Favorable Outcomes after Single Cord Blood Transplantation for Patients with High-Risk Hematologic Diseases: A Single-Institute Retrospective Analysis

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Title

Favorable outcomes after single cord blood transplantation for patients with high-risk hematological diseases; a single institute retrospective analysis

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Short title

Favorable outcomes of cord blood transplantation

Conflict of Interest Disclosure

The authors declare no competing financial interests.

Structured Abstract

Background: The donor selection algorithm for cord blood (CB) with regards to matched related and unrelated donors has not been fully investigated.

Objective: To assess the potential of CB transplantation (CBT) in patients with hematological malignancies, especially for high-risk patients, we performed a single-institute retrospective analysis and compared the clinical outcomes of CBT with those of HLA-matched sibling and unrelated donor transplantation.

Study Design: We included 394 patients aged 16 years and older with hematological diseases who received their first allogeneic hematopoietic cell transplantation between 1990 and 2018 at Kyoto University Hospital. These included 394 recipients of single unrelated cord blood units (UCB, n=108), HLA-matched sibling donors (MSDs, n=143), or HLA-matched unrelated donors (MUDs, n=143).

Results: There was no significant difference in relapse-free survival (RFS) between UCB, MSD, and MUD recipients (P=0.975). However, we found a significant interaction between transplant year and CBT outcomes (P=0.010), with significantly better outcomes observed in the more recent years. Furthermore, we found that CBT showed better RFS than matched donor transplantation (hazard ratio [HR], 0.50; 95% confidence interval [CI], 0.30–0.84). This impact was more prominent in high-risk patients (HR, 0.35; 95% CI, 0.16–0.77), with lower relapse rates (HR, 0.25; 95% CI, 0.11–0.54) and comparable non-relapse mortality (NRM) compared to matched donor transplantation. Extensive chronic GVHD was less frequently observed in CBT (HR, 0.58; 95% CI, 0.26–1.28).

Conclusions: CBT associated with favorable outcomes, particularly in high-risk patients, with good RFS and low relapse rates without an increase in NRM in the single institute study. Although the findings should be externally validated, CBT might serve as a reasonable donor choice, particularly in high-risk patients.

Introduction

Hematopoietic stem cell transplantation (HSCT) is a potentially curative strategy for a wide variety of hematological diseases. With the expansion of donor sources, unrelated cord blood (UCB) and haploidentical transplantations, especially those with post-transplant cyclophosphamide (Haplo-PTCY), have been used as alternatives when matched sibling donors (MSDs) and matched unrelated donors (MUDs) are unavailable[1, 2]. In particular, UCB has become an established source for HSCT because of its widespread availability, rapid accessibility, increased tolerance to human leukocyte antigen (HLA) mismatches, and decreased incidence of chronic graft-versus-host disease (GVHD)[3]. Serious concerns after cord blood transplantation (CBT) include graft failure and early transplant mortality. However, significant progress has been made in the implementation of CBT, particularly regarding the appropriate infused dosages of CD34+ cells and the degree of HLA disparity, the avoidance of donor-specific anti-HLA antibody (DSA) development in recipients, advances in conditioning regimens and GVHD prophylaxis, the management of severe pre-engraftment immune reactions (PIR), and center experience[4-6]. Such improvements over the past decade have decreased the risk of early mortality after CBT, which has led to an improvement in long-term overall survival (OS)[7, 8]. Several studies have demonstrated that CBT offers outcomes comparable to transplantation of other stem cell sources[9-14]. However, the rate of CBT has recently decreased in both Europe and the USA[15]. This is apparently not due to comparability between CBT and transplantation of other stem cell sources, but rather due to the increase in medical expenses associated with CBT, and the increasing use of Haplo-PTCY. CBT has shown better outcomes in patients with minimal residual diseases, potentially reflecting the potent graft-versus-leukemia (GVL) effects of this

procedure[16]. In the future, it might be important to select for donor sources according to the relapse risk of a patient. With the aim to assess the potential of CBT in patients with hematological malignancies, especially for high-risk patients, we performed a single-institute retrospective analysis and compared the clinical outcomes of CBT with those of HLA-matched sibling and unrelated donor transplantation.

Methods

Data source

A total of 571 consecutive patients aged 16–73 years who received their first allogeneic HSCT for hematological diseases at Kyoto University Hospital between 1990 and 2018 were reviewed. These included 394 recipients of single unrelated cord blood units (UCB, n=108), HLA-matched sibling donors (MSDs, n=143), or HLA-matched unrelated donors (MUDs, n=143). MSDs have remained our first choice of donor source if available, followed by MUDs. In the absence of these donor sources, HLA-1 allele mismatched unrelated donors would be considered. In the case of emergencies, UCB, followed by HLA-haploidentical donors, would be opted for instead of unrelated donors. For UCB donors, we prioritize units with total nucleated cell doses >2.0 x 10^7/kg, and select those with the maximum available number of CD34 positive cells. HLA typing with 4/6 matches (HLA-A, HLA-B, and HLA-DRB1) was considered acceptable in our institute. We have consistently utilized such practices over the years. Double-unit UCBTs (dUCBTs), were not included in the present study, as they are currently only under clinical trial in Japan. This study was approved by the institutional review board of Kyoto University, where this study was organized. This study was conducted in accordance with the Declaration of Helsinki.

Definitions

Relapse-free survival (RFS) was defined as the time from transplant to relapse, death, or the last date of follow-up. OS was defined as the time from transplant to the last date of follow-up or death. GVHD-free and relapse-free survival (GRFS) was defined as the time from transplant to grade III–IV acute GVHD, extensive chronic GVHD, relapse,

death, or the last date of follow-up. Relapse was defined based on morphological and clinical evidence of disease activity, and non-relapse mortality (NRM) was defined as the time to death without relapse. Neutrophil engraftment was defined as the first of 3 consecutive days with a neutrophil count of 500/μl, without evidence of autologous reconstitution or graft rejection within the first 100 days. Acute and chronic GVHD were diagnosed and graded using standard criteria[17, 18]. The intensity of conditioning regimens was classified as myeloablative if either total body irradiation >8 Gy, oral busulfan ≥9 mg/kg, intravenous busulfan ≥7.2 mg/kg, melphalan >140 mg/m^2, or thiotepa ≥10 mg/kg was used, and otherwise as reduced intensity[19]. We defined HLA matching based on HLA-A, HLA-B, and HLA-DR antigen levels in UCB and sibling donors, and based on HLA-A, HLA-B, and HLA-DRB1 allele levels in unrelated donors. Standard-risk diseases were defined as acute myeloid leukemia (AML) and acute lymphoid leukemia (ALL) in complete remission, myelodysplastic syndrome (MDS) with refractory anemia or refractory anemia with ringed sideroblasts, chronic myelogenous leukemia (CML) in the chronic and accelerated phases, adult T-cell leukemia (ATL) in complete remission, lymphoma in complete or partial remission, multiple myeloma in complete remission, and non-malignant hematological diseases; all other conditions were considered high-risk diseases. In the subgroup analysis, AML, ALL, MDS, CML, myeloproliferative neoplasm, and ATL were classified as very-high-risk in the presence of ≥20% blasts in the bone marrow or ≥10% blasts in the peripheral blood, and lymphoma size of ≥5 cm, spread of over 30 regions, or infiltration of the bone marrow and spleen.

Endpoints

The primary endpoint of the study was the impact of donor source on RFS. Secondary endpoints were OS, GRFS, relapse, NRM, neutrophil engraftment, grade III–IV acute GVHD, and extensive chronic GVHD.

Statistical analysis

The probabilities of RFS, OS, and GRFS were estimated using the Kaplan-Meier method, and groups were compared using the log-rank test. The incidence of relapse, NRM, neutrophil engraftment, and acute and chronic GVHD were estimated using the cumulative incidence curve[20]. Competing events included death without relapse for relapse, relapse for NRM, and death for both neutrophil engraftment and acute and chronic GVHD. The groups were compared using the Gray's test[21]. Cox proportional hazards models were used to evaluate the effects of donor source and other variables on RFS, OS, and GRFS, while Fine and Gray's proportional hazards models were used for all other endpoints[22]. Chronic GVHD was assessed in patients who survived at least 100 days. The following covariates were considered: patient sex, age (<50 or ≥50 years old), disease diagnosis (myeloid malignancies, lymphoid malignancies, or non-malignant disease), performance status (0–1 or >1), disease status (standard risk or high risk), conditioning regimen intensity (reduced intensity or myeloablative), and year of transplantation (1990–2010 or 2011–2018). GVHD prophylaxis was not considered, given that it is donor source-dependent. The effects of ATG were also not considered because it was only used in 2% of the patients in the cohort. If a variable had >5% missing values, missing data were included in the analysis as a separate category. Confounding variables were selected with a variable retention criterion of $P<0.10$ in the univariate analysis of the total cohort. Significant variables, in addition to donor source,

were subsequently included in the multivariate analysis of both the total cohort and the subgroup cohort. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan)[23].

Results

Patient characteristics for the total cohort

Table 1 summarizes the patient and transplant characteristics of the total cohort. Among the 394 patients, 108 received single UCB units, 143 received MSD transplantation (89 bone marrow grafts and 54 peripheral-blood stem cell grafts), and 143 received MUD transplantation (bone marrow grafts in all). Median age of the UCB, MSD, and MUD groups were 49, 46, and 48 years, respectively (P=0.097). Similar rates of high-risk disease were observed in each group (UCB, 36.1%; MSD, 32.9%; and MUD, 29.4%; P=0.26). The median follow-up of survivors was 3.9, 7.6, and 6.4 years, respectively. In terms of UCB unit characteristics, the median total nucleated cells (TNCs) cryopreserved and infused (x 10^7/kg), and CD34-positive cells infused (x 10^5/kg) were 2.63 (1.51–6.32) and 0.67 (0.18–1.91), respectively. Although 16 recipients (11 of UCB, 1 of MSD, and 4 of MUD) had HLA antibodies, none of them had donor-specific HLA antibodies.

RFS, OS, and GRFS of the total cohort

The 3-year RFS rates in the UCB, MSD, and MUD groups were 53.1% (95% CI, 42.8–62.3%), 50.9% (95% CI, 42.3–58.9%), and 47.9% (95% CI, 39.3– 56.1%), respectively (P=0.975, **Figure 1a**). The 3-year OS rates were 60.8% (95% CI, 50.5 – 69.6%), 59.4% (95% CI, 50.6–67.2%), and 56.6% (95% CI, 47.7–64.5%), respectively (P=0.924, **Figure 1b**). The 3-year GRFS rates were 43.0% (95% CI, 33.1–52.4%), 38.2% (95% CI, 29.7–46.6%), and 37.4% (95% CI, 29.1–45.6%), respectively (P=0.934, **Figure 1c**). Since the MSD and MUD groups showed comparable RFS, OS, and GRFS in the multivariate analysis (**Table 2**), they were treated as a single group

(matched donor transplantation, MDT) in later analyses. Furthermore, a significant interaction between the transplant period and stem cell source was demonstrated (RFS, P=0.010; OS, P=0.159; GRFS, P<0.001), indicating that RFS and GRFS of CBT significantly improved in recent years. Therefore, we decided to perform a separate analysis for each period (1990–2010 and 2011–2018), and focused on the more recent period to reflect current practices.

RFS in the old period

Patient and transplant characteristics according to donor source in the older period are summarized in **Supplementary Table 1**. The 3-year RFS rate was 37.9% (95% CI, 21.6–54.2%) after CBT and 51.4% (95% CI, 44.3–48.1%) after MDT (P=0.0942, **Figure 2a**).

RFS in the recent period

Patient and transplant characteristics according to donor source in the recent period are summarized in **Supplementary Table 2**. Among them, 75 received CBT and 81 received MDT (60 bone marrow transplants and 21 peripheral blood transplants). The performance status in the CBT cohort was higher than that in the MDT cohort (P=0.056). In CBT, the fludarabine and melphalan (Flu/Mel) regimen was most frequently used in reduced intensity conditioning (RIC), while the combination of busulfan and cyclophosphamide (BU/CY) regimen was less frequently used in myeloablative conditioning (MAC). The median follow-up periods of survivors were 3.3 and 3.5 years, respectively.

The 3-year RFS rate was 60.4% (95% CI, 47.9–70.9%) after CBT and 43.3% (95% CI, 31.4–54.6%) after MDT (P=0.11, **Figure 2b**). Multivariate analysis showed that CBT associated with significantly better outcomes than MDT in the recent period. Since disease risk was considered the strongest prognostic factor for transplant outcomes and of clinical importance, outcomes of the standard- and high-risk groups were analyzed. The 3-year RFS rates in standard-risk patients were 65.6% (95% CI, 49.0–77.9%) after CBT and 55.7% (95% CI, 40.8–68.2%) after MDT (P=0.354, **Figure 2c**). In high-risk patients, the 3-year RFS rates were 49.7% (95% CI, 29.5–67.0%) and 8.2% (95% CI, 0.7–28.3%), respectively (P=0.0256, **Figure 2d**). Multivariate analysis showed that CBT was significantly associated with better RFS in high-risk patients (**Table 3**), although no significant interaction was observed, probably due to insufficient power (P=0.278). Even after exclusion of HLA-C allele mismatched transplantations from the available data, CBT remained significantly associated with better RFS (data not shown). In the subgroup analysis, we further categorized the high-risk patients into high and very high-risk groups. A total of 26 patients after CBT and 21 patients after MDT were evaluated. The 2-year RFS rates in very high-risk patients were 45.5% (95% CI, 16.7–70.7%) after CBT and 15.0% (95% CI, 1.0 – 45.7%) after MDT (P=0.106), while those in high-risk patients were 53.3% (95% CI, 26.3–74.4%) and 18.2% (95% CI, 2.9 – 44.2%), respectively (P=0.155). In the multivariate analysis, the HRs of CBT were consistently low in both the very high- and high-risk groups (HR 0.38, P=0.09; and HR 0.48, P=0.19, respectively).

OS and GRFS in the recent period

According to donor source, the 3-year OS rates in standard-risk patients were 80.8% (95% CI, 66.2–89.5%) after CBT and 65.5% (95% CI, 50.1–77.1%) after MDT (P=0.601, **Figure 3a**), while those in high-risk patients were 49.7% (95% CI, 29.5–67.0%) and 28.0% (95% CI, 9.7–49.9%), respectively (P=0.45, **Figure 3b**). In the multivariate analysis, OS after CBT trended better than that after MDT in high-risk patients (HR 0.52, P=0.13), while OS after CBT was comparable to that after MDT in standard-risk patients (HR 0.78, P=0.54) (**Table 3**). The 3-year GRFS rates in standard-risk patients were 57.4% (95% CI, 41.2–70.7%) after CBT and 34.2% (95% CI, 21.0–47.8%) after MDT (P=0.0827, **Figure 3c**), while those in high-risk patients were 42.3% (95% CI, 23.5–60.0%) and 9.5% (95% CI, 1.6–26.1%), respectively (P=0.043, **Figure 3d**). In the multivariate analysis, GRFS after CBT was significantly better than that after MDT in high-risk patients (HR, 0.39, P=0.013), and was also better in standard-risk patients (HR, 0.59, P=0.078), although significance level of 0.05 was not reached (**Table 3**).

Relapse and NRM in the recent period

According to the donor source, the 3-year relapse rates in standard-risk patients were 19.8% (95% CI, 9.0–33.6%) after CBT and 26.0% (95% CI, 15.0–38.5%) after MDT (P=0.251, **Figure 4a**), while those in high-risk patients were 23.1% (95% CI, 9.1–40.7%) and 53.9% (95% CI, 26.3–75.1%), respectively (P=0.0145, **Figure 4b**). In the multivariate analysis, relapse risk after CBT was significantly lower than that after MDT in high-risk patients (HR, 0.25; P<0.001), while the relapse risks after CBT and MDT were comparable in standard-risk patients (HR, 0.62; P=0.29) (**Table 4**).

The 3-year NRM rates in standard-risk patients were 14.7% (95% CI, 6.4–26.3%) after CBT and 18.3% (95% CI, 8.8–30.4%) after MDT (P=0.99, **Figure 4c**), while those in high-risk patients were 27.2% (95% CI, 11.7–45.5%) and 25.9% (95% CI, 8.5–47.6%), respectively (P=0.737, **Figure 4d**). In the multivariate analysis, the risks of NRM after CBT and MDT were comparable in both high-risk (HR, 1.53; P=0.55) and standard-risk groups (HR, 1.03; P=0.95) (**Table 4**).

Neutrophil engraftment, aGVHD, and cGVHD in the more recent period

Neutrophil engraftment, grade III–IV acute GVHD, and extensive chronic GVHD were examined for all patients during the recent period. The rates of neutrophil engraftment at 56 days after CBT and MSD transplantation were 93.3% and 96.3%, respectively (P=0.0065, **Figure 5a**). The rates of Grade III–IV acute GVHD at 100 days after CBT and MSD were 12.0% and 6.3%, respectively (P=0.644, **Figure 5b**). The rate of extensive chronic GVHD at 2 years after CBT was lower (15.5%) than that after MSD transplantation (26.6%), although significance was not reached **(**P=0.131, **Figure 5c**). Neutrophil engraftment was significantly delayed after CBT as compared to MDT in the multivariate analysis (**Supplemental Table 3**). No significant difference in acute or chronic GVHD was observed, although the risk of chronic GVHD seemed to be lower in the CBT group (**Supplemental Table 3**).

Discussion

As in previous reports, RFS of CBT was comparable to that of transplantation with other donor sources for the total cohort[9-14]. In the old period, RFS after CBT and MDT were comparable, whereas in the recent period, RFS after CBT was significantly better. This impact was more prominent in patients with high-risk diseases. Furthermore, the superiority of CBT persisted regardless of the degree of disease risk in high-risk patients. To further explore this finding, we evaluated the impact of donor source on OS, relapse, and NRM, and found that relapse risk was significantly lower in the CBT group, particularly in patients with high-risk disease. These results were consistent with those of previous studies. Milano et al. found that the risk of relapse was significantly lower after CBT than after unrelated donor transplantation among patients with minimal residual disease[16]. A potential graft-versus-leukemia (GVL) effect after CBT is highly anticipated. In dUCBT, CD4+ T-cell-mediated graft-vs-graft (GVG) alloreactivity may occur and enhance the GVL effect, thereby providing an explanation for the relatively low relapse rates associated with dUCBT[24]. However, only single-unit UCBTs were included in our study, as dUCBTs are currently only under clinical trial in Japan. Our results support the notion that CBT can provide a GVL effect, although the immunological potential of CBT has not been elucidated. Kanda et al. demonstrated that mild acute and chronic GVHD associated with not only a low risk of relapse, but also a low risk of NRM following CBT[25]. Moreover, robust CD4+ T-cells and T-cell function after CBT associated with improved survival despite the high rates of acute GVHD[26]. These results may provide a better understanding of why UCB offers better outcomes in high-risk patients than other sources.

High rates of engraftment failure and NRM after CBT have been a serious concern. The higher NRM observed following CBT may be due to delayed neutrophil recovery or increased mortality from infections. Because anti-HLA antibodies were not necessarily checked in the earlier period, the presence of donor-specific HLA antibody, which can affect delayed neutrophil engraftment, could not be determined. However, significant progress has been made, and our results showed acceptable neutrophil engraftment rates (93.3% in the recent period, and 81.8% in the old period) and comparable NRM compared to transplantation with other stem cell sources. Infections during prolonged neutropenia are the main cause of NRM. In our study, mortality from infections after CBT decreased from 15.1% (5/33) in the old period, to 5.3% (4/75) in the recent period. No cell content disparities were observed between each period, with units in the old period consisting of 0.72 x 10^7/kg TNCs and 2.58 x 10^5/kg CD34-positive cells, while those in the recent period containing 0.67 x 10^7/kg TNCs and 2.72 x 10^5/kg CD34-positive cells (**Supplemental Figure 1**). Better conditioning regimens and supportive care during prolonged neutropenic periods have helped decrease NRM following CBT. Notably, Uchida et al. demonstrated the effectiveness of combined mycophenolate mofetil (MMF) and tacrolimus as GVHD prophylaxis in elderly recipients after CBT, which showed superior engraftment rates and a decrease in early NRM through better control of pre-engraftment immune reactions[27, 28]. In addition, several studies have demonstrated the importance of MMF monitoring for effective prophylaxis of acute GVHD after CBT. Since 2011, we have introduced MMF as an adjunct to tacrolimus for GVHD prophylaxis in CBT[29, 30], and have regularly monitored the plasma levels of MMF and modified its dosages throughout the clinical course after CBT[31]. In fact, 85% of our cases have received dose-monitoring of MMF as GVHD

prophylaxis since 2011. This may be one of the reasons for the better CBT outcomes observed in the more recent period.

Chronic GVHD is a serious complication that affects the OS and quality of life of long-term survivors after HSCT. Extensive chronic GVHD was observed less frequently after CBT than after MSD transplantation in this study. This advantage of CBT has been discussed in previous studies, and has been found to associate with frequent organ involvement such as the oral cavity, eye, liver, lung, and joints[32, 33]. A low incidence of chronic GVHD allows for easier discontinuation of immunosuppressive agents, and consequently earlier immune reconstitution. This may be one of the reasons for the better long-term outcomes observed after CBT. GRFS after CBT was significantly better than that after MDT. The low incidence of chronic GVHD and relapse, and the comparable NRM and grade III–IV acute GVHD rates, may reflect the better GRFS associated with CBT.

This study has several limitations. First, this is a retrospective study involving a small population with heterogeneous backgrounds from a single transplant center. The heterogeneous background of patients may have resulted in a statistical bias, although attempts were made to reduce this bias by adjusting the impact in multivariate analyses. Further, the findings should be externally validated. Second, we utilized the original disease risk definition to classify our heterogenous populations comprehensively. The refined disease risk index (rDRI) has often applied to risk stratification analyses[34]. However, it was difficult to divide our cohort using the rDRI because of the heterogeneity of the population, which included both ATL and non-malignant

hematological diseases. RFS was found to be consistent regardless of whether the rDRI was used, and significant correlation ($P<0.010$) between our staging approach and the rDRI was observed (data not shown). We therefore chose to retain our original disease risk classification system for this study. Third, we only analyzed HLA-A, HLA-B, and HLA-DRB1 alleles because of the incomplete data on HLA-C, particularly in the old period. However, our results were almost the same even after the exclusion of HLA-C mismatched cases and cases without HLA-C locus information in the recent cohort. Finally, we did not consider the effects of donor allocation time. Earlier search for unrelated donors and earlier transplantation could have helped improve the outcomes of matched unrelated transplantation.

In conclusion, our study demonstrated that CBT associated with better RFS than MDT in recent years. Notably, patients with high-risk disease benefitted more from CBT, as reflected by the significantly better RFS, and the low relapse rates without an increase in NRM observed, suggesting the safety and high potential of a GVL effect after single-unit CBT. CBT might hence serve as a reasonable donor choice, particularly for high-risk patients.

Authors' Contribution

FW and JK designed the research; JK organized the project; FW and JK performed the statistical analysis; MH, TK, KY and AT-K interpreted the data; FW wrote the first draft; and all other authors critically reviewed the draft and approved the final version for publication.

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Figure legends

Figure 1 Kaplan-Meier estimates of RFS (a), OS (b), and GRFS (c) of the entire cohort according to donor source.

Figure 2 Kaplan-Meier estimates of RFS according to each donor source, transplant period and the disease risk in the recent period.

(a) RFS in the old period, (b) RFS in the recent period, (c) RFS for standard-risk patients in the recent period, and (d) RFS for high-risk patients in the recent period.

Figure 3 Kaplan-Meier estimates of OS and GRFS according to disease risk in the recent period.

(a) OS of standard-risk patients, (b) OS of high-risk patients, (c) GRFS of standard-risk patients, and (d) GRFS of high-risk patients.

Figure 4 Cumulative incidence of relapse and NRM according to disease risk in the recent period.

(a) Relapse in standard-risk patients, (b) relapse in high-risk patients, (c) NRM in standard-risk patients, and (d) NRM in high-risk patients.

Figure 5 Cumulative incidence of neutrophil engraftment (a), grade III–IV acute GVHD (b), and extensive chronic GVHD (c) in the recent period.

1 Table 1 Patient characteristics of the total cohort

2

	Donor source (n=394)			
Characteristics	UCB (n=108)	MSD (n=143)	MUD (n=143)	P-value
Sex-no. (%)				0.071
Female	42(38.9)	53(37.1)	71(49.7)	
Male	66(61.1)	90(62.9)	72(50.3)	
Age-yr				0.097
Median	49	46	48	
Range	20-68	16-73	18-67	
Diagnosis-no. (%)				0.955
Leukemia	81(75.0)	104(72.7)	106(74.1)	
Lymphoma	22(20.4)	27(18.9)	29(20.3)	
Myeloma	2(1.9)	6(4.2)	3(2.1)	
AA/PRCA/PNH	3(2.8)	5(3.5)	4(2.8)	
other	0(0.0)	1(0.7)	1(0.7)	
Stem Cell Source-no. (%)				<0.001
Peripheral Blood	0(0.0)	54(37.8)	0(0.0)	
Bone Marrow	0(0.0)	89(62.2)	143(100.0)	
Cord Blood	108(100.0)	0(0.0)	0(0.0)	
ECOG PS-no. (%)				0.001
0-1	91(84.3)	108(75.5)	111(77.6)	
>1	14(13.0)	7(4.9)	13(9.1)	
missing	3(2.8)	28(19.6)	19(13.3)	
Stage-no. (%)				0.26
standard	69(63.9)	92(64.3)	95(66.4)	
high	39(36.1)	47(32.9)	42(29.4)	
missing	0(0.0)	4(2.8)	6(4.2)	
Conditioning Regimen-no. (%)				<0.001
RIC	52(48.1)	39(27.3)	60(42.0)	

MAC	56(51.9)	46(54.1)	80(55.9)	
missing	0(0.0)	58(40.6)	3(2.1)	
GVHD Prophylaxis-no. (%)				<0.001
CI+MTX	14(13.0)	130(90.9)	128(89.5)	
CI+MMF (+MTX/MMF)	66(61.0)	0(0.0)	12(8.4)	
CI only	28(25.9)	13(9.1)	3(2.1)	
ATG				0.199
contained	0(0.0)	2(1.4)	4(2.8)	
not contained	108(100.0)	141(98.6)	139(97.2)	
HLA-mismatch				<0.001
0	6(5.6)	143(0)	143(100)	
1	30(27.8)	0(0.0)	0(0.0)	
2	56(51.9)	0(0.0)	0(0.0)	
3	1(0.9)	0(0.0)	0(0.0)	
missing	15(13.9)	0(0.0)	0(0.0)	
Transplant Period-no. (%)				<0.001
1990-2003	2(1.9)	70(49.0)	35(24.5)	
2004-2010	31(28.7)	38(26.6)	62(43.4)	
2011-2018	75(69.4)	35(24.5)	46(32.2)	
Median Follow-up of Survivors (range)	3.9 years (0.2-13.4)	7.6 years (0.3-27.1)	6.4 years (0.1-19.0)	<0.001

Abbreviations: AA, aplastic anemia; PRCA, pure red cell aplasia; PNH, paroximal nocturnal hemogrobinuria; RIC, reduced-intensity conditioning; MAC, myeloablative conditioning; GVHD, graft-versus host disease; CI, calcineurin inhibitor; MTX, methotrexate; MMF, mycophenolate mofetil; UCB, unrelated cord blood; MSD, matched sibling donor; MUD, matched unrelated donor.

Table 2 Adjusted comparison of transplant outcomes with UCB, MSD, and MUD

Outcome	Donor source	HR (95% CI)	P-value
RFS			
	UCB (n=108)	1.00	Reference
	MSD (n=143)	1.24(0.85-1.81)	0.27
	MUD (n=143)	1.22(0.84-1.77)	0.29
OS			
	UCB (n=108)	1.00	Reference
	MSD (n=143)	1.10(0.72-1.66)	0.67
	MUD (n=143)	1.14(0.77-1.70)	0.52
GRFS			
	UCB (n=108)	1.00	Reference
	MSD (n=143)	1.07(0.75-1.52)	0.7
	MSD (n=143)	1.16(0.82-1.62)	0.4

Other significant variables included for adjustment in RFS, OS and GRFS were patient age, disease diagnosis, performance status, and disease status.

Abbreviations: HR, hazard ratio; RFS, relapse-free survival; OS, overall survival; GRFS, GVHD-free and relapse-free survival; MSD, matched sibling donor; MUD, matched unrelated donor; UCB, unrelated cord blood.

Table 3

Adjusted comparison of outcomes following CBT and MDT in the recent period

Outcome	HR (95% CI)	P-value
RFS		
All risk		
MDT (n=81)	1.00	Reference
CBT (n=75)	0.50(0.30-0.84)	0.008
High risk		
MDT (n=21)	1.00	Reference
CBT (n=26)	0.35(0.16-0.77)	0.009
Standard risk		
MDT (n=60)	1.00	Reference
CBT (n=49)	0.68(0.34-1.33)	0.25
OS		
All risk		
MDT (n=81)	1.00	Reference
CBT (n=75)	0.65(0.37-1.20)	0.14
High risk		
MDT (n=21)	1.00	Reference
CBT (n=26)	0.52(0.22-1.22)	0.13
Standard risk		
MDT (n=60)	1.00	Reference
CBT (n=49)	0.78(0.35-1.72)	0.54
GRFS		
All		
MDT (n=81)	1.00	Reference
CBT (n=75)	0.50(0.32-0.79)	0.003
High risk		
MDT (n=21)	1.00	Reference
CBT (n=26)	0.39(0.18-0.82)	0.013
Standard risk		
MDT (n=60)	1.00	Reference

CBT (n=49)	0.59(0.33-1.06)	0.078

Other variables included for adjustment in RFS, OS and GRFS were patient age, disease diagnosis, performance status, and disease status.

Table 4 Adjusted comparison of relapse and NRM following CBT and MDT in the recent period

Outcome	HR (95% CI)	P-value
Relapse*		
All risk		
MDT (n=81)	1.00	Reference
CBT (n=75)	0.37(0.19-0.72)	0.004
High risk		
MDT (n=21)	1.00	Reference
CBT (n=26)	0.25(0.11-0.54)	<0.001
Standard risk		
MDT (n=60)	1.00	Reference
CBT (n=49)	0.62(0.25-1.50)	0.29
NRM**		
All risk		
MDT (n=81)	1.00	Reference
CBT (n=75)	1.08(0.51-2.29)	0.83
High risk		
MDT (n=21)	1.00	Reference
CBT (n=26)	1.53(0.38-6.06)	0.55
Standard risk		
MDT (n=60)	1.00	Reference
CBT (n=49)	1.03(0.39-2.80)	0.95

* Other variables included for adjustment were disease diagnosis, performance status, and disease status.

** Other variables included for adjustment were patient sex, patient age, performance status, and disease status

Figure 1

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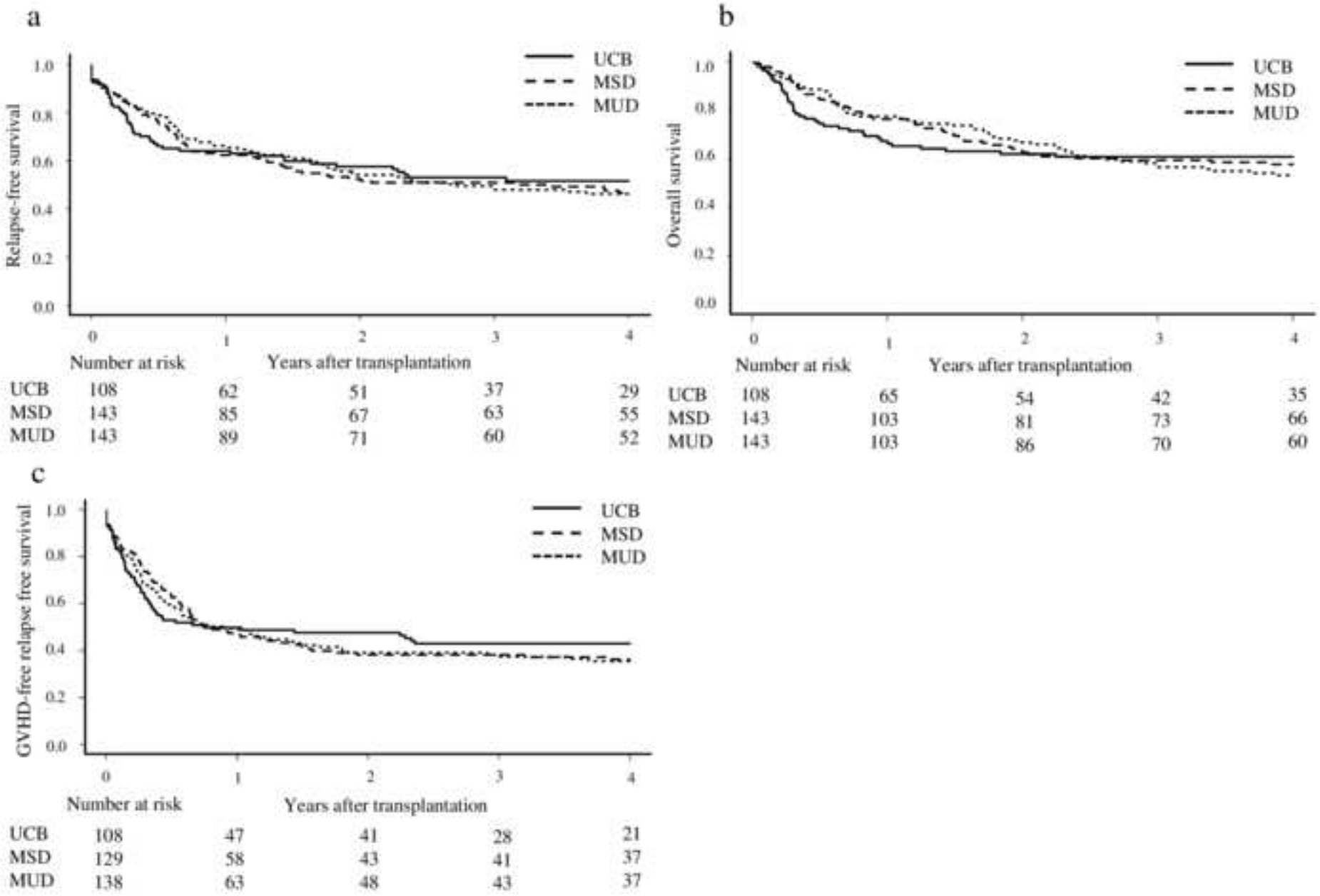

Figure 2

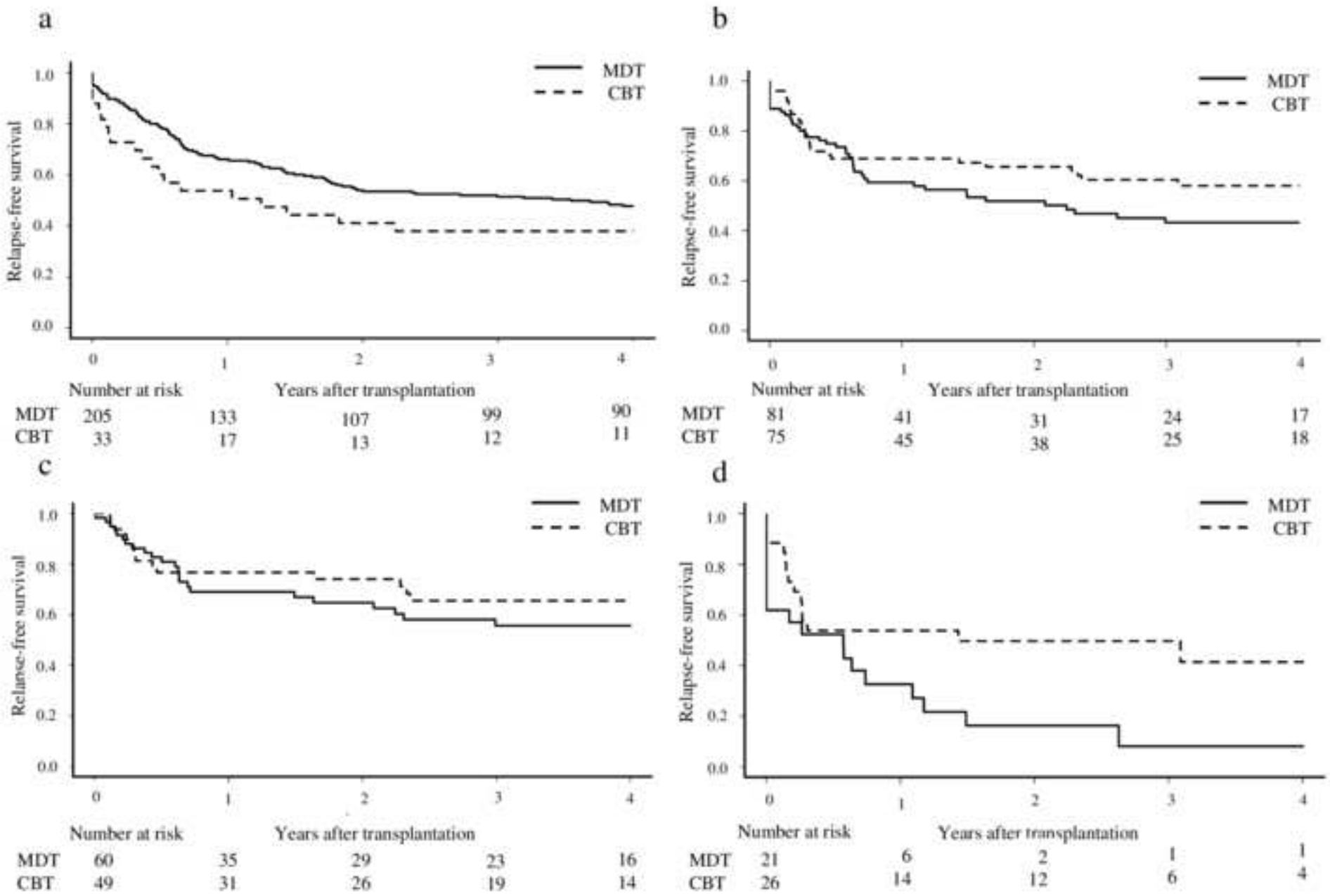

Figure 3

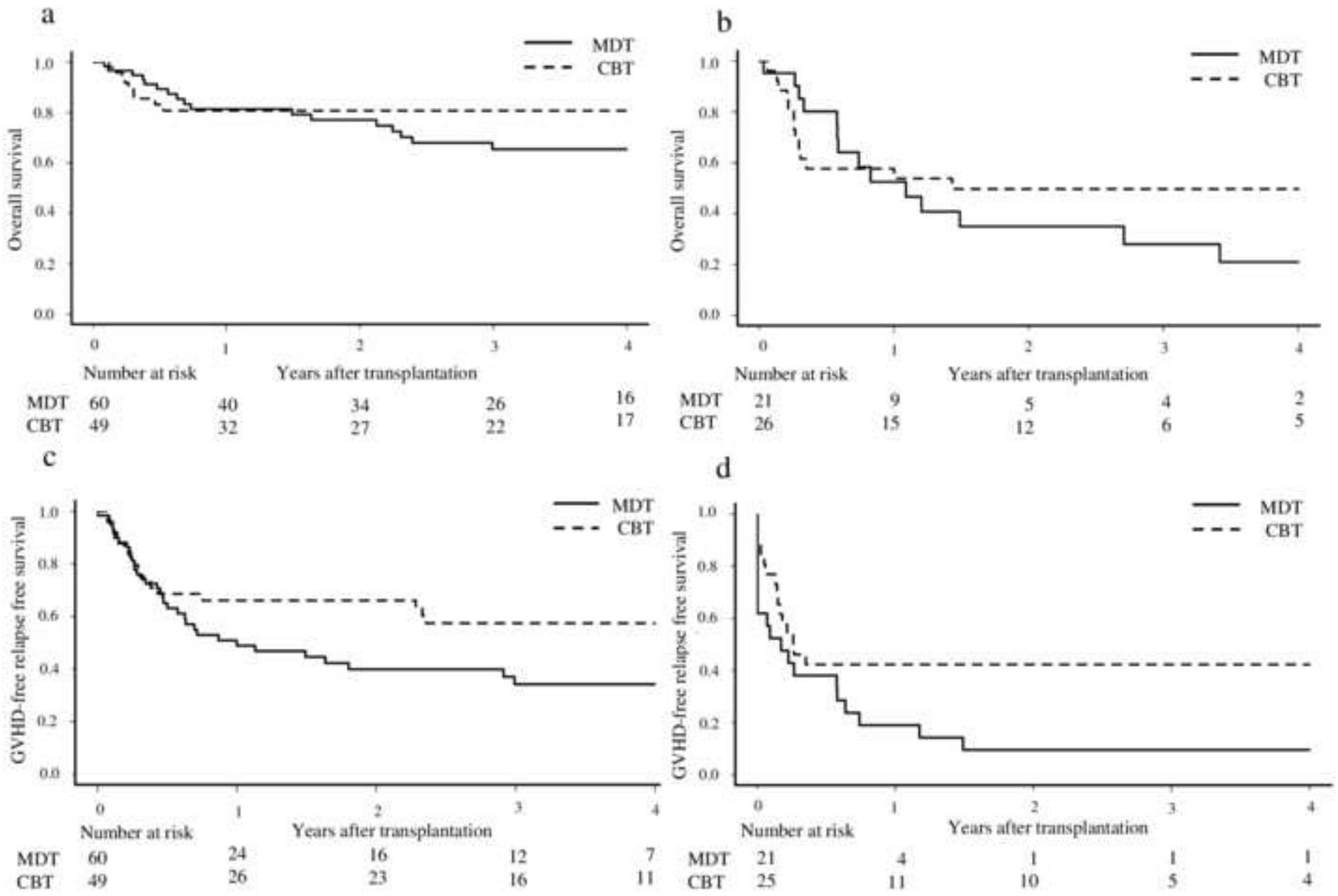

Figure 4

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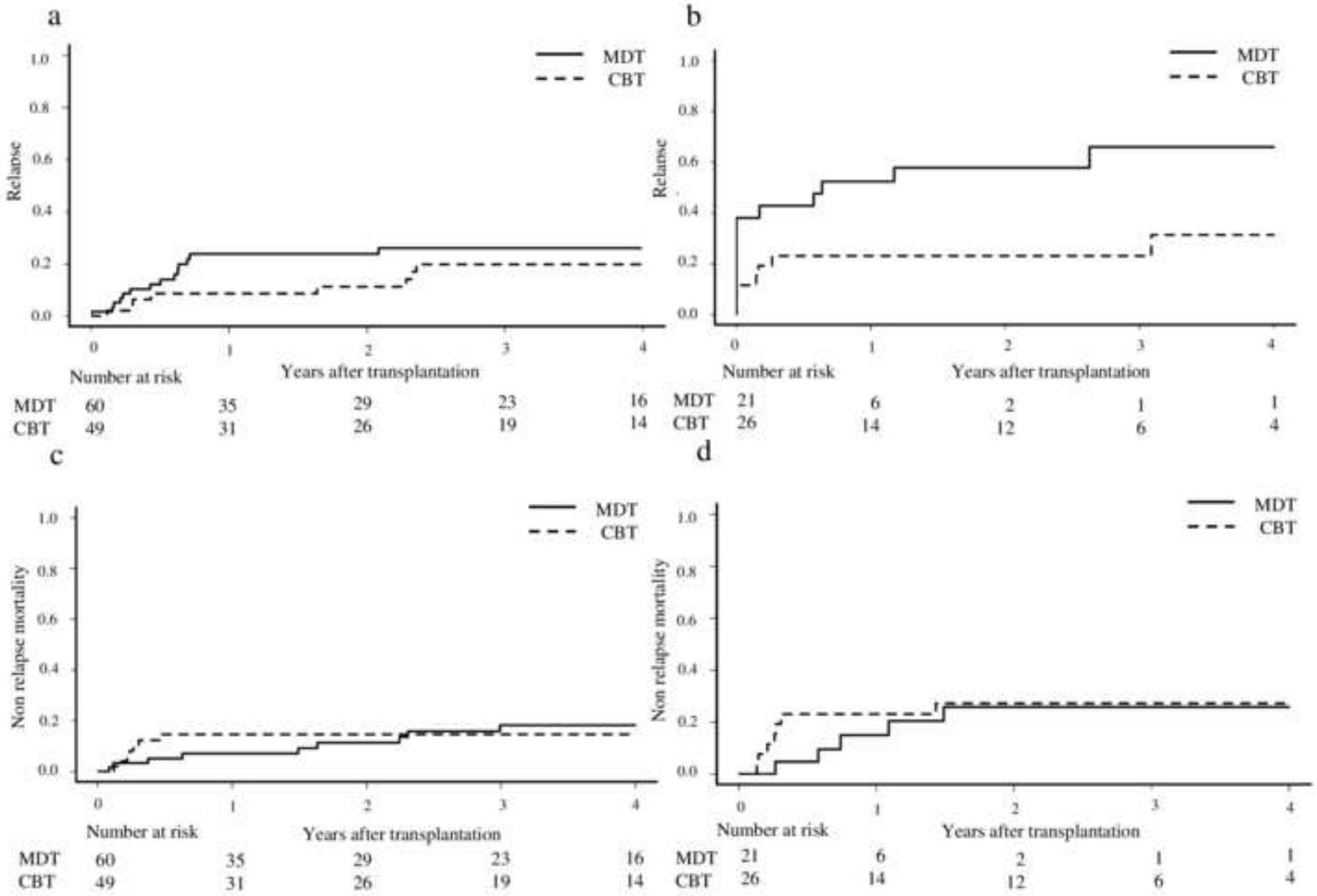

Figure 5