and Marrow Transplant Research (CIBMTR) reported that the hazard ratio for overall mortality increases by 5.5% for every 10-year increase in donor age in transplants from unrelated donors.[23] Our result is also consistent with this previously reported finding. However, it remains unclear whether transplants should be performed using older M-RD or younger M-UD. The European Group for Blood and Marrow Transplantation (EBMT) reported that the outcomes of allo-HCT with older matched sibling donors or younger M-UD for patients aged ≥55 years with acute myeloid leukemia in their first complete remission were comparable.[24] A previous CIBMTR study compared the allo-HCT outcomes between patients aged ≥50 years with matched sibling donors aged ≥50 years and those with M-UD younger than 50 years. None of the findings suggested that allo-HCT from younger M-UD was superior to that from older matched sibling donors.[25] A more recent CIBMTR study demonstrated that for allo-HCT patients with acute myeloid leukemia aged ≥50 years, using younger M-UD (age ≤35 years) was associated with decreased relapse risk and improved DFS compared with using older matched sibling donors (aged ≥50 years). However, no difference was found in OS between the two study arms.[26] On the other hand, in this study, for allo-HCT patients aged ≥50 years, those with younger M-UD showed superior OS compared with those who had M-RD, due to the comparable NRM and low relapse rates. These discrepancies between our results and those reported by the EBMT and CIBMTR may be explained by several factors. First, ethnic and genetic differences may contribute



Number at risk

M-RD	2457	1786	1344	1062	851
1MM-RD	295	187	141	99	76
23MM-RD	435	211	112	73	50
M-UD-Y	1679	1149	884	685	545
M-UD-O	134	87	63	48	39
1MM-UD-Y	1109	720	552	437	348
1MM-UD-O	114	72	57	46	36
U-CBT	2316	1365	1033	809	629

Number at risk

M-RD	1639	912	641	476	374
1MM-RD	296	119	78	69	50
23MM-RD	443	150	84	46	19
M-UD-Y	1910	1102	774	602	460
M-UD-O	172	91	58	42	28
1MM-UD-Y	1151	578	422	319	233
1MM-UD-O	88	45	26	22	15
U-CBT	3522	1483	987	723	535

Figure 2. Adjusted overall survival according to patient age groups and different donor types. (A, B) The adjusted probability of overall survival in recipients of transplants from different donor groups, classified according to two patient age groups: <50 years (A) and ≥50 years (B). The adjusted factors are the variables included in the multivariate analysis (Table 2). OS: overall survival; M-RD: related donors with HLA-A, -B, and -DR antigen match; 1MM-RD: related donors with one antigen mismatch in the graft-versus-host direction; 23MM-RD: related donors with two or three antigen mismatches in the graft-*versus*-host direction; M-UD-Y: unrelated donors with HLA-A, -B, -C, and -DRB1 allele match <50 years old; M-UD-O: unrelated donors with HLA-A, -B, -C, and -DRB1 allele match ≥50 years old; 1MM-UD-Y: unrelated donors with one allele/antigen mismatch in the graft-*versus*-host direction <50 years old; 1MM-UD-O: unrelated donors with one allele/antigen mismatch in the graft-*versus*-host direction ≥50 years old; U-CBT: unrelated cord blood transplant.

to variations in transplant immunobiology. Second, transplant practices differ across regions, particularly in GvHD prophylaxis strategies and supportive care. Finally, donor selection criteria and institutional policies can influence outcomes. These differences underscore the importance of analyzing region-specific data to optimize donor selection

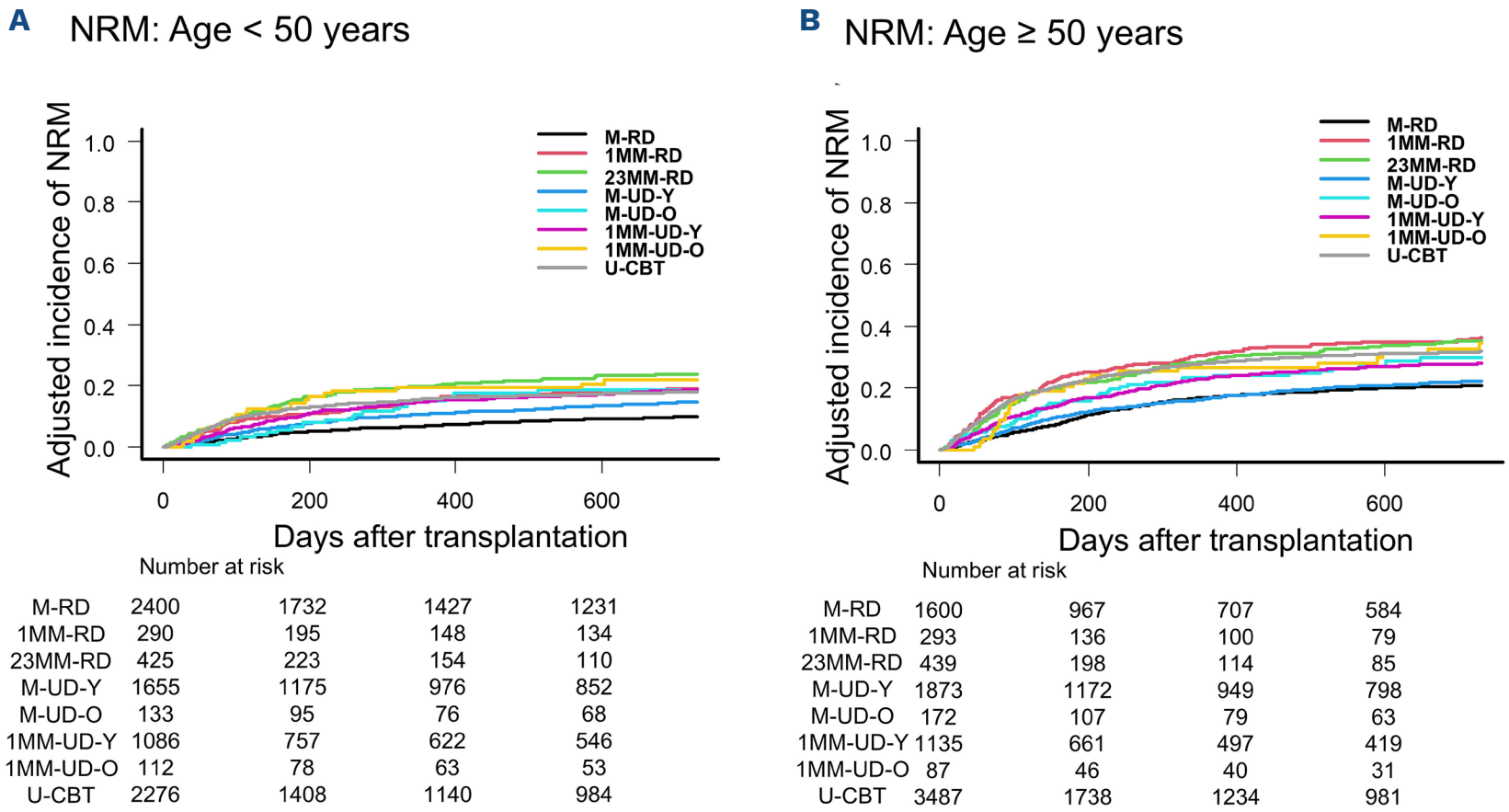


Figure 3. Adjusted cumulative incidences of non-relapse mortality and relapse according to patient age. (A, B) The adjusted cumulative incidence of non-relapse mortality in recipients of transplants from different donor groups, classified according to two patient age groups: <50 years (A) and ≥50 years (B). (C, D) The adjusted cumulative incidence of relapse in recipients of transplants from different donor groups, classified according to two patient age groups: <50 years (C) and ≥50 years (D). The adjusted factors are the variables included in the multivariate analysis (Table 2). NRM: non-relapse mortality; M-RD: related donors with HLA-A, -B, and -DR antigen match; 1MM-RD: related donors with one antigen mismatch in the graft-*versus*-host direction; 23MM-RD: related donors with two or three antigen mismatches in the graft-*versus*-host direction; M-UD-Y: unrelated donors with HLA-A, -B, -C, and -DRB1 allele match <50 years old; M-UD-O: unrelated donors with HLA-A, -B, -C, and -DRB1 allele match ≥50 years old; 1MM-UD-Y: unrelated donors with one allele/antigen mismatch in the graft-*versus*-host direction <50 years old; 1MM-UD-O: unrelated donors with one allele/antigen mismatch in the graft-*versus*-host direction ≥50 years old; U-CBT: unrelated cord blood transplant.

strategies in each healthcare setting.

In this study, the benefit is primarily attributed to donor age. A large CIBMTR analysis demonstrated that younger donor age was the only factor consistently associated with improved survival (~3% increase in 2-year OS per 10-year decrease).[27] Mechanistically, younger donor grafts are thought to support more robust immune reconstitution and disease surveillance, potentially compensating for age-related host factors such as thymic involution, inflamm-aging, and hematopoietic stem cell exhaustion.[28] These observations suggest a biological rationale for the consideration of prioritizing younger unrelated donors for older transplant recipients.

For patients aged ≥50 years without an available M-RD or M-UD, the most suitable alternative donor was a 1MM-UD-Y because of the lower risk of NRM compared with the risk when using a 1MM-RD or a 23MM-RD. The higher risk of grade 3-4 GvHD observed in the 1MM-UD-Y group compared with the M-RD group in patients aged <50 years was not noted in patients aged ≥50 years (*Online Supplementary Table S5*). This potentially leads to a lower risk of NRM in the 1MM-UD-Y group, resulting in the absence of a significant difference in OS compared with the M-RD group. In addition, U-CB may be the second suitable alternative donor for patients aged ≥50 years without an available M-RD or M-UD, because of the lower risk of acute and chronic GvHD (*Online Supplementary Table S5*). In patients aged ≥50 years, donor sources with less GvHD may lead to better survival rates. By contrast, allo-HCT from 1MM-RD or 23MM-RD was inferior compared with that from other donor source groups. In particular, the 23MM-RD group had a higher proportion of high-risk patients; other unknown confounding factors may have influenced the results. Additionally, although 34% of the patients in the 1MM-RD group and 51% of those in the 23MM-RD group underwent *in vivo* T-cell depletion, future results may differ due to the anticipated increase in the use of GvHD prophylaxis with post-transplant cyclophosphamide. Some studies using Japanese registry data have already reported that patients undergoing HLA-haploidentical peripheral blood stem cell transplantation with post-transplant cyclophosphamide have OS rates comparable to those of patients undergoing cord blood transplantation or HLA-matched unrelated bone marrow transplantation.[29,30]

The primary limitation of this study is the heterogeneity of the patient backgrounds within each donor group, which is attributable to its retrospective design and inherent selection bias. The TRUMP data do not elucidate the rationale underlying the physicians' selection of donor sources. The choice of donor source may have varied depending on whether the physician determined that allo-HCT needed to be expedited, potentially influencing the outcomes. Another limitation is that it was not possible to determine whether post-transplant cyclophosphamide was used for allo-HCT from the 1MM-RD and 23MM-RD groups according to the rules of the TRUMP data at the time of the study. This could have affected the results of the two groups. Finally, while our study demonstrated a consistent advantage of younger unrelated donors, the dataset did not provide sufficient granularity to define an exact optimal donor age threshold in matched and mismatched unrelated donor settings.

To further refine donor selection strategies, we propose the development of a comprehensive algorithm that incorporates donor age, donor-recipient sex match, cytomegalovirus serostatus, Disease Risk Index, *KIR* genotype, and other relevant clinical or immunological factors known to affect transplant outcomes. Moreover, future prospective and multicenter studies are warranted to validate the age-related associations observed in this retrospective study and to support personalized donor selection in diverse clinical settings.

In conclusion, donor selection priorities in allo-HCT should be considered based on patient and donor age. If the physician determines that the transplant can be delayed for a coordinated period, allo-HCT from a younger M-UD may be preferred over that from an M-RD, particularly in patients aged ≥50 years. However, a large prospective study is warranted to confirm these results.

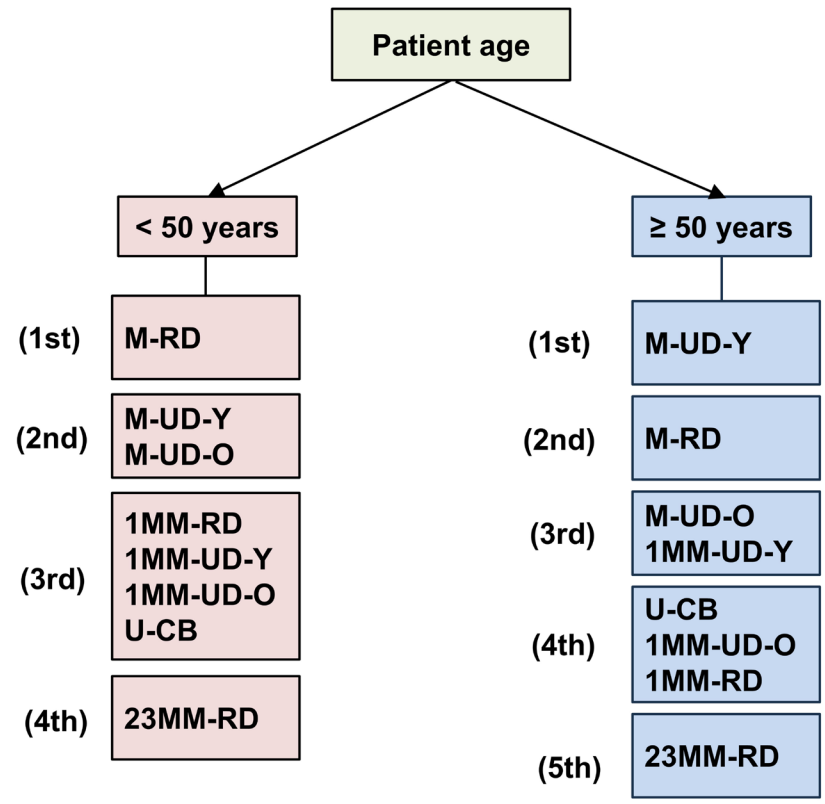


Figure 4. Donor selection priorities for allogeneic hematopoietic cell transplantation stratified by patient age. Donor selection priorities are illustrated according to two patient age groups (<50 years *vs.* ≥50 years). M-RD: related donors with HLA-A, -B, and -DR antigen match; M-UD-Y: unrelated donors with HLA-A, -B, -C, and -DRB1 allele match <50 years old; M-UD-O: unrelated donors with HLA-A, -B, -C, and -DRB1 allele match ≥50 years old; 1MM-RD: related donors with one antigen mismatch in the graft-*versus*-host direction; 1MM-UD-Y: unrelated donors with one allele/antigen mismatch in the graft-*versus*-host direction <50 years old; 1MM-UD-O: unrelated donors with one allele/antigen mismatch in the graft-*versus*-host direction ≥50 years old; U-CBT: unrelated cord blood transplant; 23MM-RD: related donors with two or three antigen mismatches in the graft-*versus*-host direction.

Disclosures

No conflicts of interest to disclose.

Contributions

KK, JK, SS, FK, MH and YK designed the study. KK and YK performed the statistical analysis and wrote the manuscript. NU, ND, WT, TN, YK, MT, MS, SY, TE, TK, HN and SO provided the patients' data. FI, JK, TF and YA collected the patients' data. All authors interpreted the data, and reviewed and approved the final manuscript.

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Data-sharing statement

The data of this study are not publicly available due to ethical restrictions that their divulgation would exceed the scope of the recipient/donor consent for research use in the registry.

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