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

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Author contributions

K.K., J.K., S.S., F.K., M.H., and Y. K. designed the study; K.K. and Y. K. performed the statistical analysis and wrote the manuscript; N.U., N.D., W.T., T.N., Y.K., M.T., M.S., S.Y., T.E., T.K., H.N., and S.O. provided the patient data; F.I., J.K., T.F., and Y.A. collected the patient data. All authors interpreted the data, and reviewed and approved the final manuscript.

Conflict of interest

The authors declare that they have no conflict of interest.

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 among human leukocyte antigen (HLA)-matched related donors (M-RDs, n=4,106), HLA 1-antigen-mismatched related donors (1MM-RDs, n=592), HLA 2-3-antigen-mismatched related donors (23MM-RDs, n=882), HLA-matched unrelated donors (M-UDs, n=3,927), HLA 1-locus-mismatched unrelated donors (1MM-UDs, n=2,474), and unrelated cord blood units (U-CBs, n=5,867) between patients aged <50 years and those aged ≥50 years. 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 (OS) in the M-UD-Y group was significantly superior to that in the M-RD group (HR: 0.87, p=0.0039), whereas the M-UD-O group showed no advantage (HR: 1.08, p=0.48). In this age group, 1MM-RD, 23MM-RD, and U-CB were associated with significantly inferior OS, 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, OS 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 OS. Therefore, donor selection priorities in allo-HCT might differ according to patient 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, an optimal 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 (PT-CY) 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 graft-versus-host disease 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] including information on HCT performed in Japan. Patients (1) aged ≥16 years; (2) diagnosed with acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), chronic myeloid leukemia (CML), or myelodysplastic syndrome (MDS); (3) who

underwent initial allo-HCT between 2007 and 2017; and (4) who were suitable donors (related donors with HLA-A, -B, and -DR antigen match (M-RD), 1 antigen mismatch in the graft-versus-host (GVH) direction (1MM-RD), or 2-3 antigen mismatches in the GVH direction (23MM-RD); unrelated donors with HLA-A, -B, -C, and -DRB1 allele match (M-UD) or 1 allele/antigen mismatch in the GVH direction (1MM-UD); or unrelated cord blood (U-CB) units) were considered eligible for the study. 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-RDs, 1MM-RDs, 23MM-RDs, M-UDs, 1MM-UDs, and U-CBs, 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 it exceeds the scope of the recipient/donor's 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 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 (*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, CML in the first or second chronic phase, and MDS 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's 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 using the log-rank test. The probability rates of acute and chronic GVHD, relapse, and NRM were estimated using the cumulative incidence methods and compared among groups using 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: the patient's age at transplantation (<50 years or ≥50 years), donor type (M-RD, 1MM-RD, 23MM-RD, M-UD, 1MM-UD, or U-CB), patient's sex (male or female), disease type (AML, ALL, MDS, or CML), 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 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 patient characteristics of 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 (16–76) in the 1MM-RD group, 50 years (16–80) in the 23MM-RD group, 51 years (16–77) in the M-UD group, 50 years (16–74) in the 1MM-UD group, and 55 years (16–85) in the U-CB group ($p<0.001$). The M-RD group had the lowest median age among all groups, while 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 the remaining groups utilized this method in only 2%–4% of patients. Notably, the 23MM-RD group more frequently used reduced-intensity regimens than myeloablative regimens, and the number of transplants performed after 2013 was significantly higher than those performed before 2013.

OS, DFS, GRFS, relapse, and NRM

Figure 1A-E illustrates the adjusted probability rates of OS, DFS, GRFS, NRM, and relapse by donor source groups. The adjusted probability rates of OS at 3years were 52.7% (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 *Supplementary Table S1*.

Acute and chronic GVHD

In the multivariate analysis, the risk of grade III–IV acute GVHD was significantly higher in the 1MM-RD (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 (Supplemental Table 3). 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-CBT donor (HR: 0.43, 95% CI: 0.38–0.49, p<0.0001) groups compared with the M-RD group (*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; *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 (8.6) years for M-RD, 36.3 (7.3) years for M-UD-Y, and 52.2 (2.4) years for M-UD-O, 37.0 (7.4) years for 1MM-UD-Y, and 51.9 (2.8) years for 1MM-UD-O. For patients aged <50 years, the mean

ages of the donors (SD) were 35.8 (10.8) years for M-RD, 36.3 (7.5) years for M-UD-Y, 51.9 (1.7) years for M-UD-O, 36.4 (7.4) years for 1MM-UD-Y, and 51.8 (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, *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 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) (Table 4). 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).

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). The other donor groups also had a statistically significantly higher NRM than 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, the other donor groups also showed higher NRM compared to the M-RD group. 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, 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 noteworthy 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 (*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 donors. 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 group. This discrepancy is likely attributed to the reduction in the NRM risk when younger M-UDs are selected for patients aged ≥50 years, while maintaining a lower recurrence rate. In other words, older M-RDs no longer hold the advantage of lower NRM risk compared with younger

M-UDs. Importantly, although selecting a younger M-RD is generally not feasible in older patients, our sub-analysis suggests that in the M-RD setting, patients aged ≥50 years who received transplants from younger M-RDs achieved outcomes comparable to those with younger M-UDs. 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-UDs 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 HR 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-RDs or younger M-UDs. The European Group for Blood and Marrow Transplantation reported that the outcomes of allo-HCT with older matched sibling donors (MSDs) or younger M-UDs for patients aged 55 years or older with AML in their first complete remission were comparable.[24] A previous CIBMTR study compared the allo-HCT outcomes between patients aged ≥50 years with MSDs aged ≥50 years and those with M-UDs younger than 50 years. None of the findings suggested that allo-HCT from younger M-UDs was superior to that from older MSDs.[25] A more recent CIBMTR study demonstrated that for allo-HCT patients with AML aged ≥50 years, using younger M-UDs (age ≤ 35 years) was associated with decreased relapse risk and improved DFS compared with using older MSDs (age ≥ 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, allo-HCT from younger M-UDs showed superior OS compared with that from M-RDs, due to the comparable NRM and low relapse rates. These discrepancies between our results and those reported by EBMT and CIBMTR may be explained by several factors. First, ethnic and genetic differences may contribute 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 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 owing to the lower risk of NRM compared with a 1MM-RD or a 23MM-RD. The higher risk of grade III–IV 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 (*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, owing to the lower

risk of acute and chronic GVHD (*Supplementary Table S5*). In patients aged ≥50 years, donor sources with less GVHD may have better survival rates. By contrast, allo-HCT from 1MM-RDs or 23MM-RDs 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 PT-CY. Some studies using the Japanese registry data have already reported that HLA-haploidentical peripheral blood stem cell transplantation with PT-CY has OS rates comparable to those of cord blood transplantation or HLA-matched unrelated bone marrow transplantation.[29,30]

The primary limitation of this study is the heterogeneity of 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 PT-CY 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 MUD/MMUD settings.

To further refine donor selection strategies, we propose the development of a comprehensive algorithm that incorporates donor age, donor–recipient sex match, CMV serostatus, disease risk index, KIR genotype, and other relevant clinical or immunologic

factors known to impact 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.

References

1. Yakoub-Agha I, Mesnil F, Kuentz M, et al. Allogeneic marrow stem-cell transplantation from human leukocyte antigen-identical siblings versus human leukocyte antigen-allelic-matched unrelated donors (10/10) in patients with standard-risk hematologic malignancy: a prospective study from the French Society of Bone Marrow Transplantation and Cell Therapy. J Clin Oncol. 2006;24(36):5695-5702.

2. Schetelig J, Bornhauser M, Schmid C, et al. Matched unrelated or matched sibling donors result in comparable survival after allogeneic stem-cell transplantation in elderly patients with acute myeloid leukemia: a report from the cooperative German Transplant Study Group. J Clin Oncol. 2008;26(32):5183-5191.

3. Kanda J, Saji H, Fukuda T, et al. Related transplantation with HLA-1 Ag mismatch in the GVH direction and HLA-8/8 allele-matched unrelated transplantation: a nationwide retrospective study. Blood. 2012;119(10):2409-2416.

4. Gragert L, Eapen M, Williams E, et al. HLA match likelihoods for hematopoietic stem-cell grafts in the U.S. registry. N Engl J Med. 2014;371(4):339-348.

5. Kawamura K. Effect of antithymocyte globulin on HLA-mismatched unrelated transplantation. Int J Hematol. 2019;110(1):22-29.

6. Kawamura K, Kanda J, Fuji S, et al. Impact of the presence of HLA 1-locus mismatch and the use of low-dose antithymocyte globulin in unrelated bone marrow transplantation. Bone Marrow Transplant. 2017;52(10):1390-1398.

7. Sugita J. HLA-haploidentical stem cell transplantation using posttransplant cyclophosphamide. Int J Hematol. 2019;110(1):30-38.

8. Fuchs EJ, O'Donnell PV, Eapen M, et al. Double unrelated umbilical cord blood vs HLA-haploidentical bone marrow transplantation: the BMT CTN 1101 trial. Blood. 2021;137(3):420-428.

9. Ciurea SO, Cao K, Fernandez-Vina M, et al. The European Society for Blood and Marrow Transplantation (EBMT) Consensus Guidelines for the Detection and Treatment of Donor-specific Anti-HLA Antibodies (DSA) in Haploidentical Hematopoietic Cell Transplantation. Bone Marrow Transplant. 2018;53(5):521-534.

10. Fuji S, Oshima K, Ohashi K, et al. Impact of pretransplant donor-specific anti-HLA antibodies on cord blood transplantation on behalf of the Transplant Complications Working Group of Japan Society for Hematopoietic Cell Transplantation. Bone Marrow Transplant. 2020;55(4):722-728.

11. D'Souza A, Fretham C, Lee SJ, et al. Current Use of and Trends in Hematopoietic Cell Transplantation in the United States. Biol Blood Marrow Transplant. 2020;26(8):e177-e182.

12. Atsuta Y, Suzuki R, Yoshimi A, et al. Unification of hematopoietic stem cell transplantation registries in Japan and establishment of the TRUMP System. Int J Hematol. 2007;86(3):269-274.

13. Atsuta Y. Introduction of Transplant Registry Unified Management Program 2 (TRUMP2): scripts for TRUMP data analyses, part I (variables other than HLA-related data). Int J Hematol. 2016;103(1):3-10.

14. Kanda J. Scripts for TRUMP data analyses. Part II (HLA-related data): statistical analyses specific for hematopoietic stem cell transplantation. Int J Hematol. 2016;103(1):11-19.

15. Przepiorka D, Weisdorf D, Martin P, et al. 1994 Consensus Conference on Acute GVHD Grading. Bone Marrow Transplant. 1995;15(6):825-828.

16. Sullivan KM, Agura E, Anasetti C, et al. Chronic graft-versus-host disease and other late complications of bone marrow transplantation. Semin Hematol. 1991;28(3):250-259.

17. Holtan SG, DeFor TE, Lazaryan A, et al. Composite end point of graft-versus-host

disease-free, relapse-free survival after allogeneic hematopoietic cell transplantation. Blood. 2015;125(8):1333-1338.

18. Giralt S, Ballen K, Rizzo D, et al. Reduced-intensity conditioning regimen workshop: defining the dose spectrum. Report of a workshop convened by the center for international blood and marrow transplant research. Biol Blood Marrow Transplant. 2009;15(3):367-369.

19. Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. Stat Med. 1999;18(6):695-706.

20. Gray RJ. A Class of K-Sample Tests for Comparing the Cumulative Incidence of a Competing Risk. Ann Stat. 1988;16(3):1141-1154.

21. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Ass. 1999;94(446):496-509.

22. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant. 2013;48(3):452-458.

23. Kollman C, Spellman SR, Zhang MJ, et al. The effect of donor characteristics on survival after unrelated donor transplantation for hematologic malignancy. Blood. 2016;127(2):260-267.

24. Peffault de Latour R, Labopin M, Cornelissen J, et al. In patients older than 55 years with AML in first CR, should we search for a matched unrelated donor when an old sibling donor is available? Bone Marrow Transplant. 2015;50(11):1411-1415.

25. Alousi AM, Le-Rademacher J, Saliba RM, et al. Who is the better donor for older hematopoietic transplant recipients: an older-aged sibling or a young, matched unrelated volunteer? Blood. 2013;121(13):2567-2573.

26. Abid MB, Estrada-Merly N, Zhang MJ, et al. Impact of Donor Age on Allogeneic

Hematopoietic Cell Transplantation Outcomes in Older Adults with Acute Myeloid Leukemia. Transplant Cell Ther. 2023;29(9):578.e1-578.e9.

27. Shaw BE, Logan BR, Spellman SR, et al. Development of an Unrelated Donor Selection Score Predictive of Survival after HCT: Donor Age Matters Most. Biol Blood Marrow Transplant. 2018;24(5):1049-1056.

28. Lin RJ, Elias HK, van den Brink MRM. Immune Reconstitution in the Aging Host: Opportunities for Mechanism-Based Therapy in Allogeneic Hematopoietic Cell Transplantation. Front Immunol. 2021;12:674093.

29. Sugita J, Atsuta Y, Nakamae H, et al. Comparable survival outcomes with haploidentical stem cell transplantation and cord blood transplantation. Bone Marrow Transplant. 2022;57(11):1681-1688.

30. Atsuta Y, Sugita J, Nakamae H, et al. Comparable survival outcomes with haploidentical stem cell transplantation and unrelated bone marrow transplantation. Bone Marrow Transplant. 2022;57(12):1781-1787.

Table 1. Patient characteristics

Variable	M-RD (n=4106)	1MM-RD (n=592)	23MM-RD (n=882)	M-UD (n=3927)	1MM-UD (n=2474)	U-CB (n=5867)	p value
Age, 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 (%)							
Female	1682 (41.0)	220 (37.2)	331 (37.5)	1608 (41.0)	980 (39.6)	2439 (41.6)	0.072
Male	2424 (59.0)	372 (62.8)	551 (62.5)	2317 (59.0)	1494 (60.4)	3426 (58.4)	
Disease (%)							
AML	2272 (55.3)	369 (62.3)	572 (64.9)	2064 (52.6)	1288 (52.1)	3700 (63.1)	<0.001
ALL	1060 (25.8)	115 (19.4)	186 (21.1)	931 (23.7)	594 (24.0)	1094 (18.6)	
MDS	630 (15.3)	89 (15.0)	92 (10.4)	797 (20.3)	494 (20.0)	881 (15.0)	
CML	144 (3.5)	19 (3.2)	32 (3.6)	135 (3.4)	98 (4.0)	192 (3.3)	
Disease risk (%)*							
Standard risk	3023 (73.7)	342 (57.8)	356 (40.4)	3005 (76.6)	1873 (75.7)	3335 (57.0)	<0.001
High risk	1081 (26.3)	250 (42.2)	526 (59.6)	918 (23.4)	600 (24.3)	2521 (43.0)	
ECOG PS (%)							
0-1	3790 (92.4)	515 (87.0)	748 (85.1)	3681 (93.9)	2286 (92.5)	5072 (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 (%)							
Myeloablative	3162 (77.1)	380 (64.3)	313 (35.5)	2870 (73.2)	1792 (72.5)	3799 (64.9)	<0.001
Reduced-intensity	941 (22.9)	211 (35.7)	568 (64.5)	1052 (26.8)	680 (27.5)	2059 (35.1)	
GVHD prophylaxis (%)							
CSA with MTX	3046 (74.2)	91 (15.4)	44 (5.0)	517 (13.2)	226 (9.1)	1321 (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)	3128 (79.7)	2090 (84.5)	2116 (36.1)	
TAC without MTX	90 (2.2)	133 (22.5)	617 (70.0)	198 (5.0)	104 (4.2)	2060 (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							

Yes	112 (2.7)	203 (34.3)	449 (50.9)	158 (4.0)	338 (13.7)	178 (3.0)	<0.001
No	3994 (97.3)	389 (65.7)	433 (49.1)	3769 (96.0)	2136 (86.3)	5689 (97.0)	
Year of transplantation (%)							
2007-2012	2280 (55.5)	322 (54.4)	259 (29.4)	1780 (45.3)	1127 (45.6)	2705 (46.1)	<0.001
2013-2017	1826 (44.5)	270 (45.6)	623 (70.6)	2147 (54.7)	1347 (54.4)	3162 (53.9)	

AML, acute myelogenous leukemia; ALL, acute lymphoblastic leukemia; CML, chronic myeloid leukemia; MDS, myelodysplastic syndrome; ECOG PS, Eastern Cooperative Oncology Group performance status; CSA, cyclosporine; TAC, tacrolimus; MTX, methotrexate

* Acute leukemia in the first or second remission, CML in the first or second chronic phase, and MDS were defined as standard-risk diseases, while others were defined as high-risk diseases.

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)

	OS*		NRM*		Relapse*	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
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

Abbreviations: OS, overall survival; DFS, disease-free survival; NRM, non-relapse mortality; HR, hazard ratio; CI, confidence interval

* Adjusted for other significant variables including recipient sex, disease, disease risk, ECOG PS, conditioning regimen, use of in vivo T-cell depletion, and year of transplantation

Figure legends

Figure 1. Adjusted survival probabilities and cumulative incidences in different donor groups. 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 M-RD, 1MM-RD, 23MM-RD, M-UD, 1MM-UD, and U-CB groups. The adjusted factors are the variables listed in the multivariate analysis (Table 2).

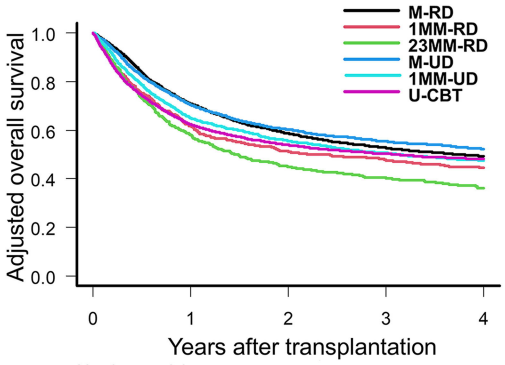
Figure 2. Adjusted overall survival according to patient age groups in different donor types. The adjusted probability of overall survival in the M-RD, 1MM-RD, 23MM-RD, M-UD-Y, M-UD-O, 1MM-UD-Y, 1MM-UD-O, and U-CB groups, classified according to two patient age groups: <50 years (A) and ≥50 years (B). The adjusted factors are the variables included in the multivariate analysis (Table 2).

Figure 3. Adjusted cumulative incidences of non-relapse mortality and relapse according to patient age. The adjusted cumulative incidence of non-relapse mortality and relapse in the M-RD, 1MM-RD, 23MM-RD, M-UD-Y, M-UD-O, 1MM-UD-Y, 1MM-UD-O, and U-CB groups, classified according to patient age group: <50 years (A and C) and ≥50 years (B and D). The adjusted factors are the variables included in the multivariate analysis (Table 2).

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).

Figure 1.

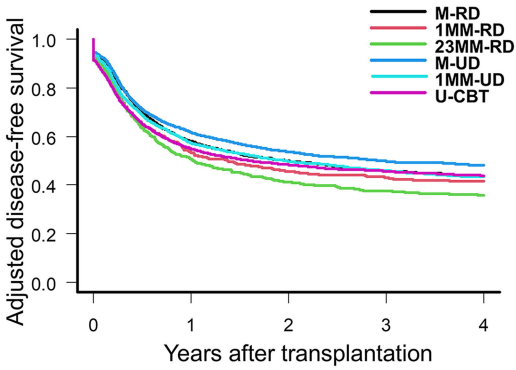
(A) OS



Number at risk

M-RD	4096	2698	1985	1538	1225
1MM-RD	591	306	219	168	126
23MM-RD	878	361	196	119	69
M-UD	3915	2438	1785	1379	1073
1MM-UD	2471	1419	1060	826	632
U-CBT	5838	2848	2020	1532	1164

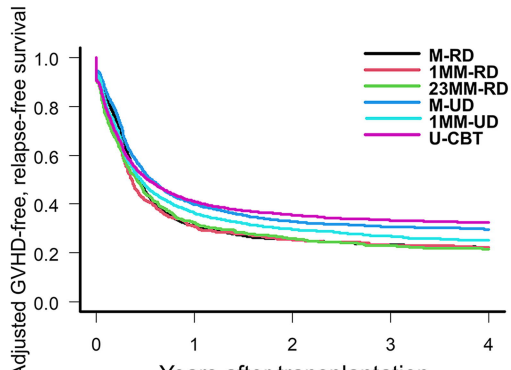
(B) DFS



Number at risk

M-RD	4000	2205	1698	1345	1083
1MM-RD	583	264	195	149	115
23MM-RD	864	293	167	101	59
M-UD	3853	2153	1621	1260	998
1MM-UD	2429	1261	956	760	581
U-CBT	5763	2456	1787	1381	1058

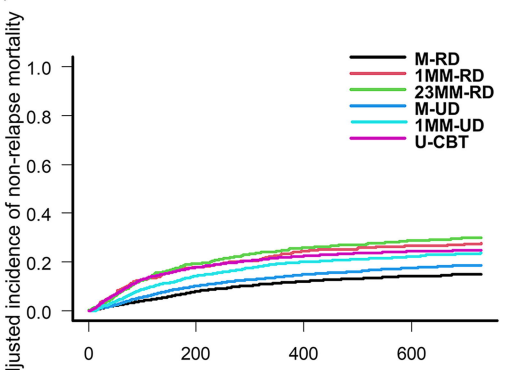
(C) GRFS



Number at risk

M-RD	3991	1262	925	720	560
1MM-RD	582	153	108	78	58
23MM-RD	864	192	111	67	38
M-UD	3850	1437	1017	777	622
1MM-UD	2422	812	578	452	328
U-CBT	5759	1873	1335	1021	795

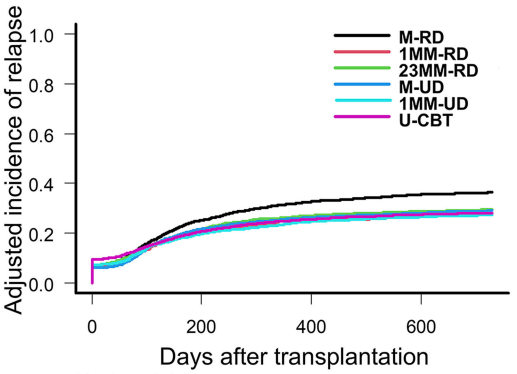
(D) NRM



Number at risk

M-RD	4000	2699	2134	1815
1MM-RD	583	331	248	213
23MM-RD	864	421	268	195
M-UD	3853	2560	2088	1787
1MM-UD	2429	1546	1225	1051
U-CBT	5763	3146	2374	1965

(E) Relapse

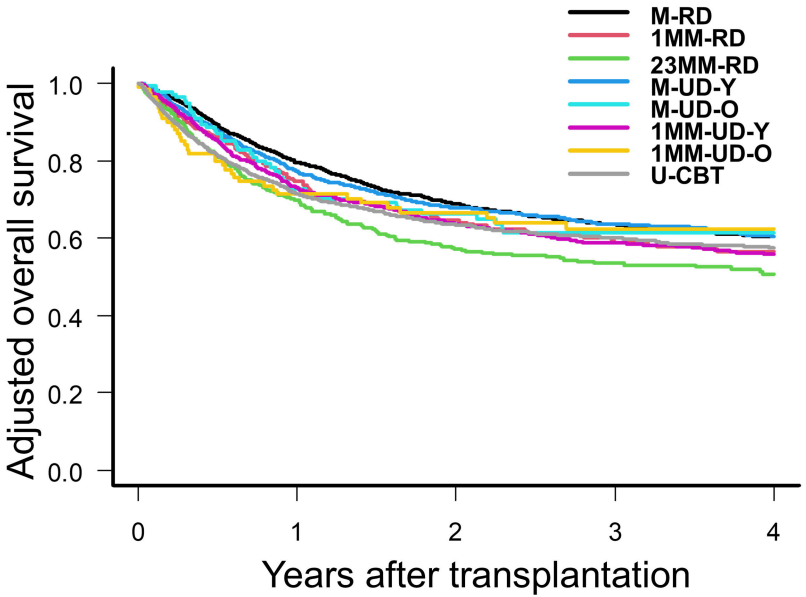


Number at risk

M-RD	4000	2699	2134	1815
1MM-RD	583	331	248	213
23MM-RD	864	421	268	195
M-UD	3853	2560	2088	1787
1MM-UD	2429	1546	1225	1051
U-CBT	5763	3146	2374	1965

Figure 2.

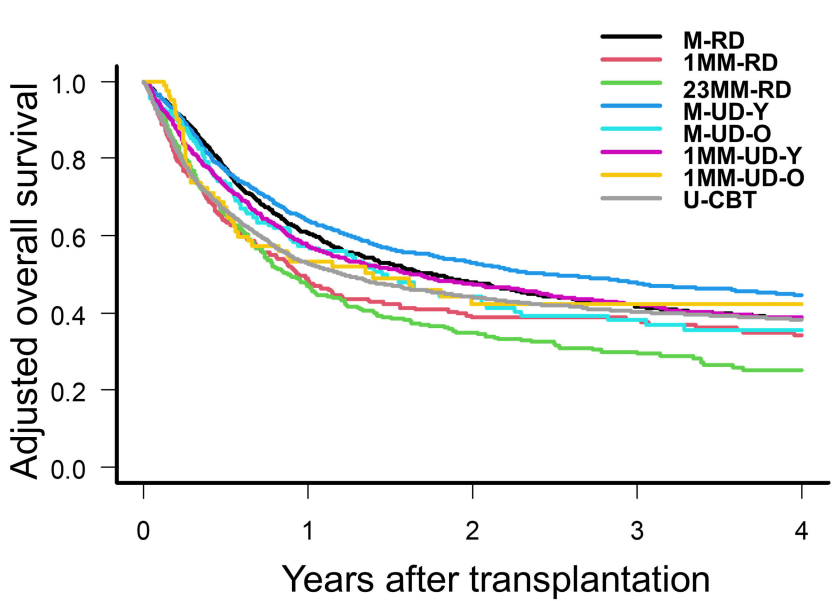
(A) OS: Age < 50 years



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

(B) OS: Age ≥ 50 years

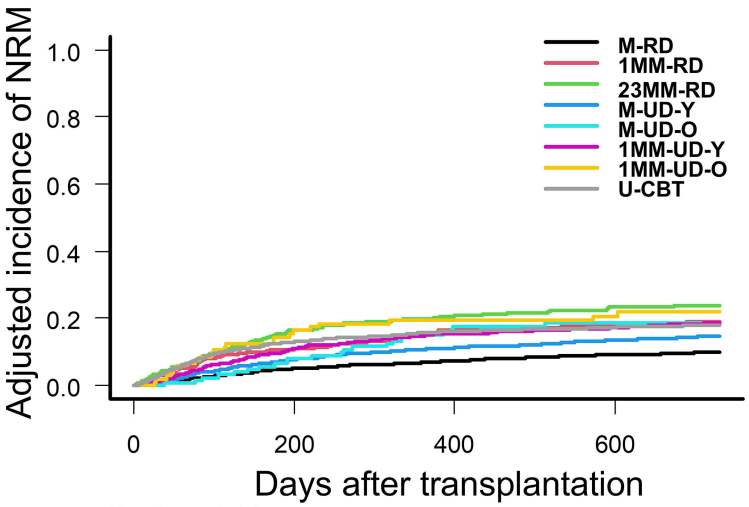


Number at risk

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 3.

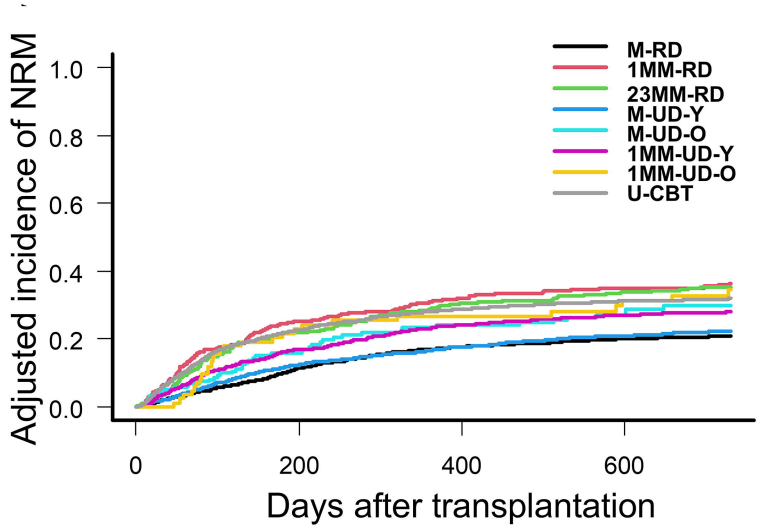
(A) NRM: Age < 50 years



Number at risk

M-RD	2400	1732	1427	1231
1MM-RD	290	195	148	134
23MM-RD	425	223	154	110
M-UD-Y	1655	1175	976	852
M-UD-O	133	95	76	68
1MM-UD-Y	1086	757	622	546
1MM-UD-O	112	78	63	53
U-CBT	2276	1408	1140	984

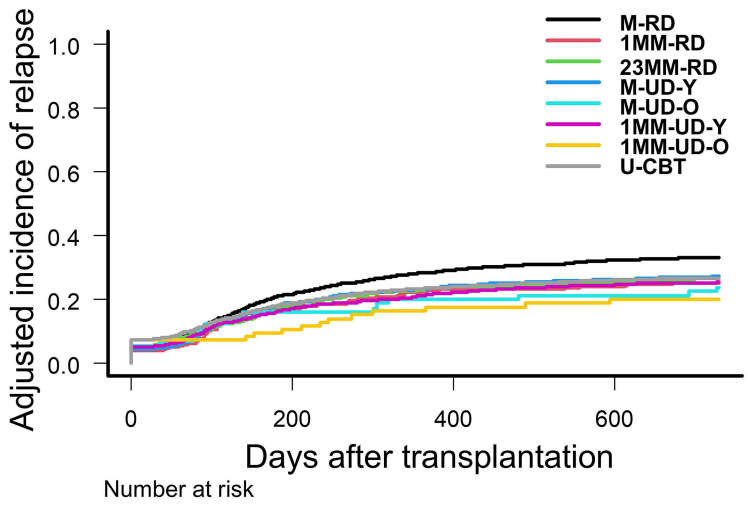
(B) NRM: Age ≥ 50 years



Number at risk

M-RD	1600	967	707	584
1MM-RD	293	136	100	79
23MM-RD	439	198	114	85
M-UD-Y	1873	1172	949	798
M-UD-O	172	107	79	63
1MM-UD-Y	1135	661	497	419
1MM-UD-O	87	46	40	31
U-CBT	3487	1738	1234	981

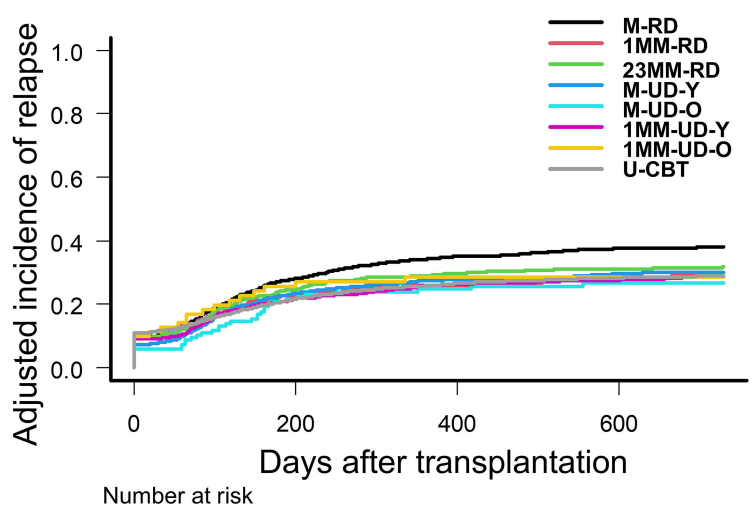
(C) Relapse: Age < 50 years



Number at risk

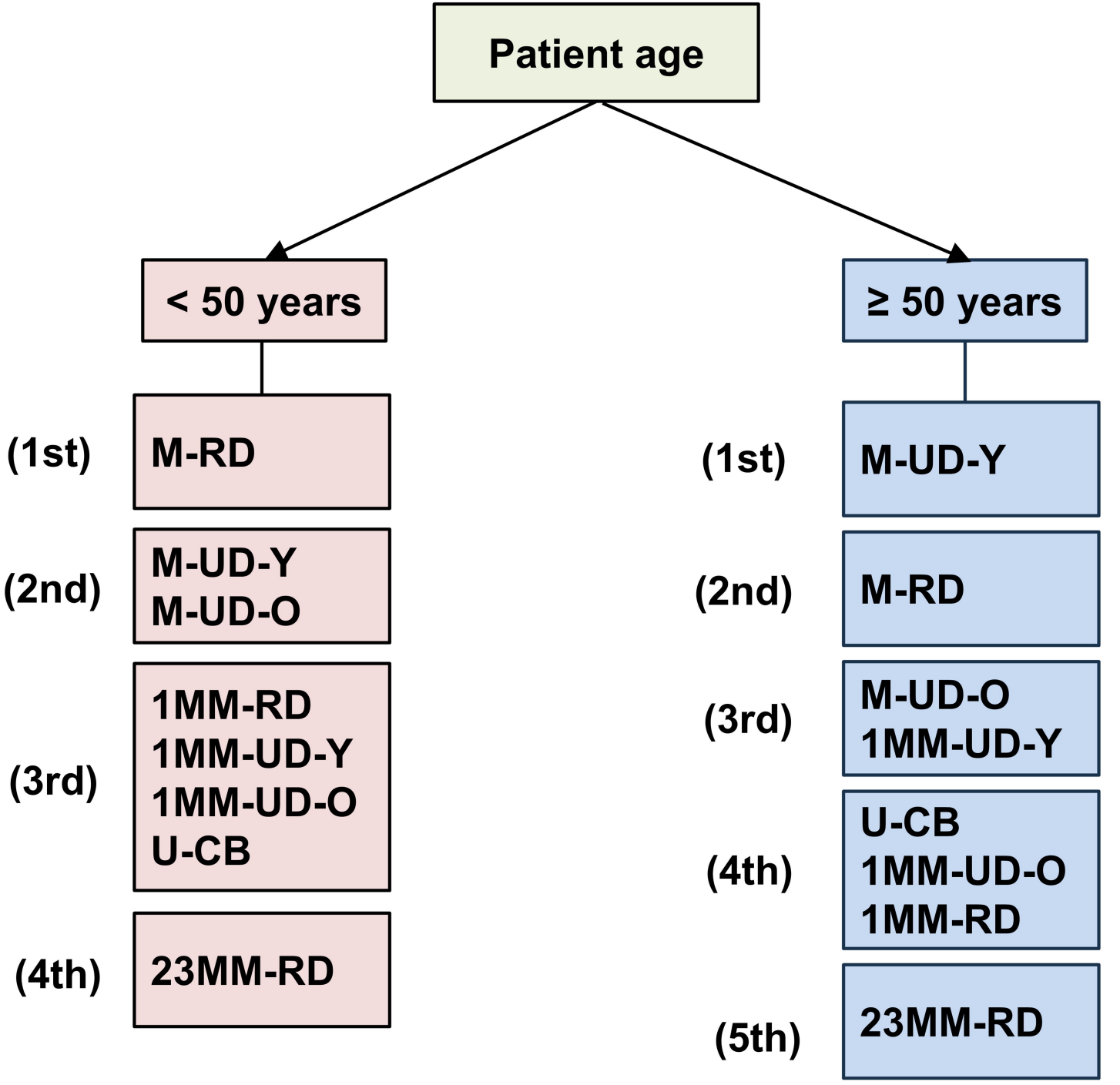
M-RD	2400	1732	1427	1231
1MM-RD	290	195	148	134
23MM-RD	425	223	154	110
M-UD-Y	1655	1175	976	852
M-UD-O	133	95	76	68
1MM-UD-Y	1086	757	622	546
1MM-UD-O	112	78	63	53
U-CBT	2276	1408	1140	984

(D) Relapse: Age ≥ 50 years



Number at risk

M-RD	1600	967	707	584
1MM-RD	293	136	100	79
23MM-RD	439	198	114	85
M-UD-Y	1873	1172	949	798
M-UD-O	172	107	79	63
1MM-UD-Y	1135	661	497	419
1MM-UD-O	87	46	40	31
U-CBT	3487	1738	1234	981


Patient age
< 50 years
≥ 50 years
(1st)
M-RD
(2nd)
M-UD-Y
M-UD-O
(3rd)
1MM-RD
1MM-UD-Y
1MM-UD-O
U-CB
(4th)
23MM-RD
(1st)
M-UD-Y
(2nd)
M-RD
(3rd)
M-UD-O
1MM-UD-Y
(4th)
U-CB
1MM-UD-O
1MM-RD
(5th)
23MM-RD

Supplementary Table S1. Results of the multivariate analyses of overall survival, disease-free survival, non-relapse mortality, and relapse in all patients

	OS*		DFS†		NRM‡		Relapse†	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
M-RD	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
1MM-RD	1.26 (1.12-1.41)	0.00012	1.11 (0.99-1.25)	0.069	1.93 (1.61-2.31)	<0.0001	0.72 (0.61-0.84)	<0.0001
23MM-RD	1.46 (1.33-1.62)	<0.0001	1.23 (1.11-1.37)	0.00012	2.15 (1.82-2.54)	<0.0001	0.77 (0.67-0.89)	0.00040
M-UD	0.94 (0.88-1.01)	0.093	0.89 (0.84-0.95)	0.00037	1.27 (1.13-1.43)	<0.0001	0.77 (0.71-0.84)	<0.0001
1MM-UD	1.12 (1.04-1.20)	0.0032	1.02 (0.95-1.10)	0.58	1.68 (1.48-1.90)	<0.0001	0.72 (0.65-0.79)	<0.0001
U-CB	1.19 (1.12-1.26)	<0.0001	1.08 (1.02-1.14)	0.011	1.70 (1.54-1.88)	<0.0001	0.76 (0.71-0.82)	<0.0001

Abbreviations: OS, overall survival; DFS, disease-free survival; NRM, non-relapse mortality; HR, hazard ratio; CI, confidence interval

* Adjusted for other significant variables including recipient age, recipient sex, disease, disease risk, ECOG PS, conditioning regimen, and year of transplantation

†Adjusted for other significant variables including recipient age, recipient sex, disease, disease risk, ECOG PS, conditioning regimen, use of *in vivo* T-cell depletion, and year of transplantation

‡Adjusted for other significant variables including recipient age, recipient sex, disease, disease risk, ECOG PS, conditioning regimen, GVHD prophylaxis, use of in vivo T-cell depletion, and year of transplantation

Supplementary Table S2. Results of multivariate analyses of acute and chronic graft-versus-host disease in all patients

	Grade II-IV acute GVHD[a]		Grade III-IV acute GVHD[b]		Chronic GVHD[c]		Extensive chronic GVHD[d]	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
M-RD	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
1MM-RD	1.35 (1.17-1.56)	<0.0001	1.59 (1.26-2.00)	0.00011	0.97 (0.82-1.14)	0.84	1.00 (0.82-1.22)	1.00
23MM-RD	1.17 (1.03-1.33)	0.016	1.74 (1.42-2.12)	<0.0001	0.71 (0.60-0.84)	<0.0001	0.66 (0.53-0.82)	0.00020
M-UD	1.09 (1.01-1.18)	0.022	0.91 (0.78-1.06)	0.24	0.85 (0.78-0.93)	0.00025	0.82 (0.73-0.92)	0.00077
1MM-UD	1.43 (1.32-1.55)	<0.0001	1.34 (1.14-1.58)	0.00038	0.91 (0.83-1.01)	0.070	0.87 (0.76-0.99)	0.033
U-CB	1.14 (1.06-1.22)	0.00022	0.98 (0.86-1.12)	0.79	0.64 (0.59-0.69)	<0.0001	0.43 (0.38-0.49)	<0.0001

Abbreviations: GVHD, graft-versus-host disease; HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; GVHD, graft-versus-host disease.

[a]Adjusted for other significant variables including recipient age, disease, disease risk, ECOG PS, and conditioning regimen.

[b]Adjusted for other significant variables including recipient age, recipient sex, disease, disease risk, GVHD prophylaxis, and use of *in vivo* T-cell depletion.

[c]Adjusted for other significant variables including recipient age, recipient sex, disease, disease risk, conditioning regimen, GVHD prophylaxis, use of in vivo T-cell depletion, and year of transplantation.

[d]Adjusted for other significant variables including recipient age, recipient sex, disease, disease risk, conditioning regimen, GVHD prophylaxis, and year of transplantation.

Supplementary Table S3. Interaction test for overall survival, disease-free survival, non-relapse mortality, and relapse between age and donor type

	OS		DFS		NRM		Relapse	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Age50 * 1MM-RD	1.02 (0.80-1.29)	0.89	1.11 (0.88-1.40)	0.39	0.86 (0.61-1.22)	0.41	1.01 (0.73-1.38)	0.97
Age50 * 23MM-RD	0.89 (0.73-1.08)	0.24	0.92 (0.76-1.11)	0.39	0.67 (0.50-0.91)	0.0094	1.01 (0.79-1.29)	0.93
Age50 * M-UD	0.88 (0.76-1.00)	0.055	0.88 (0.78-1.01)	0.063	0.78 (0.63-0.96)	0.019	0.95 (0.80-1.12)	0.50
Age50 * 1MM-UD	0.92 (0.79-1.08)	0.31	0.98 (0.85-1.13)	0.76	0.80 (0.64-1.00)	0.047	1.03 (0.85-1.25)	0.79
Age50 * U-CBT	0.92 (0.82-1.04)	0.20	0.94 (0.84-1.05)	0.26	0.88 (0.73-1.06)	0.18	0.85 (0.74-0.99)	0.031

Abbreviations: OS, overall survival; DFS, disease-free survival; NRM, non-relapse mortality; HR, hazard ratio; CI, confidence interval.

Supplementary Table S4. Interaction test for overall survival between age and donor type, classified the M-UD and 1MM-UD groups according to donor age.

	HR (95% CI)	p value
Age50 * 1MM-RD	1.06 (0.84-1.34)	0.63
Age50 * 23MM-RD	0.89 (0.74-1.08)	0.23
Age50 * M-UD-Y	0.86 (0.75-0.99)	0.035
Age50 * M-UD-O	1.08 (0.74-1.56)	0.70
Age50 * 1MM-UD-Y	0.91 (0.78-1.07)	0.25
Age50 * 1MM-UD-O	1.04 (0.67-1.59)	0.87
Age50 * U-CBT	0.94 (0.84-1.06)	0.30

Abbreviations: OS, overall survival; HR, hazard ratio; CI, confidence interval.

Supplementary Table S5. Results of multivariate analyses of acute and chronic graft-versus-host disease, classified according to two patient age groups (<50 years or ≥50 years).

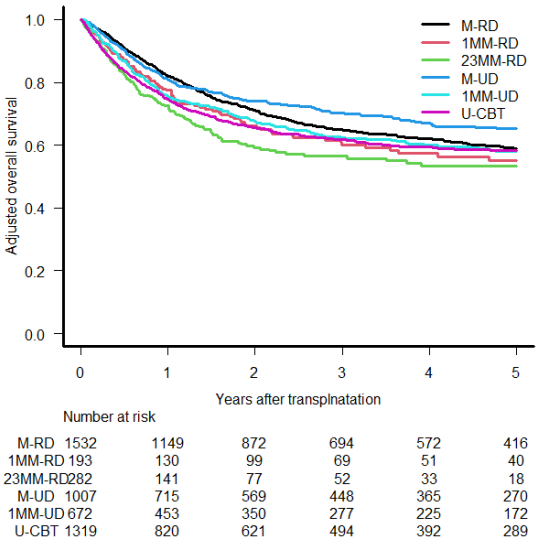
	Grade III-IV acute GVHD[a]		Extensive chronic GVHD[a]	
	HR (95% CI)	p value	HR (95% CI)	p value
Age <50 years				
M-RD	1.00	Reference	1.00	Reference
1MM-RD	1.58 (1.12-2.24)	0.0095	1.29 (0.98-1.70)	0.074
23MM-RD	1.95 (1.47-2.59)	<0.0001	0.84 (0.61-1.16)	0.29
M-UD-Y	1.07 (0.85-1.34)	0.57	0.85 (0.72-0.99)	0.042
M-UD-O	0.81 (0.42-1.55)	0.52	0.76 (0.50-1.18)	0.22
1MM-UD-Y	1.64 (1.30-2.06)	<0.0001	0.95 (0.79-1.13)	0.55
1MM-UD-O	1.38 ‘0.79-2.40(	0.26	1.35 (0.93-1.96)	0.12
U-CB	0.95 (0.77-1.16)	0.60	0.46 (0.39-0.54)	<0.0001
Age ≥50 years				
M-RD	1.00	Reference	1.00	Reference
1MM-RD	1.59 (1.16-2.18)	0.0042	0.92 (0.67-1.26)	0.60
23MM-RD	1.43 (1.06-1.93)	0.018	0.66 (0.45-0.92)	0.013
M-UD-Y	0.77 (0.61-0.96)	0.019	0.79 (0.67-0.93)	0.0056
M-UD-O	1.25 (0.81-1.91)	0.32	0.92 (0.66-1.29)	0.64
1MM-UD-Y	1.05 (0.82-1.34)	0.69	0.80 (0.66-0.97)	0.022
1MM-UD-O	1.79 (1.06-3.04)	0.030	1.22 (0.78-1.90)	0.39
U-CB	0.99 (0.81-1.17)	0.78	0.42 (0.36-0.50)	<0.0001

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

[a]Adjusted for other significant variables including recipient sex, disease, disease risk, ECOG PS, conditioning regimen, GVHD prophylaxis, and use of in vivo T-cell depletion, and year of transplantation.

Supplementary Figure S1.

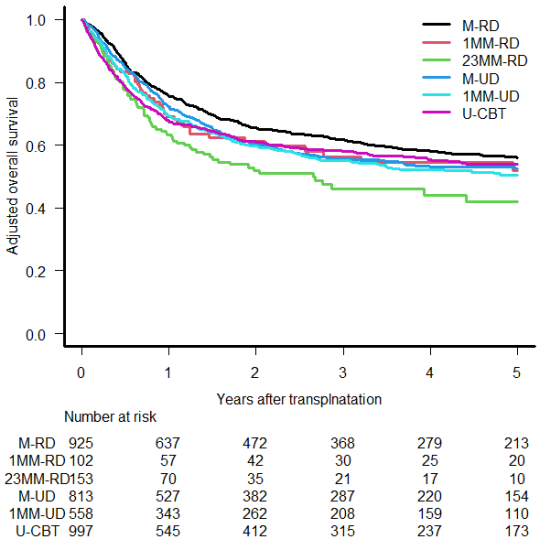
(A) Patient age: < 40 years



Number at risk

M-RD	1532	1149	872	694	572	416
1MM-RD	193	130	99	69	51	40
23MM-RD	282	141	77	52	33	18
M-UD	1007	715	569	448	365	270
1MM-UD	672	453	350	277	225	172
U-CBT	1319	820	621	494	392	289

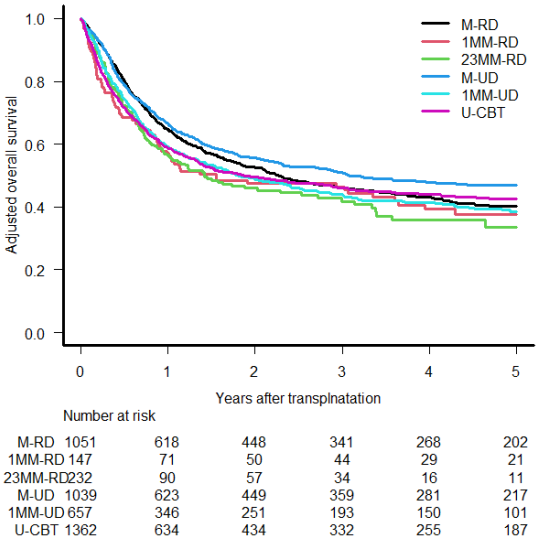
(B) Patient age: 40–49 years



Number at risk

M-RD	925	637	472	368	279	213
1MM-RD	102	57	42	30	25	20
23MM-RD	153	70	35	21	17	10
M-UD	813	527	382	287	220	154
1MM-UD	558	343	262	208	159	110
U-CBT	997	545	412	315	237	173

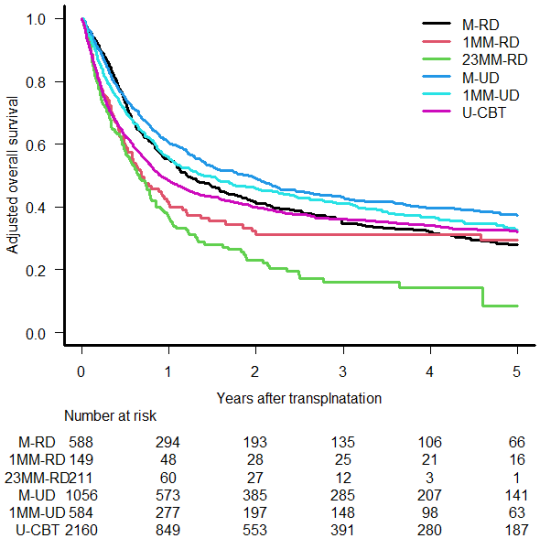
(C) Patient age: 50–59 years



Number at risk

M-RD	1051	618	448	341	268	202
1MM-RD	147	71	50	44	29	21
23MM-RD	232	90	57	34	16	11
M-UD	1039	623	449	359	281	217
1MM-UD	657	346	251	193	150	101
U-CBT	1362	634	434	332	255	187

(D) Patient age: ≥ 60 years



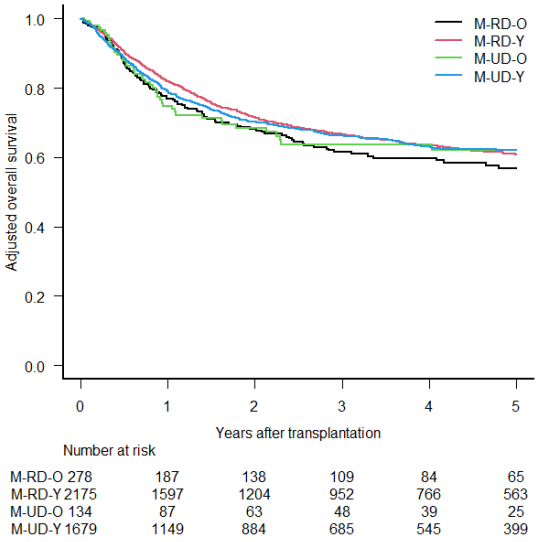
Number at risk

M-RD	588	294	193	135	106	66
1MM-RD	149	48	28	25	21	16
23MM-RD	211	60	27	12	3	1
M-UD	1056	573	385	285	207	141
1MM-UD	584	277	197	148	98	63
U-CBT	2160	849	553	391	280	187

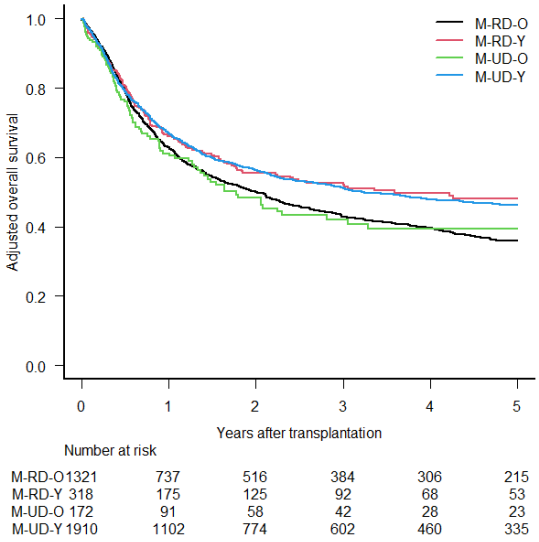
Supplementary Figure S1. Comparison of overall survival by donor source according to patient age. Overall survival by donor source stratified by patient age is shown: <40 years (A), 40–49 years (B), 50–59 years (C), and ≥60 years (D).

Supplementary Figure S2.

(A) OS: Age < 50 years



(B) OS: Age ≥ 50 years



Supplementary Figure S2. Adjusted overall survival according to patient age in related and unrelated donor groups. The adjusted probability of overall survival in the M-RD-O, M-RD-Y, M-UD-O, and M-UD-Y groups is shown, stratified by patient age: <50 years (A) and ≥50 years (B).