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Changing donors improves outcomes of second transplantation in patients who experienced graft failure after first allogeneic stem cell transplantation

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Changing donors improves outcomes of second transplantation in patients who experienced graft failure after first allogeneic stem cell transplantation

Running title: donor changing in 2nd transplantation for graft failure

Authors:

Rui Ma[1,*], Xiao-Yu Zhu[2,*], Yue Lu[3,*], Jia Chen[4,*], Li Xuan[5], Hai-Long Yuan[6], Yang Cao[7], Wei-Jie Cao[8], Xiao-Sheng Fang[9], Kou-Rong Miao[10], Xiao-Xia Hu[11], Hai Yi[12], Yan-Min Zhao[13], Yuan-Bin Wu[14], Ting Yang[15], Hong-Tao Wang[16], Yue Yin[17], Zhong-Ming Zhang[18], Xiao-Hui Zhang[1], Lan-Ping Xu[1], Yu Wang[1], Kai-Yan Liu[1], Xiao-Jun Huang[1,19#], Yu-Qian Sun[1,#]

Affiliations:

1. Peking University People's Hospital, Peking University Institute of Hematology, National Clinical Research Center for Hematologic Disease, Beijing Key Laboratory of Cell and Gene Therapy for Hematologic Malignancies, Peking University, Beijing, P.R. China
2. Department of Hematology, the First Affiliated Hospital, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei, P.R. China
3. Beijing Lu Daopei Hospital, Beijing, P.R. China
4. National Clinical Research Center for Hematologic Diseases, Jiangsu Institute of Hematology, The First Affiliated Hospital of Soochow University, Suzhou, P.R. China
5. Department of Hematology, Nanfang Hospital, Southern Medical University, Guangzhou, P.R. China
6. The First Affiliated Hospital of Xinjiang Medical University, Urumqi, P.R. China
7. Department of Hematology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, P.R. China
8. Department of Hematology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, P.R. China
9. Department of Hematology, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, P.R. China
10. People's Hospital of Jiangsu Province, Suzhou, P.R. China
11. Ruijin Hospital, Shanghai, P.R. China
12. Department of Hematology, The General Hospital of Western Theater Command, Chengdu, P.R. China
13. Bone Marrow Transplantation Center, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, P.R. China
14. Guangdong Hospital of Traditional Chinese Medicine, Guangzhou, P.R. China
15. Department of Hematology, The First Affiliated Hospital, Fujian Medical

University, Fuzhou, P.R. China
16. Department of Hematology, Shengjing Hospital of China Medical University, Shenyang, P.R. China
17. Peking University First Hospital, Beijing, P.R. China
18. Department of Hematology, The First Affiliated Hospital of Guangxi Medical University, Nanning, P.R. China
19. Peking-Tsinghua Center for Life Sciences, Academy for Advanced Interdisciplinary Studies, Peking University, Beijing, P.R. China

*RM, X-Y Z, YL, and JC contributed equally to this work.

Corresponding: Yu-Qian Sun (sunyuqian83@hotmail.com), Xiao-Jun Huang (huangxiaojun@bjmu.edu.cn)

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ABSTRACT

A second transplantation is almost the only salvage for patients encountering graft failure (GF) following the first allogeneic stem cell transplantation. However, there were no standard protocols for second transplantations, and the role of changing donors remained controversial. We retrospectively studied 272 consecutive patients from 18 Chinese centers undergoing second transplantations due to GF, aiming to assess the impact of changing donors and factors affecting second transplantation outcomes. The primary endpoint was neutrophil engraftment. Other endpoints included platelet engraftment, graft versus host disease (GVHD), transplant related mortality (TRM), relapse, and survival. Of the 272 patients, 193 (71.0%) patients experienced primary GF, and 70.6% (192) used a different second donor. Neutrophil engraftment was achieved in 218 (86.3%) patients by d28, and platelet engraftment was achieved in 164 (70.0%) patients by d100. The 3-year cumulative incidence of acute GVHD, chronic GVHD, relapse, and TRM were 43.5%, 27.8%, 15.6%, and 44.6%, respectively. The 1-year and 3-year overall survival (OS) were 56.1% and 49.5%, respectively. Compared to using the same donor, changing donors significantly improved neutrophil (92.4% vs 71.4%, p<0.001) and platelet engraftment (76.9% vs 51.8%, p<0.001), 1-year TRM (34.8% vs 56.3%, p<0.001), and OS (61.9% vs 42.7%, p<0.001). Subgroup analysis confirmed engraftment benefit of donor changing in primary GF (p<0.001), but not in secondary GF (p=0.346). This is the largest multicenter study of second transplantations for GF, suggesting that changing donors might be critical for engraftment and survival after second transplantations.

Keywords: Graft Failure, Second Transplantation, Changing Donor

INTRODUCTION

Graft failure (GF) is a rare yet potentially lethal complication following allogeneic stem cell transplantation (SCT), with its prevalence particularly marked in cord blood (CB) or haploidentical SCT (haplo-SCT)[1-4]. A second transplantation is critical to salvage the patient's life[5, 6], though there remains no standard protocol concerning conditioning regimens, donor selection, graft-versus-host disease (GVHD) prophylaxis, or other pivotal factors[7-9]. The majority of the existing literature comprises retrospective summaries, offering limited insight into the efficacy of specific techniques. Currently, the outcomes of a second transplantation were far to satisfactory, with neutrophil engraftment ranged from 58% to 100%, and 1-year overall survival (OS) ranged from 11% to 66%[10-13]. Therefore, there is pressing necessity to refine and optimize the protocols for second transplantation to improve patient outcomes.

Recently, we developed an innovative protocol for second haplo-SCT to manage GF after the first haplo-SCT, demonstrating encouraging results with 100% engraftment and 60% OS[14], which was further validated by an updated follow-up study[15]. This novel strategy is different from prior protocols by three key elements: a mini-intensity conditioning regimen based on fludarabine (Flu) and cyclophosphamide (Cy), the intentional selection of a different second donor, and rapid re-transplantation following GF identification. It seems that the efficacy of this approach might be largely attributed to change donors. Nonetheless, the role of changing donors in second transplantations was controversial from previous literature. Therefore, the current study aims to investigate determinants of second transplants outcomes, emphasizing on implications of changing donors.

METHODS

Patients

From Jan 2000 to Dec 2023, consecutive patients who received second transplantations due to GF from 18 transplant centers in China were retrospectively studied. The study was approved by the ethics committee of Peking University People's Hospital. The last follow-up date was Mar 31, 2024.

Definitions

The primary endpoint was neutrophil engraftment by day 28 post-second transplantation. Secondary endpoints included platelet engraftment by day 100, acute GVHD (aGVHD) by day 100, and chronic GVHD (cGVHD), transplant related mortality (TRM), relapse, and survival after 1 and 3 years.

Neutrophil engraftment was defined as the first of three consecutive days with neutrophil count $\geq 0.5\times10^9$/L. Platelet engraftment was the first of seven consecutive days with platelet count $\geq 20\times10^9$/L without transfusion. Complete donor chimerism was defined as having ≥95% of hematopoietic cells originating from the donor, determined using SNP and/or FISH. Primary GF was failure to achieve neutrophil engraftment by day 28 for haploidentical (HID), matched related (MRD) or unrelated (URD) donors, or day 42 for CB recipients. Secondary GF was two or three lineage cytopenias following initial engraftment, without any discernible causes such as disease relapse, infections, or drugs. HIDs refers to relatives sharing one chromosome 6 with variable non-shared HLA haplotype[16]. GVHD was diagnosed and graded by the National Institutes of Health criteria[17, 18]. For GVHD prophylaxis, combinations of calcineurin inhibitors (cyclosporine A or FK506), mycophenolate mofetil (MMF), and anti-thymocyte globulin (ATG) or basiliximab were defined as intensified regimens.

Second transplantation protocols

Preconditioning and GVHD prophylaxis were heterogenous following institutional guidelines based on transplant types. For patients with donor specific antibody (DSA) median fluorescence intensity (MFI) >2000-5000, center-specific desensitization such as rituximab, plasma exchange/immunoadsorption, intravenous immunoglobulin, or combinatorial immunosuppression was applied. Antimicrobial prophylaxis included antiviral (e.g.,

acyclovir), antifungal (e.g., posaconazole, trimethoprim-sulfamethoxazole), and antibacterial (e.g., fluoroquinolones) followed institutional protocols.

Statistics

Mann-Whitney U and Chi-square tests were applied for comparison of continuous and categorical variables. Death was a competing event for GVHD and relapse. Relapse was a competing event for TRM. OS and DFS were estimated with the Kaplan-Meier method. Variables with $p<0.1$ were included in the multivariate analysis. Statistically significance was defined as $p<0.05$. Analyses were conducted with SPSS (version 23.0; Chicago, IL) and R software.

RESULTS

Patients' characteristics

A total of 272 patients from 18 centers were analyzed. First transplant donors included HIDs (54.0%), CB (29.8%), MRDs (9.2%), and URDs (7.0%). DSA was positive in 21.1% of patients pre-first transplantation, with a median MFI of 7178 (range, 246-18039) (Table1).

Most patients (71.0%) experienced primary GF. The median interval between transplants was 55 (range, 18-2592) days, differing between primary GF (41 days, range 18–765) and secondary GF (195 days, range 43–2592; $p<0.001$). A different donor was used in 192 (70.6%) patients. DSA was positive in 14.3% of patients before second transplantations, with a median MFI of 2152 (range, 246-19682). Preconditioning regimens for second transplantations were heterogeneous, among which Flu and Cy-based regimen was the most commonly used (29.8%). The combination of CsA plus MMF was the most frequently adopted regimen for GVHD prophylaxis (22.4%) (Table 2).

Outcomes of second transplantations

Engraftment

Neutrophil engraftment was achieved in 218 (86.3%, 95% CI, 82.0-90.6) patients by d28, and in 225 (90.6%, 95% CI, 86.7-94.5) patients by day 60, respectively. Platelet engraftment was achieved in 164 (70.0%, 95% CI, 63.7-76.3) by d100. The median time for neutrophil and platelet engraftment were 13 (range, 7-50) days and 16 (range, 7-200) days, respectively (Figure 1).

GVHD

The cumulative incidences of grade 2 to 4 and grade 3 to 4 aGVHD by day 100 were 33.4% (95% CI, 26.8-39.8) and 20.3% (95% CI, 14.4-26.1), respectively (Figure 1). cGVHD developed in 36 patients, including 10 cases of moderate-to-severe cGVHD. Cumulative cGVHD incidence was 23.9% (95% CI, 16.8-31.0) at 1 year and 27.8% (95% CI, 17.7-32.5) at 3 years. Corresponding incidence for moderate to severe cGVHD was 6.2% (95% CI, 3.5-7.3) at 1 year and 7.5% (95% CI, 5.1-9.9) at 3 years.

Infections

111 (40.8%) patients developed CMV reactivation, and 26 (9.56%) developed EBV reactivation. Median time to reactivation was 28 days (range, 1-1156) for CMV and 41.5 days (range, 11-411) for EBV. The cumulative incidence of CMV and EBV reactivation on day 100 were 43.9% (95% CI, 37.6-50.6) and 10% (95% CI, 6.1-13.9), respectively (Figure 1).

Relapse

In 183 patients with hematological malignancies, 15 experienced disease relapse, within which 11 died due to relapse. The cumulative incidence of relapse for 1 year and 3 years were 9.9% (95% CI, 4.2-15.6) and 15.6% (95% CI, 7.4-23.8), respectively (Figure 1).

Survival

The median follow-up for survivors was 604 (range, 13-4061) days after second transplantation. 123 patients died, with main causes including infections (52.8%), multi-organ dysfunction (11.4%), GVHD (8.94%), and relapse (8.94%). Seven (5.69%) patients died from GF (Supplementary Table 1). The cumulative incidence of TRM at 30 days, 100 days, 1 year, and 3 years were 11.1% (95% CI, 7.4-14.8), 27.2% (95% CI, 21.9-32.5), 41.2% (95% CI, 35.1-47.2), and 44.6% (95% CI, 38.0-51.0), respectively. The 1-year and 3-year OS were 56.1% (95% CI, 50.1-62.3) and 49.5% (95% CI, 42.9-56.3), respectively (Figure 1).

Subgroup analysis for transplant outcomes

Patients with aplastic anemia (AA) exhibited advantages in platelet engraftment and survival compared to hematological malignancies (Supplementary Figure 1). Patients encountering secondary GF engrafted and survived better than primary GF (Supplementary Figure 2), but none of the above were significant in multivariate analysis. No significant disparities were observed in engraftment or survival concerning first transplant source (CB vs others, Supplementary Figure 3) or chimerism status (Supplementary Figure 4).

Primary GF patients were further stratified by possible GF etiologies, with 24 with positive DSA (Group A), 110 DSA-negative with full recipient or mixed chimerism indicative of T-cell mediated rejection (Group B), and 42 DSA-negative with full donor chimerism suggesting non-immune etiologies (Group C). Comparative analysis revealed inferior platelet engraftment, TRM, and OS in Group C, while neutrophil engraftment was similar across groups (Supplementary Figure 5).

Factors associated with second transplant outcomes

Multivariate analysis indicated changing donors (HR 0.624, *p*=0.039), and a younger second donor (HR 0.668, *p*=0.019) were related to better neutrophil engraftment, whilst changing donors (HR 0.559, *p*=0.035), younger recipients (HR 0.597, *p*=0.011), and higher CD34+ doses (HR 0.688, *p*=0.034) improved platelet engraftment. Superior TRM and OS were observed in younger recipients (TRM: HR 0.560, *p*=0.030; OS: HR 0.610, *p*=0.046), patients who changed donors (TRM: HR 0.431, *p*=0.006; OS: HR 0.405, *p*=0.004), and first transplant from MRDs/HIDs. Compared to using MRDs as second donors, grafting from URDs, HIDs, and CB were risk factors for aGVHD (URDs: HR 10.13, *p*=0.033; CB: HR 8.789, *p*=0.045; HIDs: HR 10.28, *p*=0.023). Recipient age was the only risk factor for cGVHD (<median vs ≥median, HR 0.458, *p*=0.028) (Table 3).

DSA positivity (n=22) before the second transplant showed borderline inferior neutrophil (77.3% vs. 93.2%, *p*=0.062) and platelet engraftment (50.0% vs. 77.3%, *p*=0.051), while 1-year OS was comparable (53.8% [95% CI, 32.6-75.0] vs. 63.8% [95% CI, 55.0-72.6], *p*=0.311). Although with limited cases, subgroup analysis stratified by MFI thresholds (≥2512 vs <2512) revealed DSA-high patients had impaired platelet engraftment compared to DSA-low patients (25.0% vs. 75.0%, *p*=0.046), while differences in neutrophil engraftment (55.6% vs. 88.9%, *p*=0.114) and survival (55.6% vs. 55.6%, *p*=0.100) were non-significant.

As the most commonly used preconditioning regimen, Flu/Cy had no impact on engraftment (neutrophil engraftment, *p*=0.081; platelet engraftment, *p*=0.843) or survival (*p*=0.659) (Table 3). Also, in patients conditioned with Flu/Cy with or without low-dose TBI, no significant differences were observed in engraftment (neutrophil engraftment, *p*=0.227; platelet engraftment, *p*=0.151) or survival (*p*=0.761), compared to using alternative conditioning regimens.

Univariate analysis using October 2019 (median transplant date) as the temporal demarcation point demonstrated trends toward reduced TRM (HR=0.706, p=0.072) and improved OS (HR=0.720, p=0.074), though these trends did not reach statistical significance in multivariate analysis (Table 3). Other variables, including primary diseases, GF types, chimerism, and the transplant interval had no association with outcomes, demonstrated by multivariate analysis.

The impact of changing donors in second transplantation outcomes

Details of donor type change were summarized in Supplementary Table 2. Across the entire cohort, changing donor showed improved neutrophil (92.4% [95% CI, 88.3-96.5] vs 71.4% [95% CI, 61.8-82.0], p<0.001) and platelet engraftment (76.9% [95% CI, 70.2-83.6] vs 51.8% [95% CI, 38.5-65.1], p<0.001), reduced 1-year TRM (34.8% [95% CI, 27.7-41.9] vs 56.3% [95% CI, 45.1-67.5], p<0.001), and superior 1-year OS (61.9% [95% CI, 54.6-69.2] vs 42.7% [95% CI, 31.5-51.9], p<0.001). Rates of aGVHD, cGVHD were comparable (Figure 2). Multivariate analysis confirmed changing donors was related to better neutrophil and platelet engraftment, TRM, and OS, but not to aGVHD or cGVHD (Table 3).

Subgroup analysis based on donor types of the first transplantations

As switching to a different donor is inevitable for patients with first transplants from CB, we evaluated impact of changing donors in first transplants with MRDs, URDs, and HIDs. In this cohort, changing donors improved neutrophil engraftment (94.7% [95% CI, 90.2-99.2] vs 71.4% [95% CI, 60.8-82.0], p<0.001), platelet engraftment (83.0% [95% CI, 74.3-91.1] vs 51.8% [95% CI, 38.5-65.1], p<0.001), TRM (31.9% [95% CI, 22.9-40.9] vs 56.3% [95% CI, 45.1-67.5], p<0.001), and OS (65.3% [95% CI, 56.1-74.5] vs 42.7% [95% CI, 31.5-53.9], p<0.001) (Supplementary Figure 6). Multivariate analysis reinforced benefits of switching donors in neutrophil engraftment (HR 0.632, p=0.034), platelet engraftment (HR 0.525, p=0.035), and TRM (HR 0.428, p=0.008) (Supplementary Table 3).

Among the 147 patients with first HID transplants, 82 used different second donors, including 66 HIDs, 10 URDs, 4 CB, and 2 MRDs. Changing donors exhibited better neutrophil engraftment (96.3% [95% CI, 89.0-99.9] vs 66.5% [95% CI, 54.2-78.8], p<0.001), platelet engraftment (78.5% [95% CI, 68.7-88.3] vs 45.0% [95% CI, 29.7-60.3], p<0.001), 1-year OS (67.0% [95% CI, 56.2-77.8] vs 35.7% [95% CI, 23.5-47.9], p<0.001), and TRM (30.8% [95% CI, 20.2-41.4] vs 63.1% [95% CI, 50.9-75.3], p<0.001) (Supplementary Figure 7), confirmed by

multivariate analysis (Supplementary Table 4). Similar benefits evolved in 131 patients receiving two HID transplants, in which switching to a different HID demonstrated better engraftment, OS, and TRM (Supplementary Figure 8).

Subgroup analysis based on primary diseases

In AA patients (n=87), changing donors resulted in better platelet engraftment (86.3% [95% CI, 76.9-95.7] vs 53.9% [95% CI, 30.8-77.0], p=0.028) and OS (74.2% [95% CI, 63.2-85.2] vs 53.1% [95% CI, 30.8-75.4], p=0.028), with comparable neutrophil engraftment (Supplementary Figure 9). Multivariate analysis linked changing donors to OS (HR 0.400, p=0.047), second donor age to neutrophil engraftment (≥median vs <median, HR 2.392, p=0.006), and CB as second donors to platelet engraftment (HR 9.709, p=0.028) (Supplementary Table 5).

In patients with hematological malignancies (n=181), changing donors also demonstrated superior engraftment (neutrophil engraftment: 91.8% [95% CI, 85.3-96.3] vs 66.0% [95% CI, 52.9-79.1], p<0.001; platelet engraftment: 81.3% [95% CI, 62.5-80.1] vs 51.8% [95% CI, 34.6-69.0], p=0.003) and survival (1-year OS: 56.6% [95% CI, 47.2-66.0] vs 37.9% [95% CI, 25.2-50.6], p=0.005), with comparable risks of relapse (Supplementary Figure 10). Multivariate analysis confirmed the association between changing donors and platelet engraftment (HR 0.558, p=0.043), OS (HR 0.594, p=0.030), and DFS (HR 0.585, p=0.040). Primary GF was also a risk factor for survival compared to secondary GF (HR 1.727, p=0.045) (Supplementary Table 6).

Subgroup analysis based on GF types

In 193 patients encountering primary GF, 143 used different donors, resulting in better neutrophil (91.8% [95% CI, 85.7-95.9] vs 61.9% [95% CI, 47.6-76.2], p<0.001) and platelet engraftment (73.4% [95% CI, 65.4-81.4] vs 35.7% [95% CI, 19.6-51.8], p<0.001), 1-year OS (58.3% [95% CI, 49.9-66.7] vs 28.8% [95% CI, 16.1-41.5], p<0.001), and TRM (37.3% [95% CI, 29.1-45.5] vs 69.9% [95% CI, 57.0-82.8], p<0.001) (Supplementary Figure 11). Multivariate analysis demonstrated significance of changing donors in platelet engraftment (HR 0.451, p=0.026) and OS (HR 0.573, p=0.025) (Supplementary Table 7). Transplant interval had no impact on engraftment or survival. Regression analysis in subgroups by GF etiologies also indicated significance of changing donors in neutrophil (HR=0.372, p=0.002) and platelet engraftment (HR=0.419, p=0.033) in DSA-negative patients with full recipient/mixed

chimerism (group B), though patient numbers in the other two groups were limited (Supplementary Table 8-10).

In 79 patients encountering secondary GF, 49 used a different donor. In contrast to those with primary GF, no differences were observed between using the same or a different donor regarding neutrophil (96.9% [95% CI, 91.4-99.9] vs 88.0% [95% CI, 75.3-99.9], p=0.346) and platelet engraftment (86.8% [95% CI, 76.6-97.0] vs 80.2% [95% CI, 61.8-98.6], p=0.259), 1-year TRM (27.4% [95% CI, 14.1-40.7] vs 31.5% [95% CI, 14.4-48.6], p=0.299), and OS (72.6% [95% CI, 59.3-85.9] vs 68.5% [95% CI, 51.4-85.6], p=0.424) in secondary GF (Supplementary Figure 12). Cox analysis only linked recipient age (<median vs ≥median, HR 0.388, p=0.007) and first donor type (URDs: HR 6.289, p=0.007; HIDs: HR 2.623, p=0.023) to platelet engraftment, but failed to link any other risk factors to engraftment or survival (Supplementary Table 11). Transplant interval demonstrated no association with engraftment or survival in this cohort, but critical data regarding the diagnosis-to-transplant interval following secondary GF were unavailable for analysis.

Subgroup analysis based on donor-recipient chimerisms

In 77 patients having full recipient chimerism, most (81.8%) chose a different donor for second transplantations. Comparison showed patients grafted from a different donor achieved superior neutrophil (92.8% [95% CI, 85.7-99.9] vs 64.3% [95% CI, 39.2-89.4], p=0.009) and platelet reconstitution (87.1% [95% CI, 78.3-65.9] vs 52.4% [95% CI, 11.2-93.6], p=0.014), and reduced TRM (31.8% [95% CI, 19.8-43.8] vs 64.3% [95% CI, 39.2-89.4], p=0.007) (Supplementary Figure 13). Regression analysis demonstrated associations between changing donors and platelet engraftment (HR 0.328, p=0.049). Notably, a reduced 3-year cGVHD was seen in the changing donor group (10.7% [95% CI, 7.0-20.7] vs 77.1% [95% CI, 38.5-99.9], p<0.001), and was confirmed by multivariate analysis (Supplementary Table 12).

In the 80 patients with full donor chimerism, 42 changed to different donors, resulting in better platelet recovery (73.8% [95% CI, 58.7-88.9] vs 46.6% [95% CI, 28.0-65.2], p=0.026) and 1-year OS (61.9% [95% CI, 46.4-77.4] vs 39.0% [95% CI, 22.7-55.3], p=0.023) (Supplementary Figure 14). Multivariate analysis confirmed the positive impact of changing donors on platelet recovery (HR 0.432, p=0.032) and survival (HR 0.320, p=0.036). A Flu/Cy based preconditioning was related to enhanced neutrophil engraftment (HR 0.393, p=0.049),

and intensified GVHD prophylaxis was a protective factor for TRM (HR 0.212, *p*=0.008) and OS (HR 0.239, *p*=0.014) (Supplementary Table 13).

In the 97 patients with mixed chimerism, no statistical significance was observed between using the same or a different donor, although a trend toward better engraftment (neutrophil: 95.7% [95% CI, 90.4-99.9] vs 71.9% [95% CI, 54.2-89.5], *p*=0.052; platelet: 72.3% [95% CI, 60.3-84.3] vs 59.4% [95% CI, 39.0-79.8], *p*=0.140) was shown (Supplementary Figure 15). Cox analysis identified no influencing factors for transplant outcomes (Supplementary Table 14).

Subgroup analysis based on second transplantations conditioning regimens

Preconditioning regimens for second transplantations were heterogeneous, with Flu/Cy-based (29.8%) and TBI-based (18.4%) regimens accounted for half of cases. Among patients receiving Flu/Cy-based regimen, changing donors led to improved 1-year TRM (34.6% [95% CI, 21.7-47.5] vs 60.0% [95% CI, 40.6-79.4], *p*=0.008) and OS (61.5% [95% CI, 48.2-74.8] vs 40.0% [95% CI, 20.6-59.4], *p*=0.033), with a trend toward better platelet engraftment (75.1% [95% CI, 62.6-87.6] vs 51.3% [95% CI, 27.6-75.0], *p*=0.094) (Supplementary Figure 16). Cox analysis identified changing donors as the only protective factor for TRM (HR 0.373, *p*=0.006) and OS (HR 0.459, *p*=0.034, Supplementary Table 15).

In patients receiving TBI-based conditioning, changing donors brought about better platelet engraftment (77.1% [95% CI, 61.8-92.4] vs 41.9% [95% CI, 15.0-68.8], *p*=0.004) and survival (1-year OS: 70.2% [95% CI, 52.8-87.6] vs 40.0% [95% CI, 18.4-61.6], *p*=0.040) (Supplementary Figure 17). Multivariate analysis revealed an association between changing donors and increased platelet engraftment (HR 0.180, *p*=0.027) and OS (HR 0.157, *p*=0.025, Supplementary Table 16).

How to further optimize second transplantations outcomes?

Among 192 patients who changed donors, multivariate analysis showed that patient age (<20y vs ≥20y) significantly impacted platelet engraftment (HR 0.615, *p*=0.036), cGVHD (HR 0.438, *p*=0.048), TRM (HR 0.472, *p*=0.015), and OS (HR 0.377, *p*=0.002). Additionally, MNC dose was also a determinant for platelet engraftment (<10.7^10^8/kg vs ≥10.7^10^8/kg, HR 1.564, *p*=0.045). Younger second donors (<36y vs ≥36y) was associated with a lower risk of aGVHD (HR 0.411, *p*=0.008). Thus, although with limited data, evidence suggests that

selecting a younger second donor, and infusing higher MNC doses may potentially improve outcomes in the context of changing donors (Table 4).

We also assessed effectiveness of HIDs as the second donors. Both engraftment and survival were comparable between patients grafted with HIDs and other donor types. Incidences of aGVHD were higher in HID group (47.4% [95% CI, 40.0-54.8] vs 29.2% [95% CI, 16.3-40.9], p=0.029), but cGVHD were similar (Supplementary Figure 18). These data suggested HIDs present a viable and effective option for second transplantations despite increased aGVHD risk.

DISCUSSION

A second transplantation usually represents the only salvage for GF[19]; however, the optimized protocols remain undefined. Among variables potentially affecting outcomes, the role of changing donors remains contentious. In the present study, we demonstrated that changing donors is important for the success of a second transplant, impacting both engraftment and survival.

Previous studies have shown GF risk factors on first transplant include bone marrow grafts, myeloproliferative disorders, HLA mismatch, male recipients grafted from female donors, ABO incompatibility, busulfan/Cy conditioning, stem cells cryopreservation, and low Karnofsky/Lansky score[20]. However, few studies focused on factors predicting GF following second transplantations. Studies in Japan demonstrated in salvaging CB transplantations, the combination of CNI and methotrexate (MTX) as immunosuppressive regimens increased the risk of GF. Additional contributing factors include poor disease risk index, conditioning other than Flu/Mel, and the absence of TBI[21]. Cryopreserved CB $CD34^+$ counts $<0.8 \times 10^5$/kg, HCT-CI scores ≥3, and non-remission at initial SCT were also possible risk factors[22]. In the present study, we identified changing donors and a younger second donor as protective factors for neutrophil engraftment, and changing donors, younger recipient, and higher CD34 doses as protective factors for platelet engraftment.

There were controversies regarding the effect of changing donors in literature. A Spanish study found no impact of changing donors on engraftment or survival[5]. Similarly, the National Marrow Donor Program (NMDP) study yielded comparable results in URD transplantations[23]. In contrast, a small-scale study by Giammaco et al. involving HIDs

reported GF rate of 30% (4/13) in patients grafted from the same donor, compared to 16% (1/6) in those from different donors, indicating a potential benefit of donor change[7]. Additionally, research by Kongtim P. suggested second transplantations utilizing a different HID resulted in lower TRM[24].

Unlike the ambiguity present in earlier research, our study strongly suggests changing donors is likely a key determinant of both engraftment and survival. Several reasons may account for this disparity. First, most prior studies had limited sample sizes. Second, the population and transplant regimens may differ markedly between previous studies and our own. Third, all previous research was performed in earlier periods, whereas substantial advancements have occurred in recent years. Last but not least, while previous studies were mainly from CBT, after which GF occurred frequently, a significant proportion of transplants in our study was haplo-SCT. Currently there was few research addressing donor change in haplo-SCT, likely attributable to limited studies incorporating HIDs as a salvage option[8]. Overall, our study demonstrated changing donors is important for the success of second transplantations.

Notably, when donors are changed, conditioning regimens appear less impactful. This was initially proposed in our earlier studies, and has since been corroborated by the current analysis involving a much larger cohort. Nevertheless, the heterogeneity of conditioning regimens across centers necessitates further prospective studies with standardized protocols.

Another interesting finding was that, unlike primary GF, secondary GF outcomes were not associated with donor change, suggesting distinct mechanisms underlying primary and secondary GF. Possible risk factors for secondary GF from prior research included GVHD and viral infections. CD34 cell exhaustion may play a significant role, as evidenced by good efficacies of CD34 boost and thrombopoietin receptor agonists in this context[25, 26]. We also observed a weaker correlation between changing donors and engraftment in AA and in mixed donor-recipient chimerism. We do not know the explanations for these observations yet but it may be related to relatively small sample sizes within subgroups, requiring further studies for validation.

In addition to changing donors, we identified patient age and first donor type as factors related to OS. Previous research highlighted various elements influencing survival following second transplantations. A Japanese study revealed old age, poor performance status,

ongoing antimicrobials, and severe organ dysfunction were associated with inferior OS and TRM[27]. A European group demonstrated advancing age, second remission, low Karnofsky performance status, and myeloablative conditioning pre-first SCT were adverse prognostic factors for TRM, LFS, and OS[10]. There were no prognostic factors reported in URD transplants from NMDP[23].

Despite general application of prophylaxis, infection remained the major contributor for mortality in our cohort. Although not significant in regression analysis, the trend toward improved TRM and OS in transplants post-October 2019 likely reflects advancements in supportive care including antimicrobial strategies. Introduction of novel antimicrobials and diagnostic tools, with immune reconstitution monitoring could offer insights for better infection management.

Our study also proposed a preliminary principle for selecting a different second donor. In line with the established donor selection principles for first transplantations, a younger donor was associated with reduced aGVHD following second transplantations, and higher MNC doses may enhance the efficacy. Despite limited sample size, our study suggests opting for a different, younger second donor and increasing MNC dose could potentially improve second transplant outcomes.

It is important to acknowledge the limitations in our study. Firstly, due to the retrospective, multicenter design, precise documentation of some critical information (e.g. GF diagnosis to salvage transplantation interval, DSA desensitization) was unavailable in some cases, and baseline disparities between groups may exist, highlighting the need for prospective studies. Secondly, the underlying mechanism of donor changing remains unclear. We hypothesize there may be unidentified rejection mechanisms between initial donor and recipient, and further investigation into donor-recipient immune interactions might provide valuable insights.

In conclusion, our study highlighted the importance of changing donors for successful second transplantations in GF salvage. To our knowledge, this represents the largest multicentre analysis of second transplantations for GF. Nevertheless, the underlying pathogenesis is still unclear and prospective studies are needed.

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Variables	Number (%)
Age	26 (3-67)
Sex, male (%)	128 (59.3%)
Disease	
AA	87 (32.0%)
AML	75 (27.6%)
ALL	50 (18.4%)
MDS	34 (12.5%)
CML	10 (3.7%)
CMML	7 (2.6%)
PMF	2 (0.7%)
NHL	2 (0.7%)
Other	5 (1.8%)
Donor Age	34 (2-64)
Donor Sex, male (%)	164 (61.7%)
Donor Type	
MRD	25 (9.2%)
URD	19 (7.0%)
CB	81 (29.8%)
Haplo	147 (54.0%)
DSA prior to 1st transplant	
Available	161 (59.2%)
Positive	34 (21.1%)
MFI	7178 (246-18039)
Conditioning regimen	
Bu/Cy/ATG	112 (41.2%)
TBI-based	42 (15.4%)
Bu/Cy/Flu	36 (13.2%)
Bu/Cy/Flu/ATG	23 (8.5%)
Bu/Cy	15 (5.5%)
Bu/Flu/ATG	11 (4.0%)
Cy/ATG	10 (3.7%)
Other	22 (8.1%)
Graft	
BM+PB	105 (39.0%)
PB	83 (30.9%)
CB	81 (30.1%)
MNC, (range), 10^8/kg	7.69 (0.22-24.2)
CD34, (range), 10^6/kg	2.77 (0.14-15.1)

Table 1. Patient characteristics of the first transplantations.

AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; MDS, myelodysplastic syndrome; CMML, chronic myelomonocytic leukemia; CML, chronic myeloid leukemia; NHL, non-Hodgkin lymphoma; MRD, matched related donor; URD, unrelated donor; CB, cord blood; Haplo, haploidentical transplantation; DSA, Donor specific antibody; MFI, median fluorescence intensity; Bu, busulfan; Cy, cyclophosphamide; ATG, anti-thymocyte globulin; TBI, total body irradiation; BM, bone marrow; PB, peripheral blood; MNC, mononucleated cell.

Variables	Number (%)
GF type	
Primary	193 (71.0%)
Secondary	79 (29.0%)
Chimerism	
Full donor	80 (31.5%)
Mix	97 (38.2%)
Full recipient	77 (30.3%)
Time from 1st Tx to 2nd Tx	55 (18-2592)
Changing Donor	
Yes	192 (70.6%)
No	80 (39.4%)
Donor Age	35 (2-68)
Donor Sex, male (%)	155 (57.8%)
2nd Donor type	
MRD	21 (7.7%)
URD	16 (5.9%)
CB	19 (7.0%)
Haplo	216 (79.4%)
2nd Donor ABO type	
Match	152 (55.9%)
Minor mismatch	55 (20.2%)
Major mismatch	43 (15.8%)
Bidirectional mismatch	22 (8.1%)
DSA prior to 2nd Tx	
Available	154 (56.6%)
Positive	22 (14.3%)
MFI	2512 (246-19682)
Conditioning	
Flu/Cy	81 (29.8%)
TBI/Flu/CY	50 (18.4%)
Bu/Cy/Flu	29 (10.7%)
Flu	23 (8.5%)
Bu/Cy	13 (4.8%)
Bu/Flu	10 (3.7%)
Bu	9 (3.3%)
TBI/Flu	9 (3.3%)
Cy	8 (2.9%)
TBI/Cy	6 (2.2%)
Other	34 (12.5%)
Graft	
BM+PB	141 (51.8%)
PB	110 (40.4%)
CB	21 (7.7%)
MNC, (range), 10^8/kg	9.36 (0.28-30.7)
CD34, (range), 10^6/kg	4.50 (0.16-22.1)
GVHD prophylaxis	
CSA+MMF	61 (22.4%)

CSA+MMF+ATG	53 (19.5%)
CSA+MMF+CD25	49 (18.0%)
CSA+MMF+MTX+ATG	45 (16.5%)
FK506+MMF+MTX+ATG	16 (5.9%)
CSA+MMF+MTX	9 (3.3%)
CSA+MMF+Cy+ATG	9 (3.3%)
FK506+MMF+ATG	4 (1.5%)
CSA+MMF+CD25+PtCy	3 (1.1%)
CSA+ATG+PtCy	3 (1.1%)
Other	20 (7.4%)

Table 2. Patient characteristics of the second transplantations.

GF, graft failure; Tx, transplantation; MRD, matched related donor; URD, unrelated donor; CB, cord blood; Haplo, haploidentical transplantation; MFI, median fluorescence intensity; Cy, cyclophosphamide; Flu, fludarabine; TBI, total body irradiation; BM, bone marrow; PB, peripheral blood; CB, cord blood; MNC, mononucleated cell; CSA, cyclosporine A; MMF, mycophenolate mofetil; PtCy, post-transplant cyclophosphamide; MTX, methotrexate.

Outcomes / Variables	ANC Engraftment				Platelet Engraftment				aGVHD				cGVHD				TRM				OS			
	Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate	
	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*
Recipient Gender (Male vs Female)	1.062	0.652			0.860	0.339			0.901	0.604			1.129	0.716			1.188	0.375			0.876	0.473		
Recipient Age (< Median vs ≥Median)	0.717	0.014			0.611	0.002	0.597	0.011	0.785	0.947			2.514	0.008	2.185	0.028	0.613	0.011	0.560	0.030	0.627	0.011	0.610	0.046
Disease (AA vs Other)	1.010	0.771			1.054	0.183			1.307	0.223			2.291	0.032			0.633	0.035			1.861	0.004		
1st Donor Type																								
MRD	1.000				1.000				1.000				1.000				1.000		1.000		1.000		1.000	
URD	1.029	0.932			1.595	0.203			3.128	0.040			0.568	0.488			2.101	0.141	3.596	0.033	2.093	0.120	4.230	0.015
CB	1.174	0.508			1.681	0.049			2.032	0.147			0.515	0.233			1.707	0.202	3.208	0.044	1.728	0.163	4.181	0.014
Haplo	0.620	0.038			2.128	0.003			2.888	0.023			0.995	0.992			2.081	0.066	1.867	0.177	2.055	0.054	2.053	0.117
GF Type (Primary vs Secondary)	1.613	0.524			1.708	<0.001			0.724	0.155			1.505	0.227			1.658	0.028			1.642	0.023		
Chimerism																								
Full donor	1.000				1.000				1.000				1.000				1.000				1.000			
Mixed	1.276	0.175			0.864	0.470			0.696	0.153			0.868	0.716			0.702	0.127			0.690	0.101		
Full recipient	1.111	0.521			0.684	0.066			1.026	0.918			0.513	0.145			0.651	0.086			0.759	0.234		
Time from 1st Tx to 2nd Tx (< Median vs ≥Median)	0.994	0.963			1.302	0.090			0.763	0.175			1.635	0.157			1.171	0.408			0.834	0.317		
DSA prior to 2nd Tx (Neg. vs Pos.)	0.615	0.062			0.537	0.051			0.671	0.354			0.714	0.649			0.790	0.542			1.421	0.314		
Disease Status prior to 2nd Tx (Relapse vs CR)	0.066	0.797			1.317	0.485			0.627	0.433			0.043	0.379			1.208	0.715			0.902	0.824		
Change donor (No vs Yes)	1.745	<0.001	1.603	0.039	2.006	<0.001	1.788	0.035	1.135	0.577			0.600	0.149			2.074	<0.001	2.320	0.006	1.881	<0.001	2.469	0.004
2nd Donor Age (< Median vs ≥Median)	0.744	0.057	0.668	0.019	0.814	0.217			1.480	0.069			1.171	0.657			0.714	0.107			0.699	0.071		
2nd Donor Gender (Male vs Female)	0.244	0.852			0.907	0.538			0.896	0.592			1.126	0.723			0.772	0.176			1.223	0.269		

2nd Donor Type																								
MRD	1.000				1.000				1.000		1.000		1.000				1.000				1.000			
URD	1.297	0.451			0.913	0.806			11.669	0.022	10.125	0.033	1.036	0.970			1.008	0.989			0.902	0.857		
CB	3.058	0.002			3.623	0.003			9.983	0.031	8.789	0.045	1.222	0.827			1.733	0.276			1.588	0.342		
Haplo	1.427	0.142			1.712	0.038			11.849	0.014	10.275	0.023	1.285	0.680			1.463	0.332			1.471	0.294		
ABO of 2nd Tx (Matched/Minor mismatched vs Major/Bidirectional mismatched)	0.855	0.457			0.406	0.197			0.788	0.464			1.023	0.783			0.445	0.282			0.798	0.457		
Conditioning Regimen of 2nd Tx (FC vs Other)	0.966	0.081			1.034	0.843			1.014	0.951			0.790	0.509			1.063	0.770			0.917	0.659		
Graft Source of 2nd Tx																								
PB+BM	1.000				1.000				1.000				1.000				1.000				1.000			
PB	1.859	0.047			1.362	0.058			0.734	0.148			1.611	0.166			1.424	0.077			1.303	0.162		
CB	3.021	0.002			2.770	0.006			0.935	0.858			1.205	0.803			1.598	0.176			1.406	0.319		
Infused MNCs (< Median vs ≥Median)	1.646	<0.001			1.820	<0.001			1.050	0.809			1.208	0.580			1.629	0.012			1.493	0.030		
Infused CD34 cells (< Median vs ≥Median)	1.495	0.006			1.851	<0.001	1.453	0.034	0.948	0.804			1.727	0.142			1.701	0.013			1.938	0.001		
GVHD Prophylaxis for 2nd Tx (Non-intensified vs Intensified)	1.754	<0.001			2.125	<0.001			1.256	0.345			0.699	0.284			2.037	<0.001			1.957	<0.001		
Time of 2nd transplantation (Before vs After Oct 2019)	1.473	0.004			1.762	<0.001			1.143	0.500			0.265	0.683			0.706	0.072			0.720	0.074		

Table 3. Univariate and multivariate analysis for 2nd transplant outcomes in all patients.

ANC, absolute neutrophil count; aGVHD, acute graft versus host disease; cGVHD, chronic graft versus host disease; TRM, transplant-related mortality; OS, overall survival; AA, aplastic anemia; GF, graft failure; MRD, matched related donor; URD, unrelated donor; CB, cord blood; Haplo, haploidentical transplantation; Tx, transplantation; DSA, Donor specific antibody; CR, complete remission; FC, fludarabine/cyclophosphamide; BM, bone marrow; PB, peripheral blood; MNCs, mononucleated cells; GVHD, graft versus host disease.

Outcomes / Variables	ANC Engraftment				Platelet Engraftment				aGVHD				cGVHD				TRM				OS			
	Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate	
	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*
Recipient Gender (Male vs Female)	0.836	0.252			0.673	0.027			0.889	0.617			1.404	0.407			1.147	0.590			1.072	0.767		
Recipient Age (< Median vs ≥Median)	0.819	0.205			0.685	0.030	0.615	0.036	1.207	0.413			0.438	0.048			0.538	0.002	0.472	0.015	0.454	0.003	0.377	0.002
Disease (AA vs Other)	4.012	0.674			0.725	0.071			1.322	0.263			0.418	0.066			0.637	0.104			0.502	0.011		
1st Donor Type																								
MRD	1.000				1.000				1.000				1.000				1.000				1.000			
URD	1.000	1.000			2.000	0.114			1.606	0.439			0.498	0.445			3.221	0.139			3.709	0.094		
CB	9.368	0.864			2.169	0.026			1.094	0.867			0.451	0.291			2.806	0.157			3.262	0.104		
Haplo	1.000	1.000			1.862	0.071			1.617	0.361			0.769	0.624			2.029	0.337			2.540	0.202		
GF Type (Primary vs Secondary)	0.031	0.723			1.565	0.019			0.935	0.796			1.385	0.453			0.662	0.183			0.663	0.154		
Chimerism																								
Full donor	1.000				1.000				1.000				1.000				1.000				1.000			
Mixed	0.002	0.723			1.052	0.834			0.720	0.309			1.445	0.456			0.961	0.904			0.918	0.790		
Full recipient	0.002	0.736			0.791	0.326			1.158	0.628			0.379	0.133			0.783	0.479			0.909	0.947		
Time from 1st Tx to 2nd Tx (< Median vs ≥Median)	1.398	0.237			1.329	0.104			1.081	0.738			1.873	0.148			1.222	0.419			0.637	0.443		
DSA prior to 2nd Tx (Neg. vs Pos.)					0.812	0.550			0.610	0.341			0.042	0.336			1.082	0.881			1.240	0.622		
Disease Status prior to 2nd Tx (Relapse vs CR)	0.042	0.823			1.397	0.402			0.588	0.377			0.040	0.464			1.550	0.465			1.344	0.571		
2nd Donor Age (< Median vs ≥Median)	0.015	0.607			0.782	0.195			0.411	0.008			1.532	0.344			0.542	0.038			0.521	0.017		
2nd Donor Gender (Male vs Female)	0.020	0.642			1.019	0.916			0.281	0.771			1.275	0.553			0.775	0.310			0.850	0.486		
2nd Donor Type																								
MRD	1.000				1.000				1.000				1.000				1.000				1.000			

URD	1.000	1.000			0.977	0.960			2.229	0.897			2.170	0.954			0.843	0.844			0.857	0.859		
CB	1.000	1.000			4.484	0.004			2.070	0.898			2.402	0.953			1.734	0.482			1.835	0.438		
Haplo	2.918	0.894			1.580	0.243			2.459	0.896			2.331	0.953			1.074	0.921			1.316	0.703		
ABO of 2nd Tx (Matched/Minor mismatched vs Major/Bidirectional mismatched)	0.808	0.219			0.642	0.187			0.878	0.506			0.870	0.735			0.648	0.215			0.774	0.265		
Conditioning Regimen of 2nd Tx (FC vs Other)	0.004	0.594			1.056	0.777			1.356	0.833			0.686	0.371			0.933	0.801			0.969	0.901		
Graft Source of 2nd Tx																								
PB+BM	1.000				1.000				1.000				1.000				1.000				1.000			
PB	0.026	0.730			0.635	0.022			0.888	0.672			1.449	0.418			0.564	0.117			0.533	0.067		
CB	0.026	0.817			2.874	0.004			0.988	0.976			1.192	0.816			1.618	0.169			1.413	0.316		
Infused MNCs (< Median vs ≥Median)	6.458	0.611			1.562	0.013	1.564	0.045	1.063	0.795			1.193	0.667			1.381	0.205			3.509	0.285		
Infused CD34 cells (< Median vs ≥Median)	6.458	0.611			1.381	0.072			0.839	0.462			1.509	0.321			1.220	0.439			1.441	0.133		
GVHD Prophylaxis for 2nd Tx (Other vs Intensified)	1.925	0.004			2.231	0.004			1.121	0.727			3.762	0.195			1.923	0.023			1.862	0.021		

Table 4. Univariate and multivariate analysis for 2nd transplant outcomes in patients who changed to a different donor.

ANC, absolute neutrophil count; aGVHD, acute graft versus host disease; cGVHD, chronic graft versus host disease; TRM, transplant-related mortality; OS, overall survival; AA, aplastic anemia; GF, graft failure; MRD, matched related donor; URD, unrelated donor; CB, cord blood; Haplo, haploidentical transplantation; Tx, transplantation; DSA, Donor specific antibody; CR, complete remission; FC, fludarabine/cyclophosphamide; BM, bone marrow; PB, peripheral blood; MNCs, mononucleated cells; GVHD, graft versus host disease.

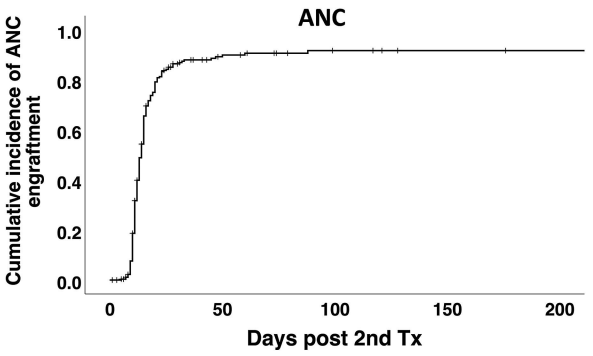
Figure legends

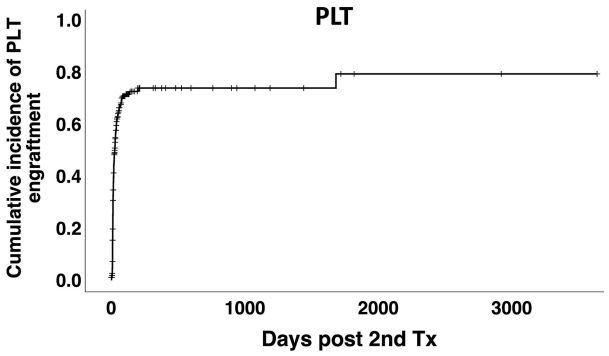
Figure 1. Outcomes of the 2nd transplantations for the entire cohort.

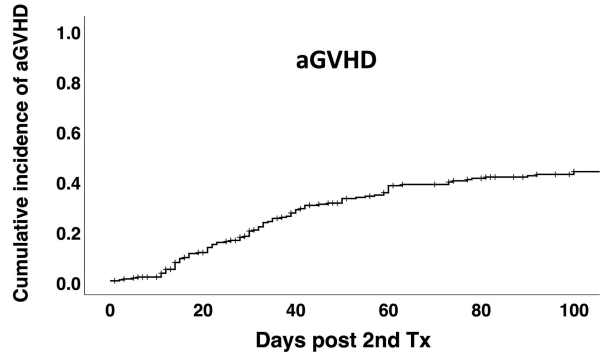
ANC, absolute neutrophil count; PLT, platelet; aGVHD, acute graft versus host disease; cGVHD, chronic graft versus host disease; TRM, transplant-related mortality; OS, overall survival; DFS, disease-free survival; CMV, cytomegalovirus; EBV, Epstein-Barr virus.

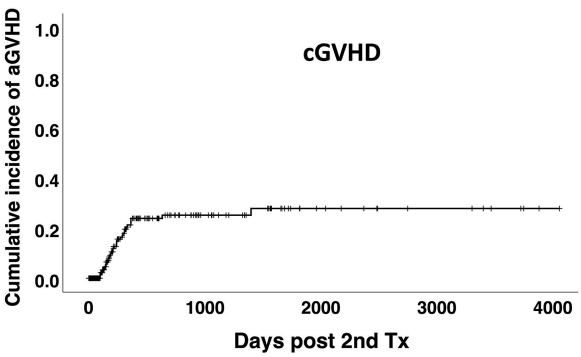
Figure 2. Comparison of the second transplantation outcomes in patients who received grafts from the same or a different donor.

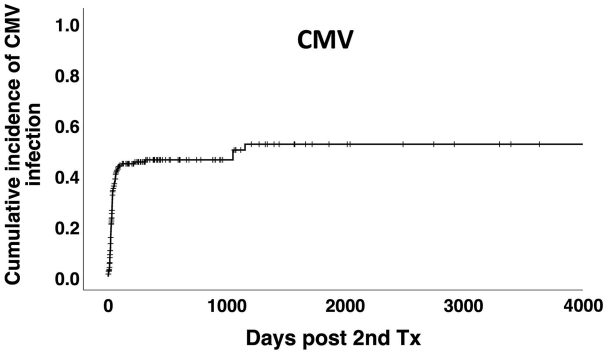
Solid line, using a different donor; dashed line, using the same donor.

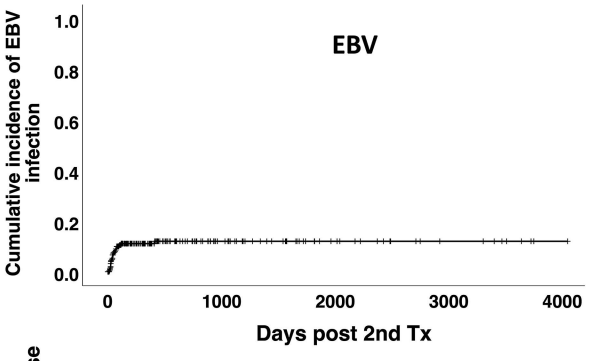

ANC
Cumulative incidence of ANC engraftment
1.0
0.8
0.6
0.4
0.2
0.0
0
50
100
150
200
Days post 2nd Tx

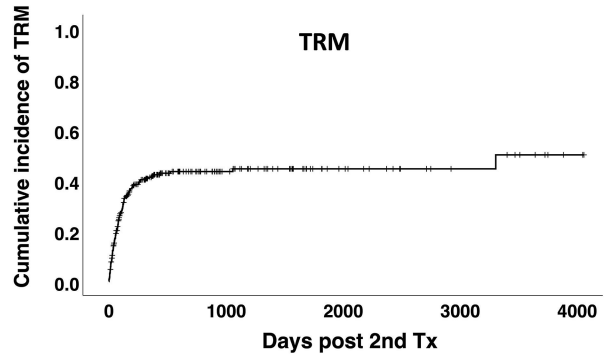

PLT
Cumulative incidence of PLT engraftment
1.0
0.8
0.6
0.4
0.2
0.0
0
1000
2000
3000
Days post 2nd Tx

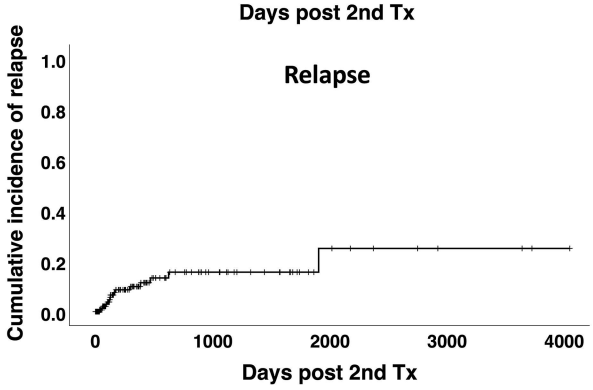

aGVHD
Cumulative incidence of aGVHD
1.0
0.8
0.6
0.4
0.2
0.0
0
20
40
60
80
100
Days post 2nd Tx

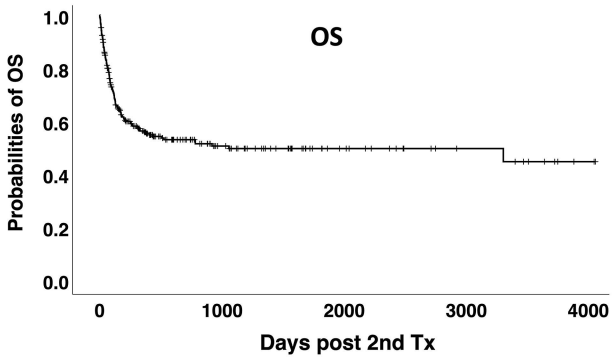

cGVHD
Cumulative incidence of aGVHD
1.0
0.8
0.6
0.4
0.2
0.0
0
1000
2000
3000
4000
Days post 2nd Tx

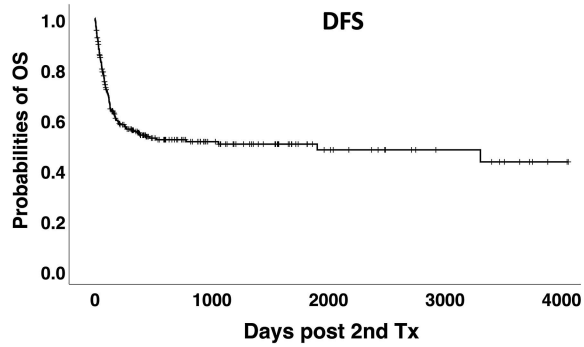

CMV
Cumulative incidence of CMV infection
1.0
0.8
0.6
0.4
0.2
0.0
0
1000
2000
3000
4000
Days post 2nd Tx

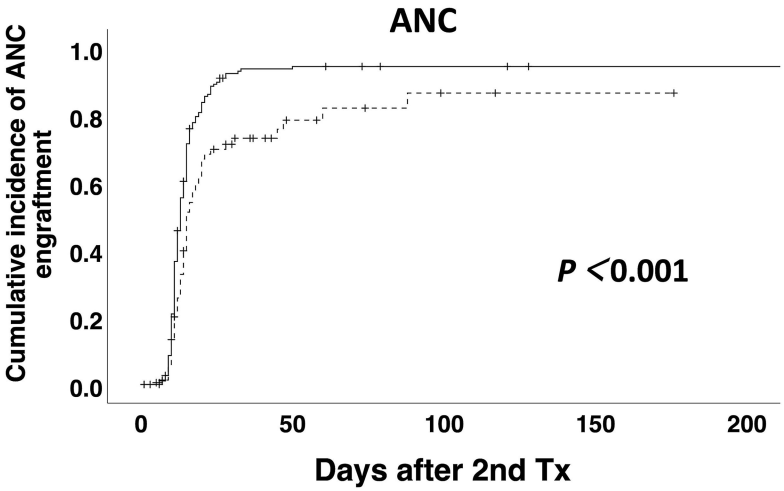

EBV
Cumulative incidence of EBV infection
1.0
0.8
0.6
0.4
0.2
0.0
0
1000
2000
3000
4000
Days post 2nd Tx

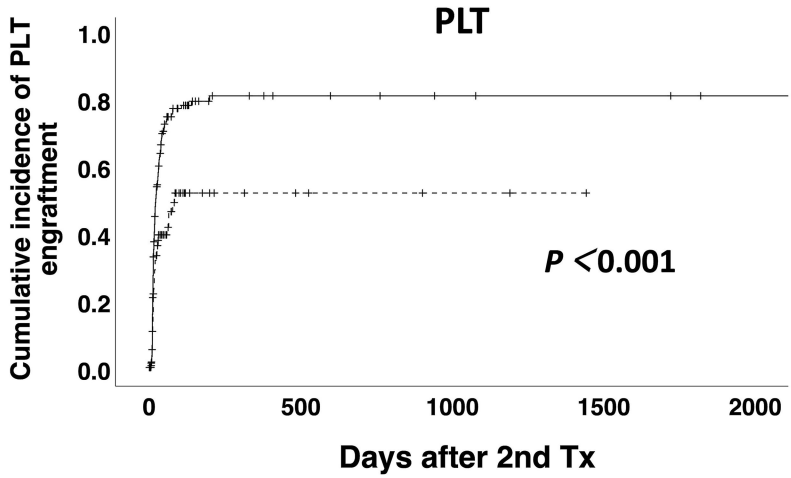

TRM
Cumulative incidence of TRM
1.0
0.8
0.6
0.4
0.2
0.0
0
1000
2000
3000
4000
Days post 2nd Tx

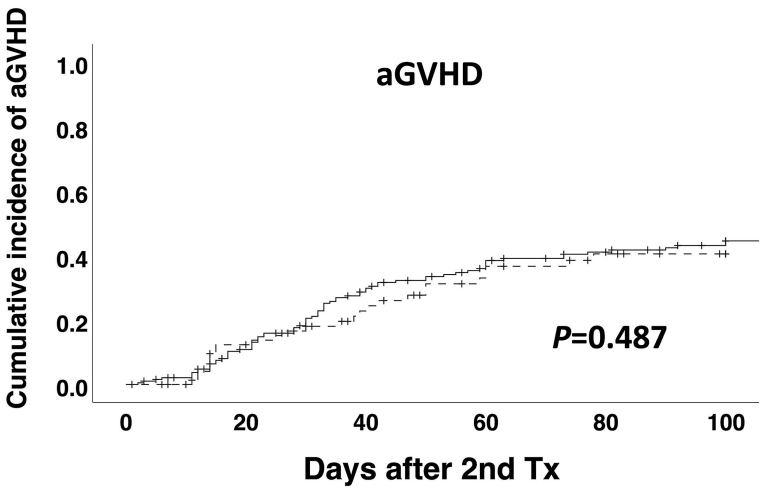

Relapse
Cumulative incidence of relapse
1.0
0.8
0.6
0.4
0.2
0.0
0
1000
2000
3000
4000
Days post 2nd Tx

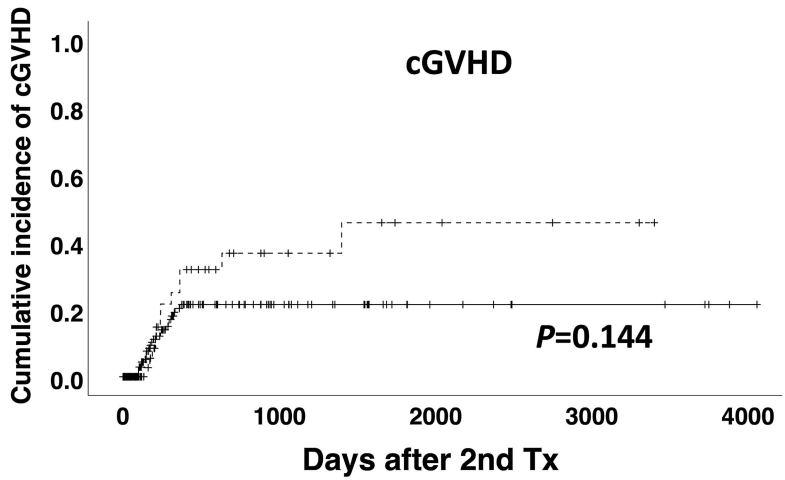

OS
Probabilities of OS
1.0
0.8
0.6
0.4
0.2
0.0
0
1000
2000
3000
4000
Days post 2nd Tx

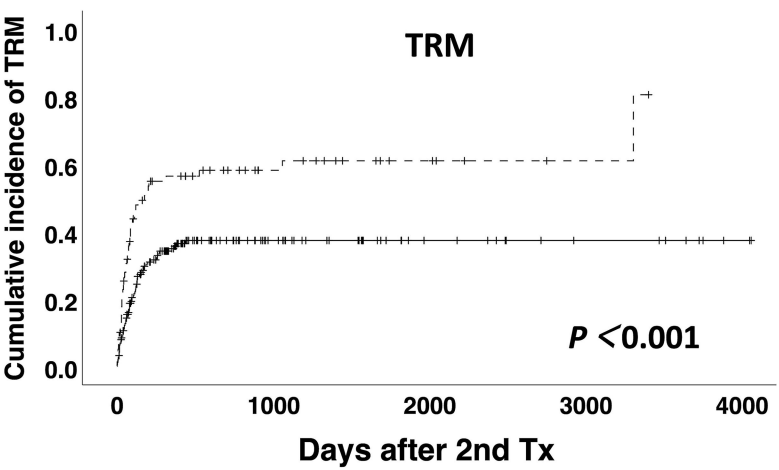

DFS
Probabilities of OS
1.0
0.8
0.6
0.4
0.2
0.0
0
1000
2000
3000
4000
Days post 2nd Tx

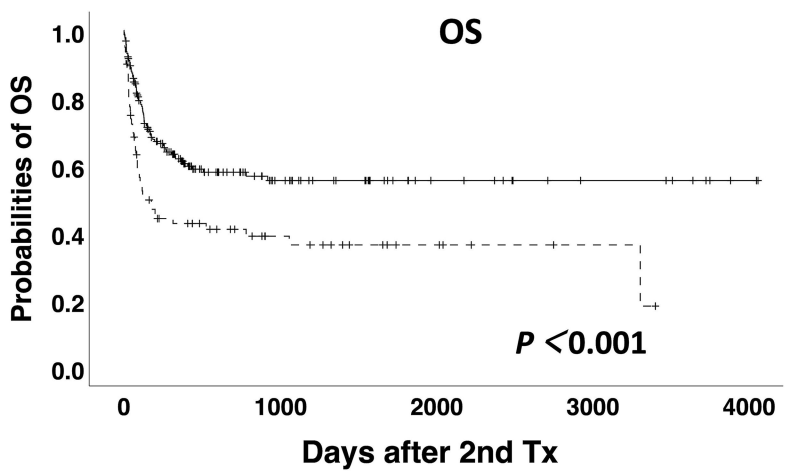

ANC
Cumulative incidence of ANC engraftment
1.0
0.8
0.6
0.4
0.2
0.0
0
50
100
150
200
Days after 2nd Tx
P <0.001

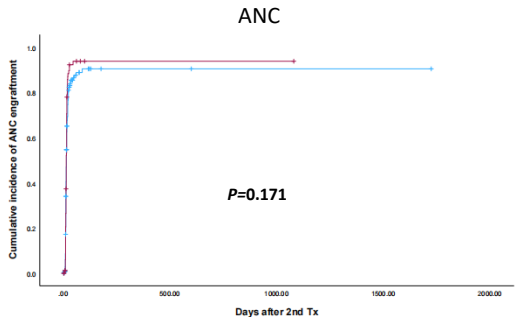

PLT
Cumulative incidence of PLT engraftment
1.0
0.8
0.6
0.4
0.2
0.0
0
500
1000
1500
2000
Days after 2nd Tx
P <0.001

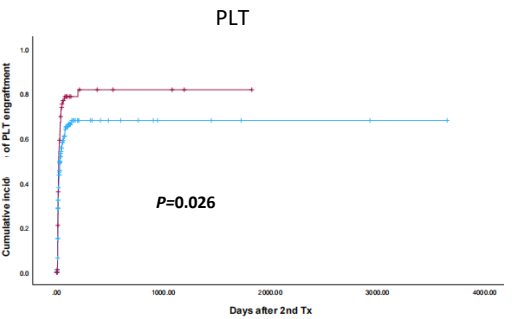

aGVHD
Cumulative incidence of aGVHD
1.0
0.8
0.6
0.4
0.2
0.0
0
20
40
60
80
100
Days after 2nd Tx
P=0.487

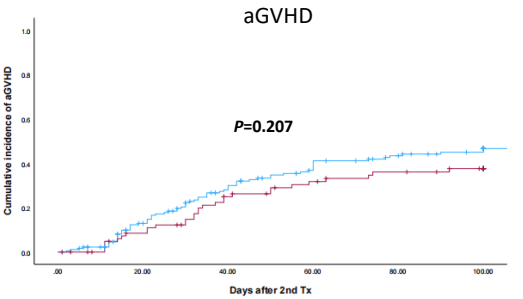

cGVHD
Cumulative incidence of cGVHD
1.0
0.8
0.6
0.4
0.2
0.0
0
1000
2000
3000
4000
Days after 2nd Tx
P=0.144

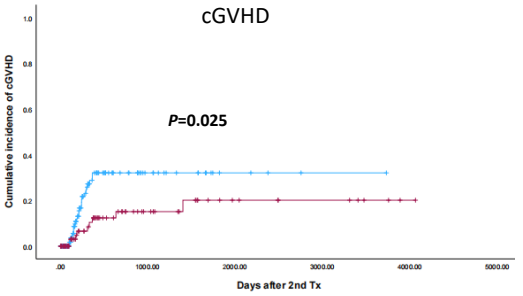

TRM
Cumulative incidence of TRM
1.0
0.8
0.6
0.4
0.2
0.0
0
1000
2000
3000
4000
Days after 2nd Tx
P <0.001

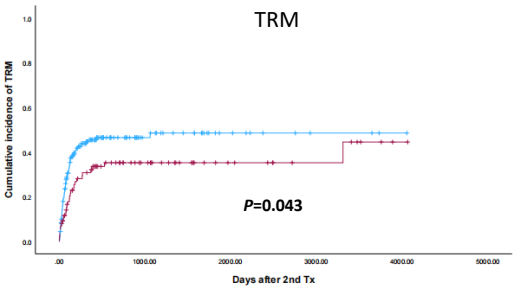

OS
Probabilities of OS
1.0
0.8
0.6
0.4
0.2
0.0
0
1000
2000
3000
4000
Days after 2nd Tx
P <0.001

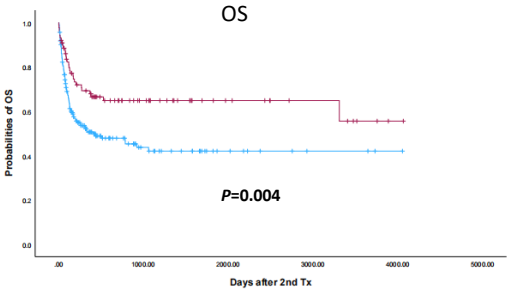






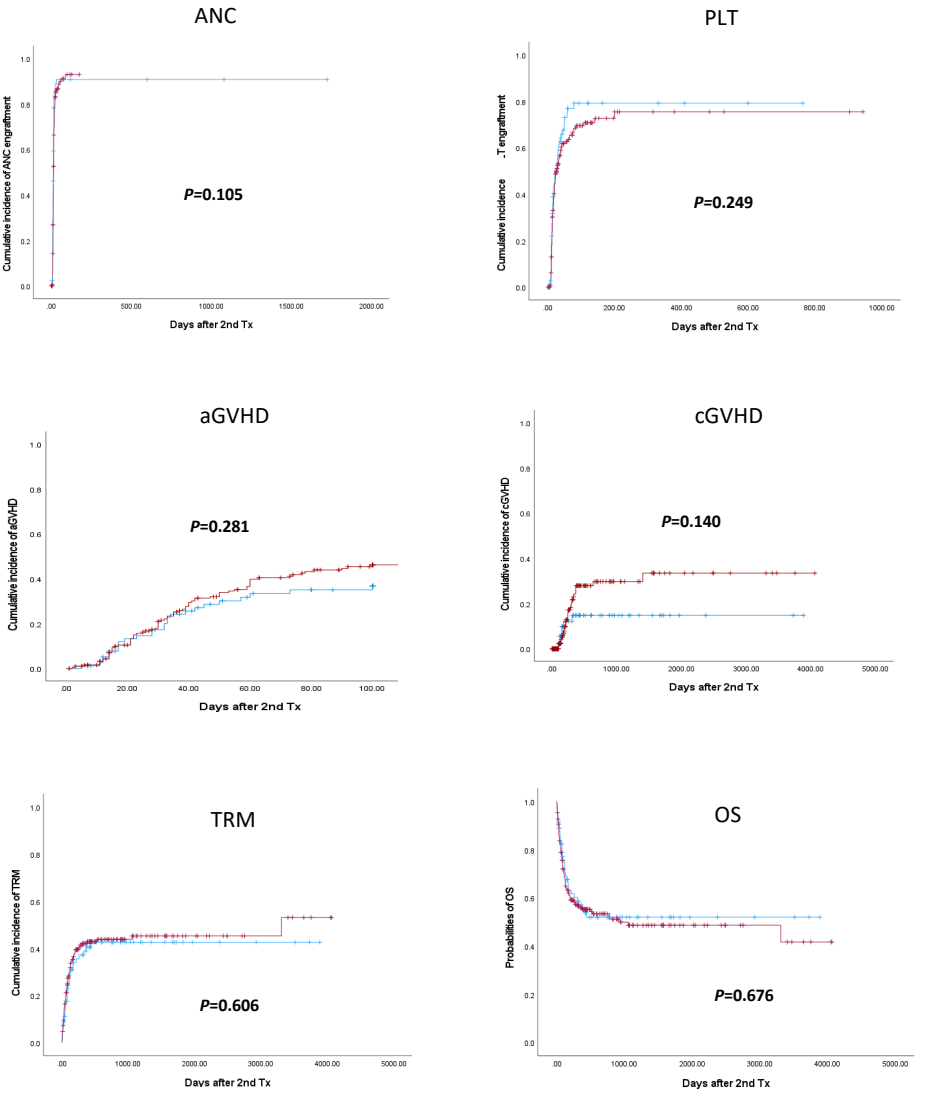






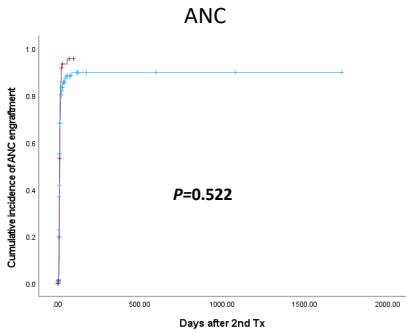
Supplementary Figure 1. Outcomes of 2nd transplantation in patients with AA and hematopoietic malignancies.

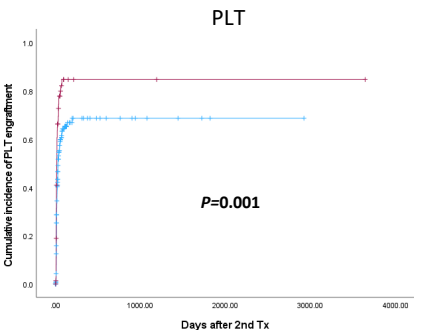
Red line: AA; blue line: hematopoietic malignancies.

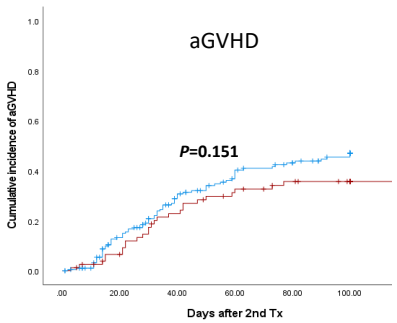


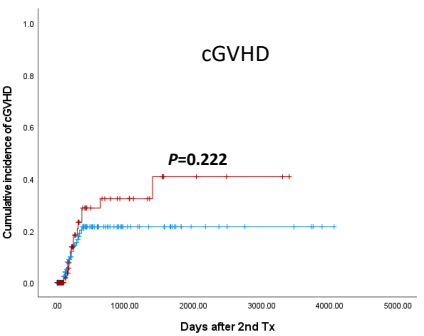
Supplementary Figure 2. Outcomes of 2nd transplantation in patients grafted from CB and other donor types for the 1st transplantation.

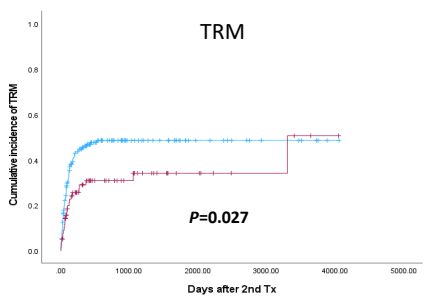
Red line: other donor types including MRD, URD, and HID; blue line: CB.

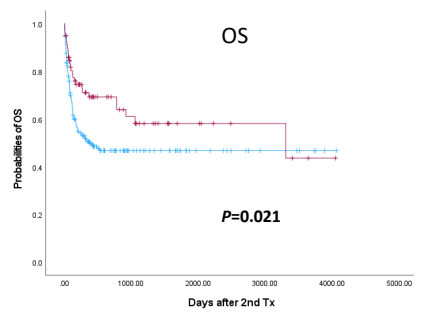




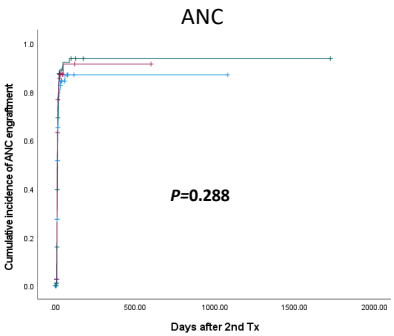


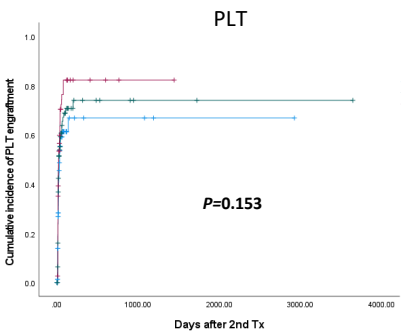


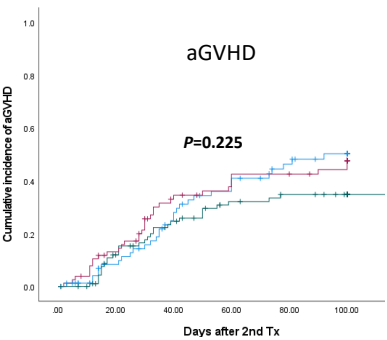


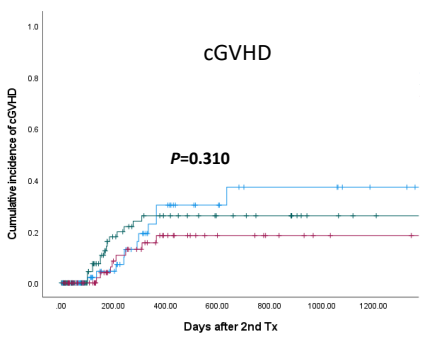


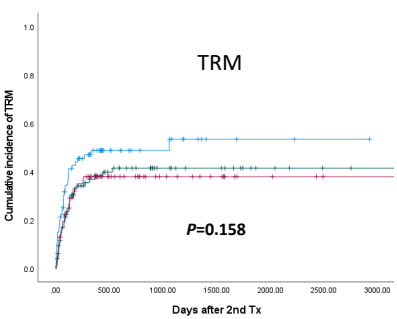
Supplementary Figure 3. Outcomes of 2nd transplantation in patients experiencing primary or secondary graft failures after the 1st transplantation. Red line: secondary GF; blue line: primary GF.

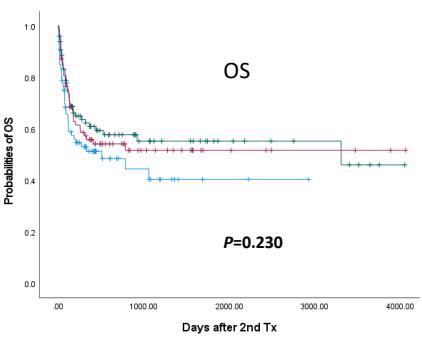






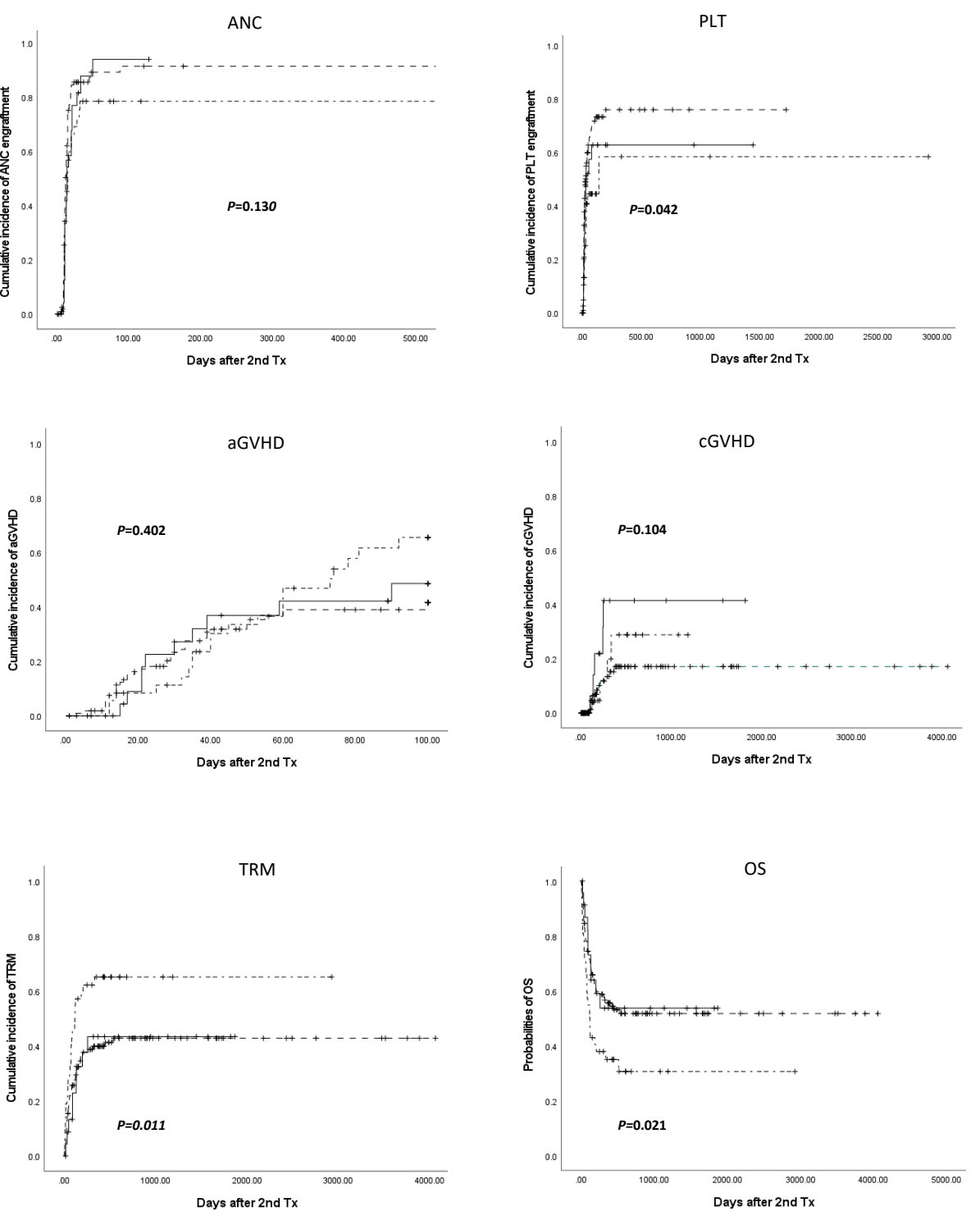






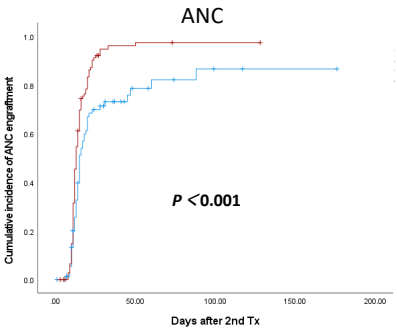
Supplementary Figure 4. Outcomes of 2nd transplantation in patients with different chimerism status after the 1st transplantation.

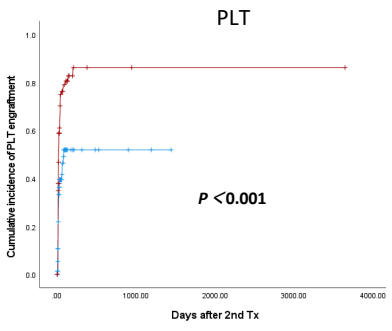
Red line: full recipient; blue line: full donor; green line: mixed.

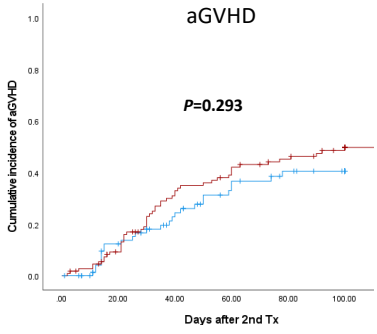


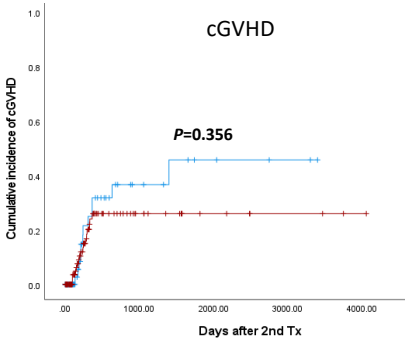
Supplementary Figure 5. Outcomes of 2nd transplantation in primary graft failure patients with various etiologies.

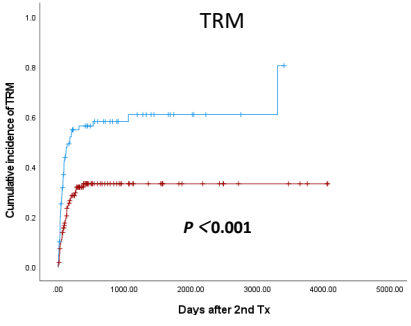
Solid line: group A; dashed line: group B; dash-dot line: group C.

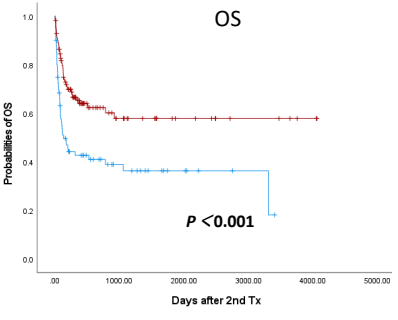






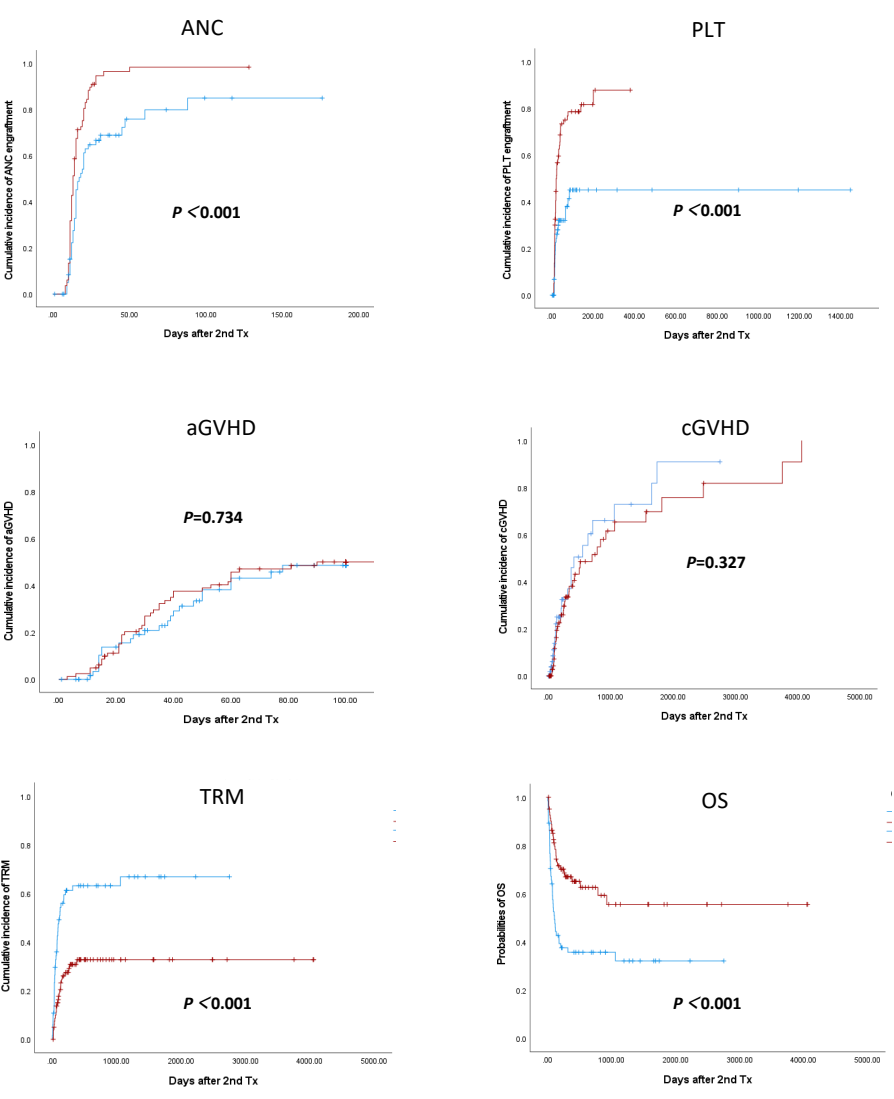






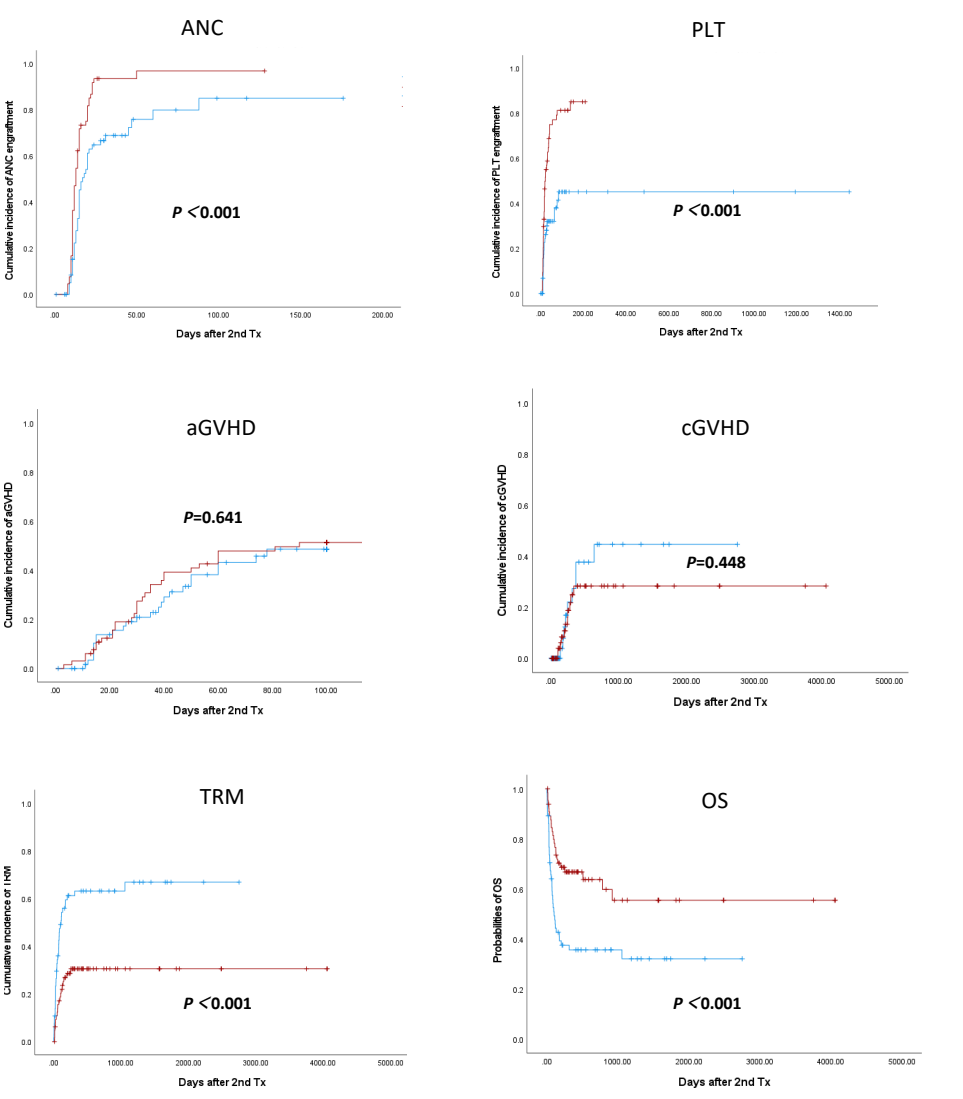
Supplementary Figure 6. Comparison of 2nd transplant outcomes in using the different or the same donor in patients who received grafts from MRDs, URDs, and HIDs.

Red line: using a different donor; blue line: using the same donor.



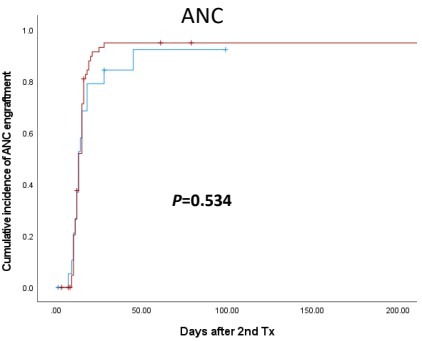
Supplementary Figure 7. Comparison of 2nd transplant outcomes in patients who used the different or the same donor and received grafts from HIDs for the 1st transplantation.

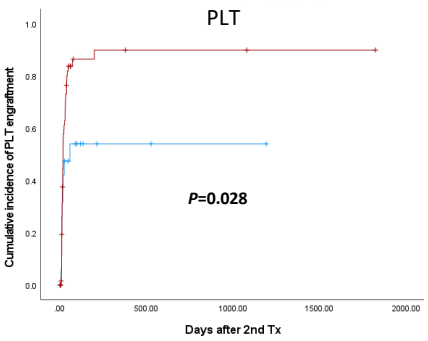
Red line: using a different donor; blue line: using the same donor.

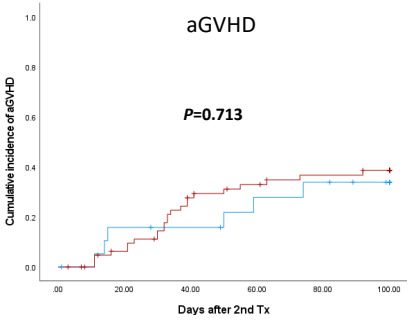


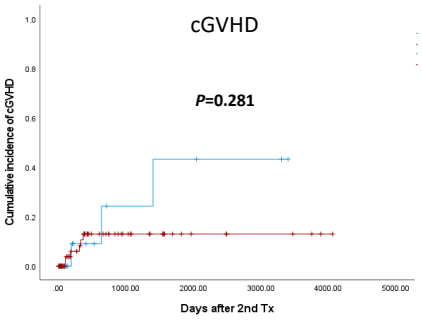
Supplementary Figure 8. Comparison of 2nd transplant outcomes in patients who used the different or the same donor and received grafts from HIDs for both transplantations.

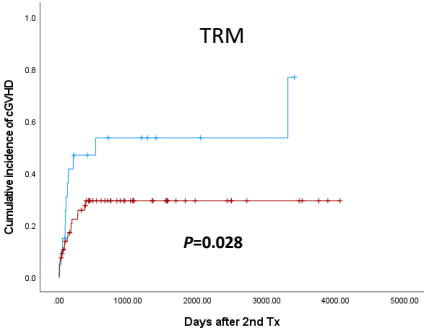
Red line: using a different donor; blue line: using the same donor.

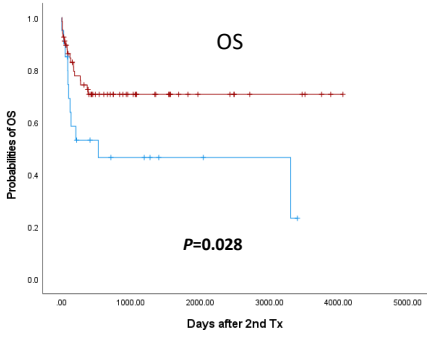






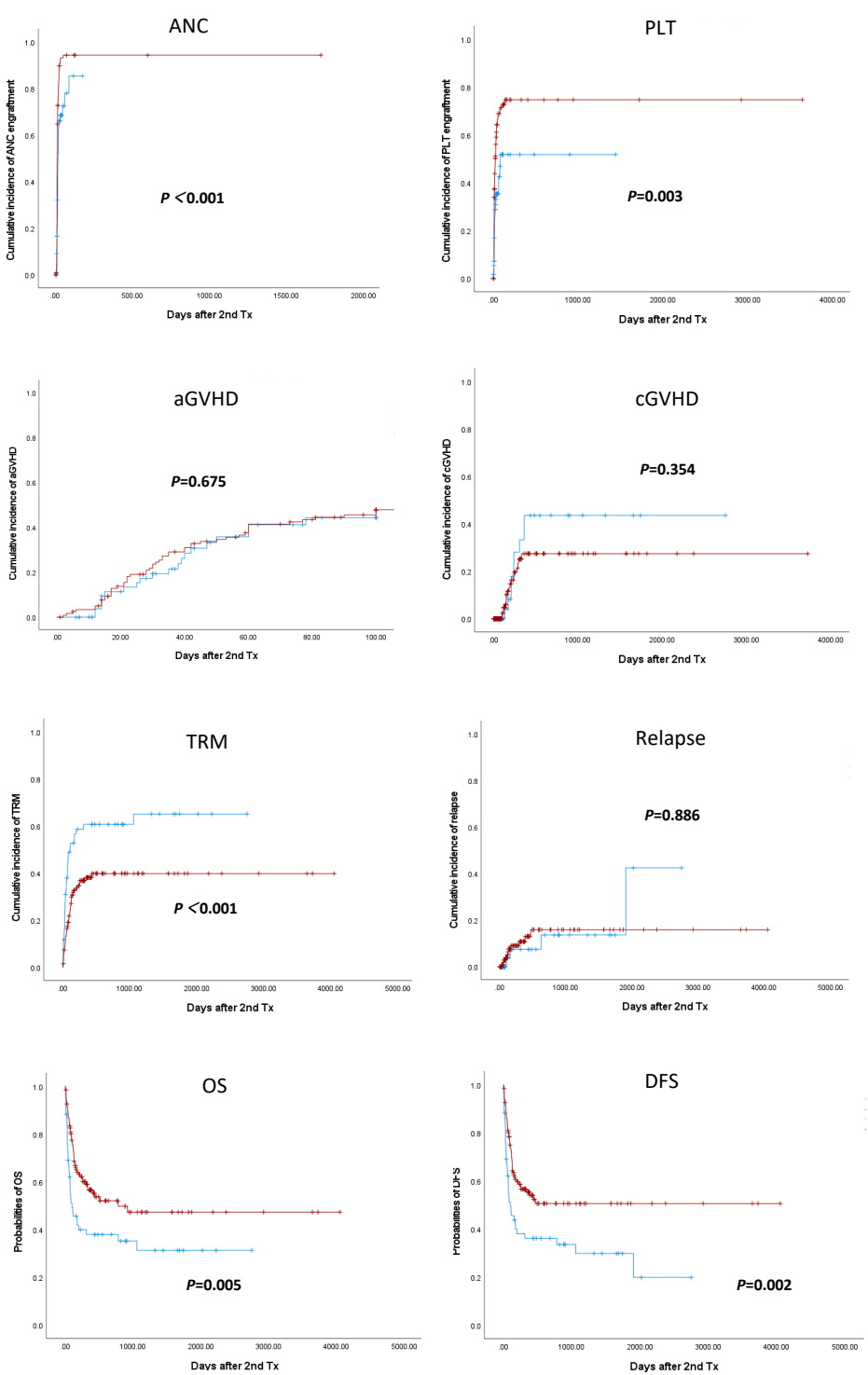




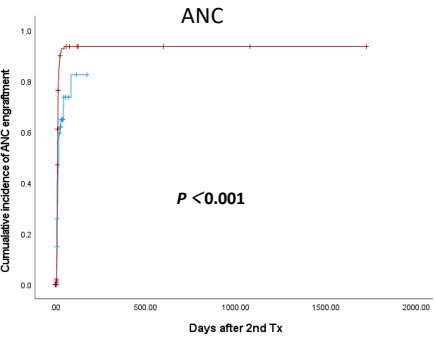


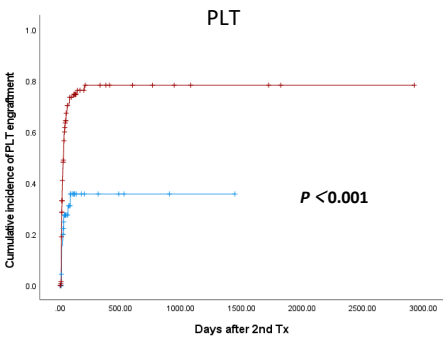
Supplementary Figure 9. Comparison of 2nd transplant outcomes in AA patients who used the different or the same donor.

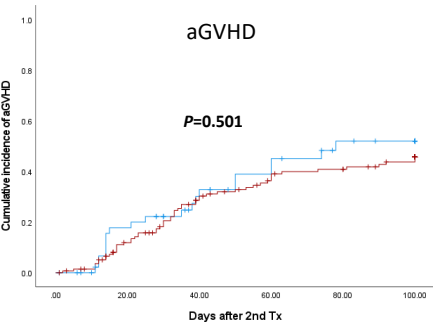
Red line: using a different donor; blue line: using the same donor.

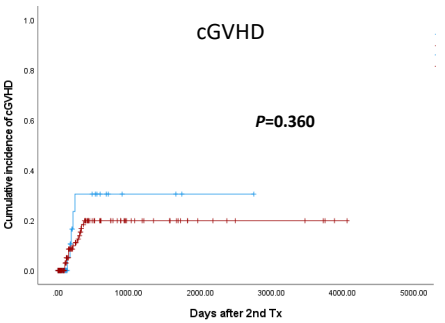


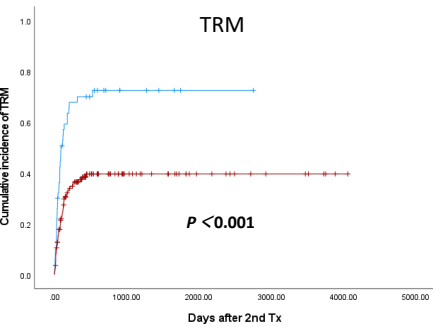
Supplementary Figure 10. Comparison of 2nd transplant outcomes in patients with hematopoietic malignancies who used the different or the same donor. Red line: using a different donor; blue line: using the same donor.

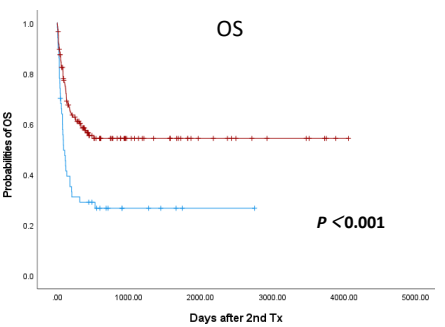






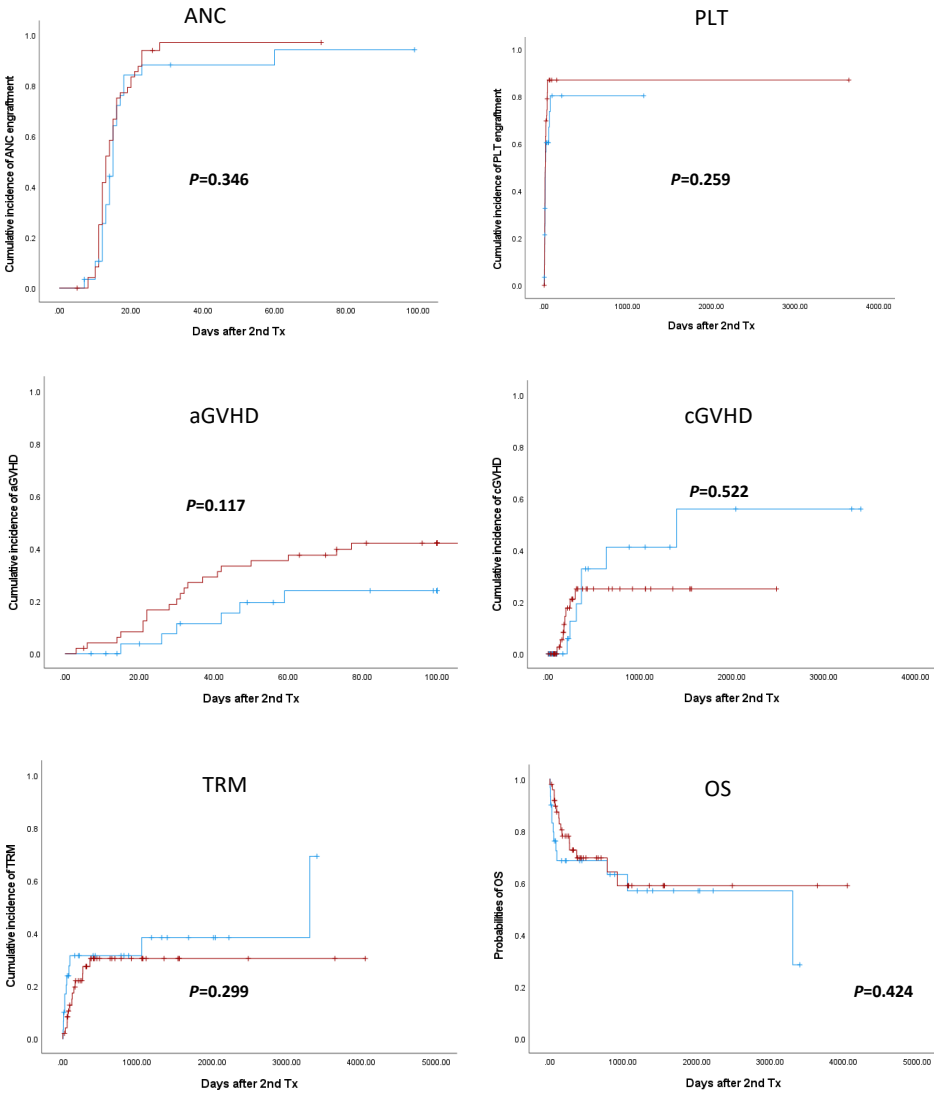






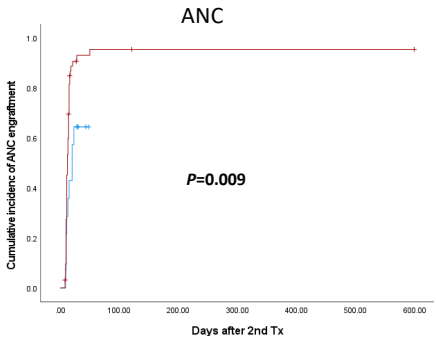
Supplementary Figure 11. Comparison of 2nd transplant outcomes in patients with primary GF who used the different or the same donor.

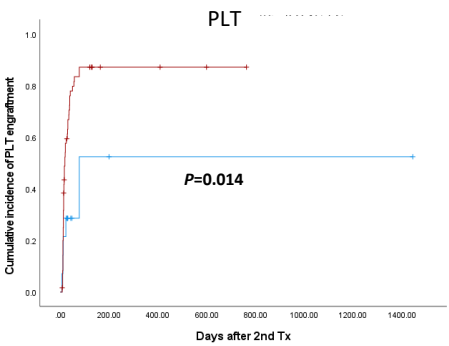
Red line: using a different donor; blue line: using the same donor.

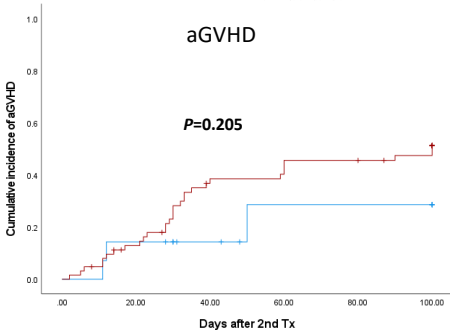


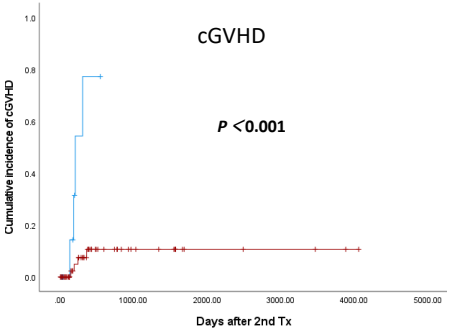
Supplementary Figure 12. Comparison of 2nd transplant outcomes in patients with secondary GF who used the different or the same donor.

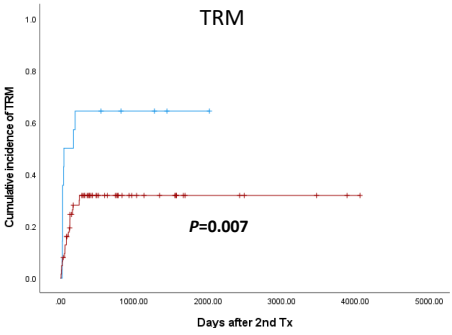
Red line: using a different donor; blue line: using the same donor.

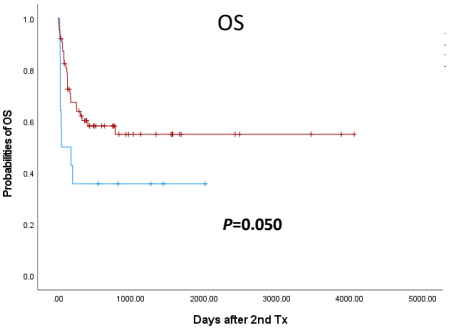




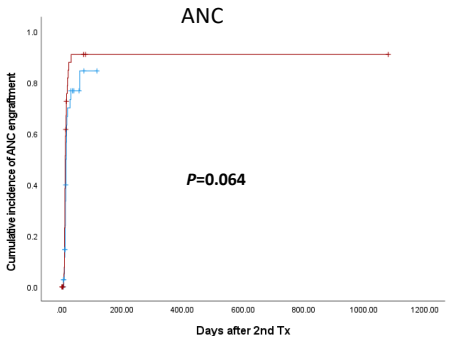


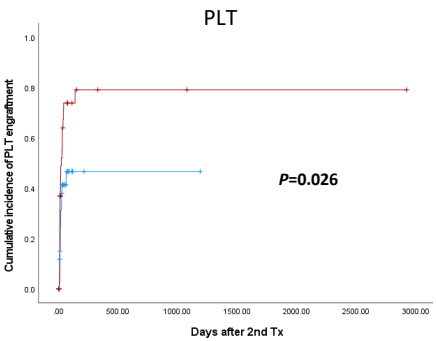


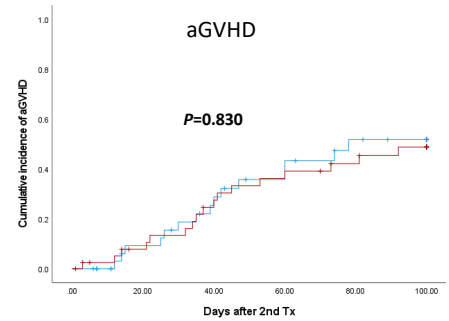


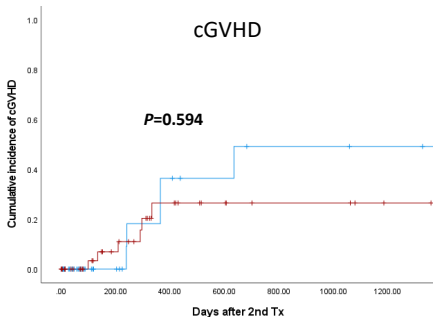


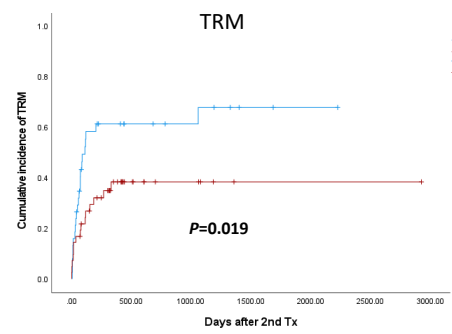
Supplementary Figure 13. Comparison of 2nd transplant outcomes in patients with full recipient chimerism who used the different or the same donor.
Red line: using a different donor; blue line: using the same donor.

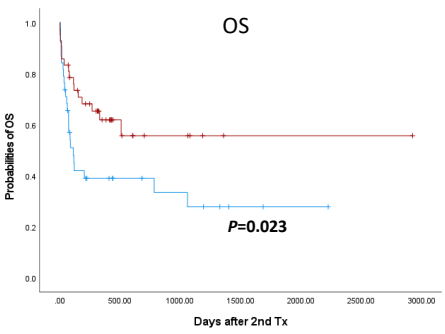




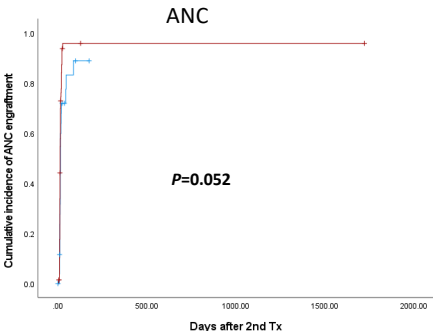


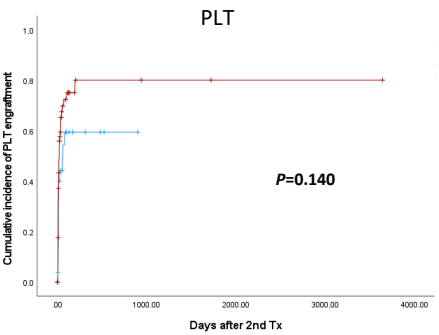


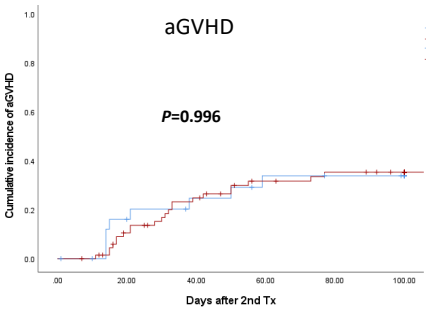


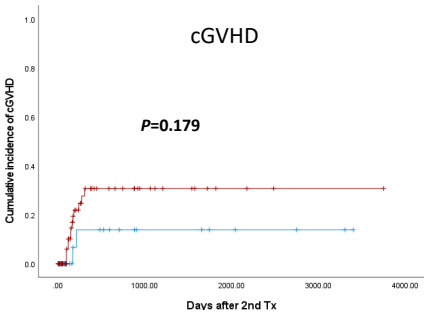


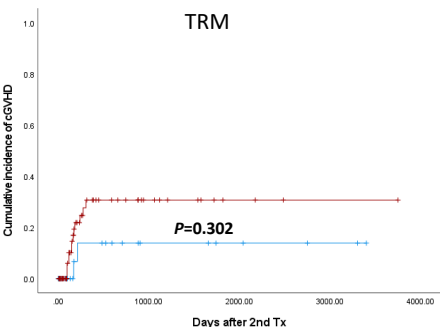
Supplementary Figure 14. Comparison of 2nd transplant outcomes in patients with full donor chimerism who used the different or the same donor.
Red line: using a different donor; blue line: using the same donor.

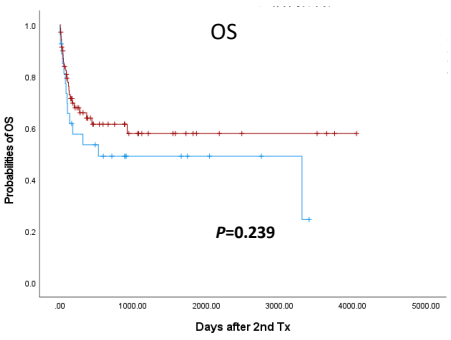




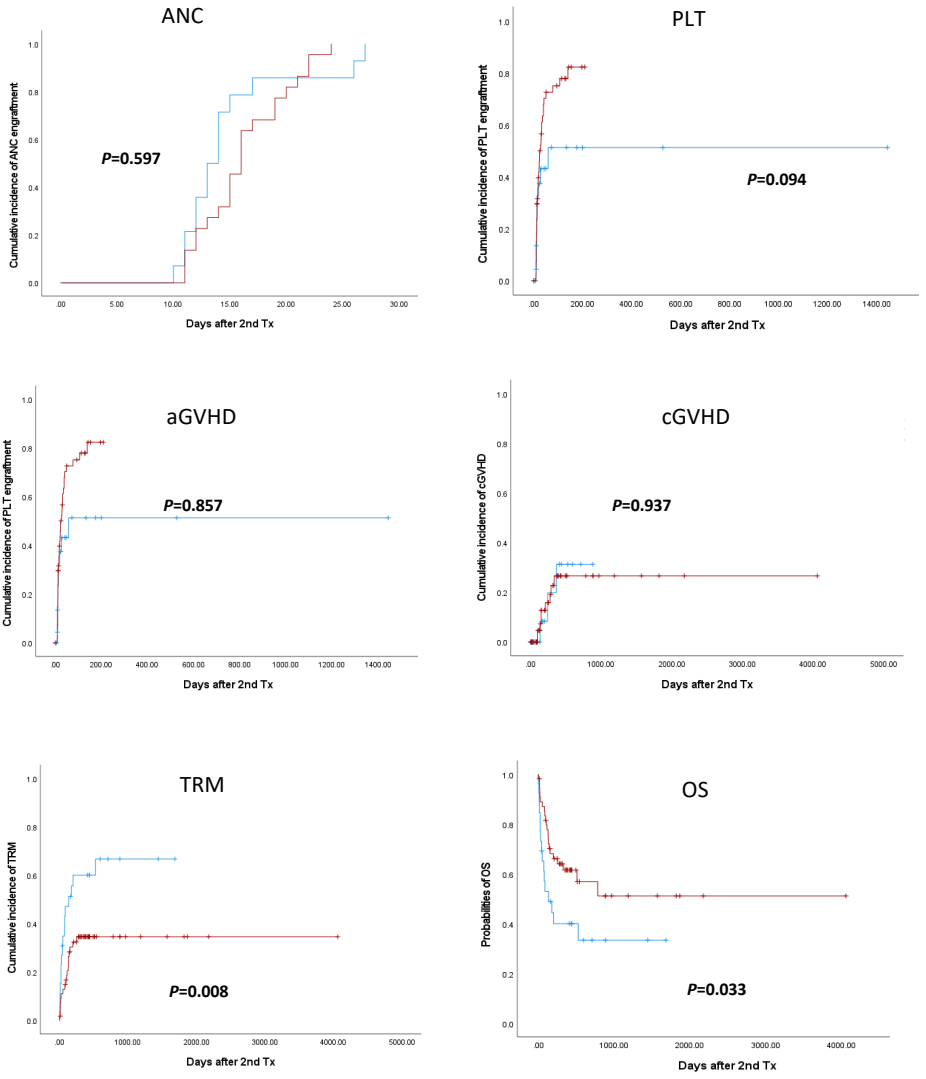




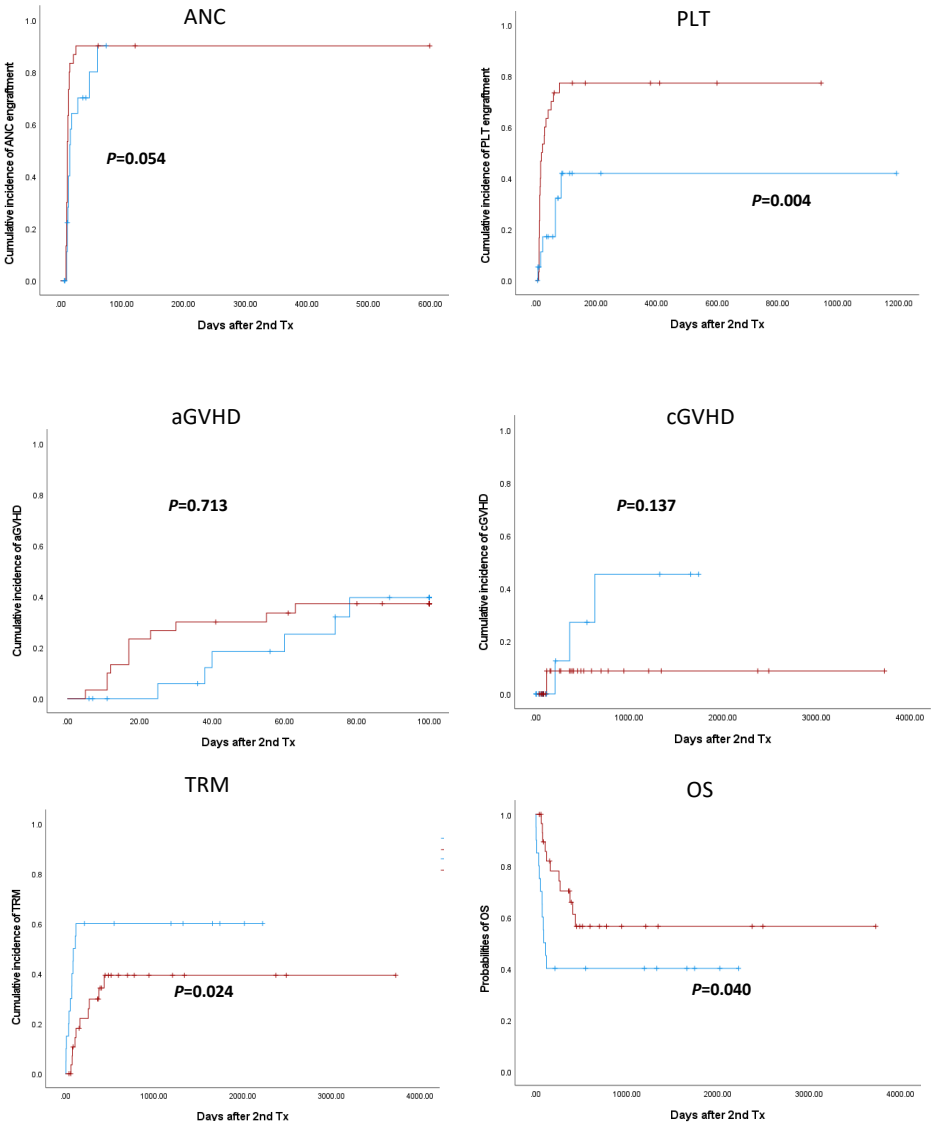




Supplementary Figure 15. Comparison of 2nd transplant outcomes in patients with mixed chimerism who used the different or the same donor.
Red line: using a different donor; blue line: using the same donor.

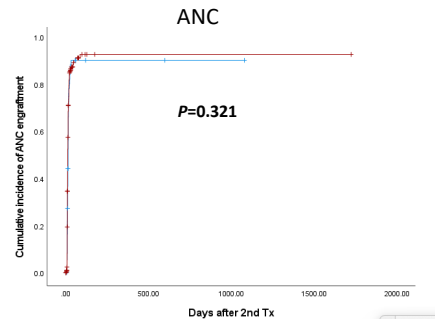


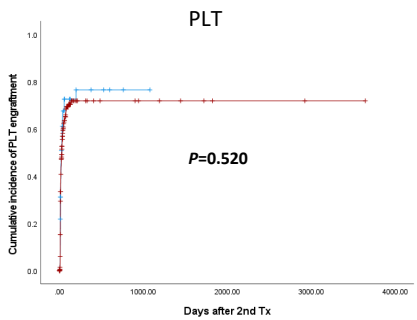
Supplementary Figure 16. Comparison of 2nd transplant outcomes in patients receiving FC as conditioning regimen who used the different or the same donor. Red line: using a different donor; blue line: using the same donor.

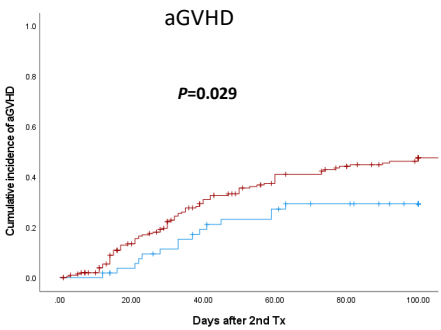


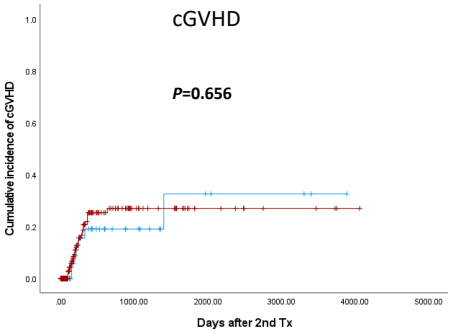
Supplementary Figure 17. Comparison of 2nd transplant outcomes in patients receiving TBI-based conditioning regimen who used the different or the same donor.

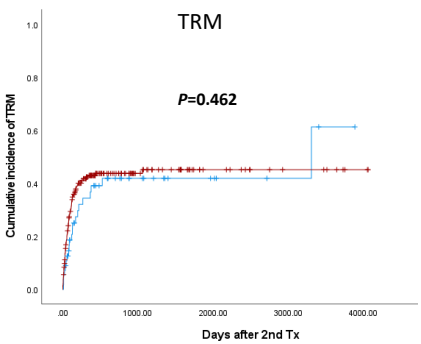
Red line: using a different donor; blue line: using the same donor.

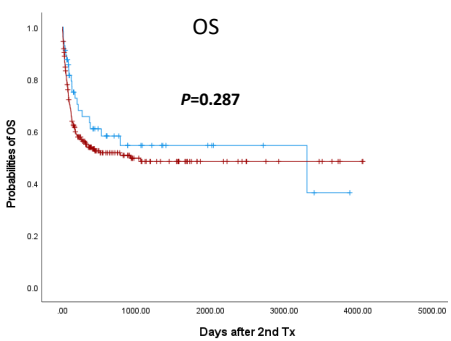












Supplementary Figure 18. Outcomes of 2nd transplantation in patients receiving grafts from haploidentical donors and other donors for the 2nd transplantation.

Red line: using haploidentical donors; blue line: using other donors.

Cause	All patients (n=272)
Death by Infection	**65**
Death by Multi-organ dysfunction	**14**
Death by GVHD	**11**
Death by Relapse	**11**
Death by Hemorrhage	**9**
Death by Graft failure	**7**
Death by TMA	**6**

Supplementary Table 1. Causes of Death.

GVHD, graft versus host disease; TMA, thrombotic microangiopathy.

Donor of Tx1 to Tx2	Number
Haplo-Haplo	66
CB-Haplo	59
URD-Haplo	17
CB-CB	14
Haplo-URD	10
MRD-Haplo	9
CB-MRD	4
CB-URD	4
Haplo-CB	4
Haplo-MRD	2
MRD-MRD	1
MRD-URD	1
URD-URD	1

Supplementary Table 2. Donors of the first and the second transplantations.

Variables \ Outcomes	ANC Engraftment				Platelet Engraftment				aGVHD				cGVHD				TRM				OS			
	Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate	
	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*
Recipient Gender (Male vs Female)	1.101	0.548			0.933	0.715			0.862	0.522			1.307	0.471			1.214	0.394			1.233	0.335		
Recipient Age (＜Median vs ≥Median)	1.038	0.817			0.766	0.156			0.956	0.843			1.771	0.128			0.662	0.069			0.636	0.037		
Disease (AA vs Other)	0.770	0.132			0.704	0.075			1.135	0.622			0.357	0.026			0.622	0.072			0.531	0.015		
1st Donor Type																								
MRD	1.000				1.000				1.000				1.000				1.000		1.000		1.000			
URD	1.058	0.865			1.577	0.213			3.171	0.039			0.573	0.495			2.077	0.147	3.841	0.018	2.072	0.125		
Haplo	1.675	0.025			2.096	0.003			2.923	0.021			1.015	0.975			2.071	0.068	1.787	0.177	2.047	0.056		
GF Type (Primary vs Secondary)	1.231	0.201			2.009	<0.001			0.644	0.069			1.153	0.701			1.908	0.009			1.859	0.008		
Chimerism																								
Full donor	1.000				1.000				1.000				1.000				1.000				1.000			
Mixed	1.091	0.639			0.911	0.674			0.769	0.334			0.482	0.101			0.629	0.075			0.615	0.054		
Full recipient	1.001	0.997			0.816	0.427			1.153	0.635			0.766	0.578			0.759	0.360			0.850	0.561		
Time from 1st Tx to 2nd Tx (＜Median vs ≥Median)	1.243	0.177			1.715	0.005			0.691	0.113			0.896	0.768			1.244	0.333			1.222	0.350		
DSA prior to 2nd Tx (Neg. vs Pos.)	0.501	0.016			0.497	0.042			0.698	0.415			0.640	0.552			0.815	0.633			0.825	0.630		
Disease Status prior to 2nd Tx (Relapse vs CR)	1.086	0.810			1.321	0.497			0.600	0.403			0.037	0.312			1.112	0.843			1.046	0.927		
Change donor (No vs Yes)	1.815	<0.001	1.583	0.034	2.183	<0.001	1.905	0.035	1.287	0.298			0.708	0.360			2.353	<0.001	2.336	0.008	2.088	<0.001		
2nd Donor Age (＜Median vs ⩾Median)	0.860	0.364			0.768	0.170			1.139	0.588			1.008	0.983			0.762	0.244			0.737	0.171		
2nd Donor Gender (Male vs Female)	1.097	0.568			0.985	0.936			0.920	0.719			0.795	0.540			0.919	0.796			0.925	0.717		
2nd Donor Type																								
MRD	1.000				1.000				1.000				1.000				1.000				1.000			
URD	0.897	0.785			0.982	0.966			9.347	0.041			0.565	0.622			0.717	0.630			0.636	0.505		
CB	0.475	0.152			4.831	0.038			20.06	0.007			0.100	0.978			1.535	0.535			1.392	0.626		
Haplo	0.674	0.151			1.852	0.039			10.23	0.021			1.213	0.752			1.218	0.621			1.195	0.632		
ABO of 2nd Tx (Matched/Minor mismatched vs Major/Bidirectional mismatched)	0.651	0.228			0.486	0.219			0.716	0.326			1.112	0.694			0.441	0.278			0.658	0.439		
Conditioning Regimen of 2nd Tx (FC vs Other)	0.800	0.183			1.193	0.374			1.107	0.944			0.812	0.593			1.037	0.676			1.125	0.598		
Graft Source of 2nd Tx																								
PB+BM	1.000		1.000		1.000				1.000				1.000				1.000				1.000			
PB	1.855	<0.001	1.538	0.031	1.531	0.025			0.648	0.069			1.176	0.664			1.567	0.057			1.440	0.101		
CB	2.257	0.057	2.410	0.055	4.219	0.046			2.071	0.127			0.100	0.978			2.113	0.161			1.867	0.238		
Infused MNCs (＜Median vs ≥Median)	1.414	0.032			1.677	0.007			0.983	0.940			1.434	0.353			1.656	0.027			1.517	0.053		
Infused CD34 cells (＜Median vs ≥Median)	1.361	0.074			1.879	0.002			0.712	0.175			1.546	0.286			1.462	0.138			1.634	0.046		
GVHD Prophylaxis for 2nd Tx (Other vs Intensified)	1.732	0.004			2.265	0.001			1.108	0.659			0.597	0.178			2.203	<0.001			2.110	<0.001		

Supplementary Table 3. Univariate and multivariate analysis for 2nd transplant outcomes in patients grafted with MRDs, URDs, and HIDs in the 1st transplantation.

Abbreviations: AA, aplastic anemia; GF, graft failure; MRD, matched related donor; URD, unrelated donor; CB, cord blood; Haplo, haploidentical transplantation; Tx, transplantation; DSA, Donor specific antibody; CR, complete remission; FC, fludarabine/cyclophosphamide; BM, bone marrow; PB, peripheral blood; MNCs, mononucleated cells; GVHD, graft versus host disease.

Outcomes / Variables	ANC Engraftment				Platelet Engraftment				aGVHD				cGVHD				TRM				OS			
	Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate	
	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*
Recipient Gender (Male vs Female)	1.199	0.321			1.032	0.887			0.913	0.721			1.606	0.292			1.231	0.406			1.218	0.409		
Recipient Age (＜Median vs ≥Median)	1.009	0.963			0.698	0.105			1.249	0.386			1.756	0.200			0.554	0.023	0.508	0.034	0.566	0.021		
Disease (AA vs Other)	0.828	0.377			0.866	0.570			1.000	1.000			3.300	0.057			0.585	0.106			0.506	0.039		
GF Type (Primary vs Secondary)	1.236	0.270			1.665	0.025	3.445	0.010	0.731	0.262			0.811	0.650			1.919	0.027			1.859	0.030		
Chimerism																								
Full donor	1.000				1.000				1.000				1.000				1.000				1.000			
Mixed	0.861	0.482			1.075	0.782			0.742	0.332			0.599	0.332			0.700	0.231			0.723	0.259		
Full recipient	0.801	0.376			1.224	0.488			1.168	0.650			0.869	0.801			0.924	0.807			1.032	0.918		
Time from 1st Tx to 2nd Tx (＜Median vs ≥Median)	1.252	0.221			1.256	0.307			0.621	0.067			0.847	0.704			1.164	0.544			0.882	0.602		
DSA prior to 2nd Tx (Neg. vs Pos.)	0.547	0.039			0.569	0.109			0.662	0.361			0.559	0.446			0.893	0.798			0.909	0.817		
Disease Status prior to 2nd Tx (Relapse vs CR)	1.074	0.854			2.580	0.046			0.391	0.205			0.035	0.378			1.845	0.411			1.399	0.588		
Change donor (No vs Yes)	2.053	<0.001	1.703	0.025	2.743	<0.001	4.751	0.013	1.092	0.736			0.631	0.298			2.801	<0.001	2.075	0.047	2.387	<0.001		
2nd Donor Age (＜Median vs ≥Median)	0.952	0.799			1.045	0.849			1.194	0.512			0.650	0.328			0.945	0.830			0.901	0.677		
2nd Donor Gender (Male vs Female)	1.252	0.227			1.296	0.248			0.852	0.535			0.654	0.322			1.092	0.729			1.101	0.689		
2nd Donor Type																								
MRD	1.000				1.000				1.000				1.000				1.000				1.000			
URD	1.919	0.396			1.477	0.622			5.665	0.914			0.517	0.520			0.164	0.202			0.155	0.188		
CB	3.497	0.138			9.009	0.029			1.573	0.904			3.862	0.985			0.839	0.890			0.804	0.851		
Haplo	2.695	0.169			3.676	0.072			8.562	0.910			2.465	0.813			0.742	0.768			0.793	0.767		
ABO of 2nd Tx (Matched/Minor mismatched vs Major/Bidirectional mismatched)	0.802	0.413			0.644	0.123			0.903	0.697			1.125	0.881			0.471	0.237			0.548	0.336		
Conditioning Regimen of 2nd Tx (FC vs Other)	0.769	0.165			0.993	0.976			0.939	0.813			0.509	0.136			0.945	0.826			0.996	0.986		
Graft Source of 2nd Tx																								
PB+BM	1.000				1.000				1.000				1.000				1.000				1.000			
PB	2.198	<0.001			1.730	0.015			0.691	0.164			0.990	0.982			1.786	0.033			1.604	0.064		
CB	2.299	0.055	1.653	0.062	1.724	0.242			1.844	0.208			3.862	0.985			2.090	0.177			1.816	0.269		
Infused MNCs (＜Median vs ≥Median)	1.681	0.005	3.597	0.018	2.154	<0.001			1.004	0.987			1.642	0.292			1.821	0.019			1.555	0.068		
Infused CD34 cells (＜Median vs ≥Median)	1.319	0.158			2.204	0.001			0.886	0.664			2.111	0.131			2.208	0.008			2.415	0.002	2.208	0.017
GVHD Prophylaxis for 2nd Tx (Other vs Intensified)	1.230	0.270			1.885	0.004			1.059	0.827			2.724	0.178			2.469	<0.001			2.262	<0.001		

Supplementary Table 4. Univariate and multivariate analysis for 2nd transplant outcomes in patients grafted from HIDs in the 1st transplantation.

Abbreviations: AA, aplastic anemia; GF, graft failure; MRD, matched related donor; URD, unrelated donor; CB, cord blood; Haplo, haploidentical transplantation; Tx, transplantation; DSA, Donor specific antibody; CR, complete remission; FC, fludarabine/cyclophosphamide; BM, bone marrow; PB, peripheral blood; MNCs, mononucleated cells; GVHD, graft versus host disease.

Outcomes / Variables	ANC Engraftment				Platelet Engraftment				aGVHD				cGVHD				OS			
	Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate	
	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*
Recipient Gender (Male vs Female)	1.230	0.394			0.929	0.783			1.258	0.548			0.023	0.185			1.008	0.984		
Recipient Age (＜Median vs ≥Median)	0.883	0.590			0.860	0.554			0.567	0.134			1.398	0.618			0.539	0.114		
1st Donor Type																				
MRD	1.000				1.000				1.000				1.000				1.000			
URD	1.302	0.565			1.517	0.394			0.503	0.368			0.959	0.973			1.578	0.519		
CB	1.414	0.324			1.786	0.117			0.876	0.844			0.812	0.820			1.184	0.776		
Haplo	7.518	0.591			2.421	0.020			0.437	0.193			0.716	0.716			1.217	0.737		
GF Type (Primary vs Secondary)	0.985	0.949			1.179	0.535			0.560	0.182			1.472	0.567			1.131	0.759		
Chimerism																				
Full donor	1.000				1.000				1.000				1.000				1.000		1.000	
Mixed	0.960	0.896			0.624	0.187			1.845	0.183			1.210	0.827			0.946	0.899	0.951	0.922
Full recipient	0.664	0.204			0.408	0.015			1.721	0.253			0.476	0.462			0.266	0.028	0.185	0.042
Time from 1st Tx to 2nd Tx (＜Median vs ≥Median)	0.717	0.149			0.856	0.541			0.614	0.192			1.768	0.421			1.104	0.793		
DSA prior to 2nd Tx (Neg. vs Pos.)	0.556	0.227			0.377	0.182			0.643	0.667			0.045	0.688			0.368	0.199		
Change donor (No vs Yes)	1.171	0.571			2.091	0.034			1.183	0.714			0.475	0.283			2.273	0.032	2.500	0.047
2nd Donor Age (＜Median vs ⩾Median)	0.552	0.020	0.418	0.006	0.850	0.563			1.963	0.106			1.074	0.919			0.499	0.109		
2nd Donor Gender (Male vs Female)	1.140	0.584			1.124	0.652			0.666	0.315			1.085	0.904			1.447	0.362		
2nd Donor Type																				
MRD	1.000				1.000		1.000		1.000				1.000				1.000			
URD	1.493	0.374			0.855	0.744	1.672	0.528	0.635	0.921			2.800	0.405			1.123	0.887		
CB	4.630	0.006			5.435	0.011	9.709	0.028	1.127	0.925			0.200	0.989			1.838	0.459		
Haplo	3.636	0.693			1.572	0.203	4.016	0.055	1.282	0.926			1.433	0.741			1.374	0.609		
ABO of 2nd Tx (Matched/Minor mismatched vs Major/Bidirectional mismatched)	0.772	0.359			0.407	0.218			0.924	0.876			1.034	0.519			0.312	0.227		
Conditioning Regimen of 2nd Tx (FC vs Other)	0.978	0.939			1.443	0.290			2.082	0.229			2.666	0.405			1.316	0.549		
Graft Source of 2nd Tx																				
PB+BM	1.000				1.000				1.000				1.000				1.000			
PB	1.235	0.385			1.385	0.230			1.429	0.387			2.292	0.217			1.175	0.685		
CB	3.663	0.007			4.505	0.013			0.933	0.912			0.200	0.989			1.523	0.507		
Infused MNCs (＜Median vs ≥Median)	1.528	0.077			1.554	0.107			0.878	0.732			0.456	0.268			1.786	0.130		
Infused CD34 cells (＜Median vs ≥Median)	1.777	0.026			1.785	0.039			1.423	0.374			5.567	0.112			2.110	0.085		
GVHD Prophylaxis for 2nd Tx (Other vs Intensified)	1.556	0.140			2.723	0.010			1.686	0.332			1.226	0.848			2.070	0.083		

Supplementary Table 5. Univariate and multivariate analysis for 2nd transplant outcomes in AA patients.

Abbreviations: AA, aplastic anemia; GF, graft failure; MRD, matched related donor; URD, unrelated donor; CB, cord blood; Haplo, haploidentical transplantation; Tx, transplantation; DSA, Donor specific antibody; CR, complete remission; FC, fludarabine/cyclophosphamide; BM, bone marrow; PB, peripheral blood; MNCs, mononucleated cells; GVHD, graft versus host disease.

Variables \ Outcomes	ANC Engraftment				Platelet Engraftment				aGVHD				cGVHD				TRM				Relapse				OS				DFS			
	Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate	
	1.429	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*
Recipient Gender (Male vs Female)	1.067	0.696			0.869	0.480			0.736	0.200			1.754	0.159			1.332	0.211			1.429	0.502			1.284	0.238			1.326	0.179		
Recipient Age (＜Median vs ≥Median)	0.997	0.987			0.776	0.202			0.859	0.519			2.109	0.062			0.735	0.175			0.815	0.693			0.746	0.165			0.779	0.234		
1st Donor Type																																
MRD	1.000				1.000				1.000				1.000				1.000				1.000				1.000				1.000			
URD	1.212	0.710			1.538	0.451			4.967	0.056			0.451	0.476			2.157	0.314			1.504	0.774			2.036	0.290			1.591	0.512		
CB	1.045	0.901			1.502	0.311			2.903	0.154			0.368	0.158			1.907	0.299			1.819	0.585			1.791	0.282			1.932	0.223		
Haplo	0.736	0.359			1.724	0.149			3.421	0.089			0.818	0.716			2.426	0.136			1.442	0.731			2.217	0.145			2.220	0.123		
GF Type (Primary vs Secondary)	1.149	0.446			2.131	<0.001			0.812	0.437			1.443	0.349			1.832	0.035	2.028	0.038	0.935	0.902			1.770	0.030	1.727	0.045	1.580	0.070	1.818	0.050
Chimerism																																
Full donor	1.000				1.000				1.000				1.000				1.000				1.000				1.000				1.000			
Mixed	0.857	0.452			0.992	0.976			0.794	0.451			0.881	0.772			0.602	0.073			0.519	0.391			0.590	0.053			0.588	0.046		
Full recipient	0.869	0.529			0.870	0.592			1.319	0.348			0.651	0.407			0.826	0.500			1.958	0.286			1.007	0.979			0.958	0.867		
Time from 1st Tx to 2nd Tx (＜Median vs ≥Median)	1.102	0.559			1.602	0.019			0.870	0.557			1.599	0.240			0.881	0.574			1.142	0.799			1.163	0.476			1.117	0.595		
DSA prior to 2nd Tx (Neg. vs Pos.)	0.667	0.166			0.632	0.200			0.630	0.334			0.680	0.610			1.031	0.946			0.752	0.723			0.903	0.796			0.941	0.877		
Disease Status prior to 2nd Tx (Relapse vs CR)	0.968	0.924			1.409	0.399			0.545	0.315			0.037	0.272			1.208	0.721			1.269	0.822			1.212	0.685			1.183	0.722		
Change donor (No vs Yes)	1.993	<0.001			1.988	0.004	1.793	0.043	1.116	0.677			0.687	0.358			2.119	<0.001			0.919	0.886			1.808	0.006	1.684	0.030	1.808	0.003	1.709	0.040
2nd Donor Age (＜Median vs ≥Median)	0.923	0.650			0.994	0.976			1.107	0.686			0.708	0.400			1.045	0.854			1.397	0.548			1.042	0.854			1.120	0.611		
2nd Donor Gender (Male vs Female)	0.787	0.158			0.831	0.361			0.981	0.937			1.110	0.787			0.601	0.024	0.575	0.047	1.828	0.301			0.666	0.053			0.699	0.085		
2nd Donor Type																																
MRD	1.000				1.000				1.000				1.000				1.000				1.000				1.000				1.000			
URD	1.009	0.987			0.906	0.982			1.340	0.836			1.001	0.979			0.884	0.887			1.001	0.991			0.784	0.772			0.776	0.762		
CB	1.992	0.185			2.545	0.123			3.675	0.245			1.287	0.801			1.363	0.632			1.003	0.986			1.181	0.784			1.154	0.814		
Haplo	1.133	0.749			1.543	0.305			4.934	0.113			0.812	0.778			1.085	0.874			1.116	0.916			1.046	0.923			1.097	0.842		
ABO of 2nd Tx (Matched/Minor mismatched vs Major/Bidirectional mismatched)	0.687	0.263			0.322	0.174			0.952	0.913			1.012	0.974			0.539	0.342			0.883	0.824			0.613	0.481			0.922	0.498		
Conditioning Regimen of 2nd Tx (FC vs Other)	0.802	0.210			0.918	0.679			0.850	0.515			0.723	0.410			0.922	0.731			0.923	0.885			0.554	0.711			0.885	0.578		
Graft Source of 2nd Tx																																
PB+BM	1.000		1.000		1.000				1.000				1.000				1.000				1.000				1.000				1.000			
PB	2.198	<0.001	1.661	0.019	1.381	0.123			0.754	0.259			1.502	0.314			1.651	0.034			1.052	0.924			1.428	0.103			1.540	0.046		
CB	2.695	0.005	2.387	0.030	2.174	0.096			0.885	0.796			1.889	0.402			1.816	0.151			1.112	0.986			1.518	0.307			1.478	0.340		
Infused MNCs (＜Median vs ≥Median)	1.687	0.002			2.204	<0.001			1.048	0.847			1.480	0.343			1.908	0.006			1.845	0.752			1.767	0.009			1.724	0.012		
Infused CD34 cells (＜Median vs ≥Median)	1.426	0.047			1.738	0.009			0.715	0.198			1.671	0.210			1.522	0.099			2.358	0.156			1.603	0.048			1.637	0.036		
GVHD Prophylaxis for 2nd Tx (Other vs Intensified)	1.829	0.002			2.045	0.004			1.202	0.489			1.788	0.284			2.020	0.002			1.119	0.848			1.845	0.005			1.908	0.003		

Supplementary Table 6. Univariate and multivariate analysis for 2nd transplant outcomes in patients with hematological malignancies.

Abbreviations: GF, graft failure; MRD, matched related donor; URD, unrelated donor; CB, cord blood; Haplo, haploidentical transplantation; Tx, transplantation; DSA, Donor specific antibody; CR, complete remission; FC, fludarabine/cyclophosphamide; BM, bone marrow; PB, peripheral blood; MNCs, mononucleated cells; GVHD, graft versus host disease.

Variables \ Outcomes	ANC Engraftment				Platelet Engraftment				aGVHD				cGVHD				TRM				OS			
	Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate	
	HR	*P*	HR	*P*	HR	*P*	HR	*P*	1.468	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*
Recipient Gender (Male vs Female)	1.169	0.330			0.921	0.667			1.113	0.685			2.023	0.129			1.468	0.079			1.332	0.165		
Recipient Age (＜Median vs ≥Median)	0.764	0.096			0.669	0.037			0.882	0.634			1.903	0.146			0.636	0.038			0.634	0.028		
Disease (AA vs Other)	0.827	0.273			0.613	0.014			1.043	0.882			2.240	0.117			0.584	0.035			0.504	0.007	0.390	0.035
1st Donor Type																								
MRD	1.000				1.000				1.000				1.000				1.000				1.000			
URD	0.705	0.563			0.123	0.051			2.487	0.415			5.228	0.935			0.699	0.639			0.873	0.852		
CB	1.186	0.828			0.175	0.085			1.502	0.692			5.949	0.934			0.750	0.634			0.862	0.805		
Haplo	1.592	0.366			0.255	0.177			2.416	0.385			1.382	0.928			1.097	0.876			1.210	0.748		
Chimerism																								
Full donor	1.000				1.000				1.000				1.000				1.000				1.000			
Mixed	0.786	0.286			0.729	0.268			0.826	0.598			1.109	0.972			0.595	0.055			0.585	0.043		
Full recipient	0.759	0.216			0.510	0.014			1.062	0.859			0.411	0.160			0.472	0.007			0.559	0.026		
Time from 1st Tx to 2nd Tx (＜Median vs ≥Median)	0.822	0.222			1.161	0.435			1.306	0.314			2.116	0.106			0.834	0.399			0.827	0.354		
DSA prior to 2nd Tx (Neg. vs Pos.)	0.590	0.101			0.466	0.055			0.614	0.700			1.524	0.581			0.605	0.232			0.527	0.088		
Disease Status prior to 2nd Tx (Relapse vs CR)	0.857	0.830			0.459	0.440			0.047	0.502			0.049	0.808			0.357	0.084			0.392	0.115		
Change donor (No vs Yes)	2.050	<0.001			3.100	<0.001	2.216	0.026	0.860	0.616			0.629	0.366			2.494	<0.001			2.309	＜0.001	1.745	0.025
2nd Donor Age (＜Median vs ⩾Median)	0.813	0.236			0.804	0.303			1.095	0.745			1.354	0.533			0.722	0.166			0.737	0.173		
2nd Donor Gender (Male vs Female)	0.733	0.063			0.936	0.735			0.803	0.428			0.777	0.586			0.741	0.166			0.840	0.401		
2nd Donor Type																								
MRD	1.000		1.000		1.000				1.000				1.000				1.000				1.000			
URD	1.637	0.379	2.660	0.133	0.792	0.711			6.791	0.098			2.273	0.940			1.093	0.907			1.089	0.910		
CB	3.257	0.008	3.367	0.024	2.145	0.153			3.693	0.233			2.652	0.939			1.296	0.672			1.313	0.657		
Haplo	1.524	0.223	2.062	0.098	1.076	0.851			4.322	0.147			2.435	0.939			1.259	0.654			1.425	0.489		
ABO of 2nd Tx (Matched/Minor mismatched vs Major/Bidirectional mismatched)	0.713	0.220			0.412	0.273			0.545	0.614			0.926	0.618			0.417	0.321			0.564	0.419		
Conditioning Regimen of 2nd Tx (FC vs Other)	0.878	0.448			0.879	0.523			1.139	0.650			0.521	0.145			0.924	0.732			0.929	0.734		
Graft Source of 2nd Tx																								
PB+BM	1.000				1.000				1.000				1.000				1.000				1.000			
PB	2.320	<0.001			2.119	<0.001			1.255	0.450			1.336	0.558			2.067	0.001			1.801	0.007		
CB	3.155	<0.001			2.793	0.010			1.242	0.649			1.274	0.751			1.554	0.233			1.315	0.452		
Infused MNCs (＜Median vs ≥Median)	2.194	<0.001			0.380	<0.001	1.740	0.033	0.992	0.977			1.305	0.554			2.028	0.002			1.866	0.004		
Infused CD34 cells (＜Median vs ≥Median)	1.564	0.010			1.794	0.004			1.188	0.528			1.782	0.212			1.783	0.018			2.016	0.003		
GVHD Prophylaxis for 2nd Tx (Other vs Intensified)	2.249	<0.001			3.211	<0.001			1.007	0.979			2.304	0.262			2.160	<0.001			1.696	0.002		

Supplementary Table 7. Univariate and multivariate analysis for 2nd transplant outcomes in patients with primary GF.

Abbreviations: AA, aplastic anemia; GF, graft failure; MRD, matched related donor; URD, unrelated donor; CB, cord blood; Haplo, haploidentical transplantation; Tx, transplantation; DSA, Donor specific antibody; CR, complete remission; FC, fludarabine/cyclophosphamide; BM, bone marrow; PB, peripheral blood; MNCs, mononucleated cells; GVHD, graft versus host disease.

Variables \ Outcomes	ANC Engraftment		Platelet		aGVHD		cGVHD		TRM		OS	
	Univariate		Univariate		Univariate		Univariate		Univariate		Univariate	
	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*
Recipient Gender (Male vs Female)	3.208	0.260	1.639	0.629	0.937	0.951	2.400	0.627	3.788	0.098	3.401	0.123
Recipient Age (＜Median vs ≥Median)	0.702	0.425	0.770	0.630	0.564	0.377	1.699	0.572	0.352	0.145	0.308	0.092
Time from 1st Tx to 2nd Tx (＜Median vs ≥Median)	1.201	0.677	1.157	0.785	1.118	0.861	2.114	0.414	0.620	0.477	0.524	0.318
DSA prior to 2nd Tx (Neg. vs Pos.)	0.811	0.644	0.629	0.393	0.585	0.407	0.622	0.604	0.817	0.764	0.694	0.572
Change donor (No vs Yes)	1.028	1.961	1.790	0.446	2.810	0.329	0.142	0.053	1.408	0.671	1.241	0.786
2nd Donor Age (＜Median vs ⩾Median)	0.634	0.346	0.673	0.466	0.655	0.555	0.363	0.270	1.124	0.880	1.513	0.561
2nd Donor Gender (Male vs Female)	1.901	0.182	2.743	0.062	1.366	0.629	0.220	0.179	1.241	0.761	1.441	0.598
Conditioning Regimen of 2nd Tx (FC vs Other)	0.687	0.425	0.631	0.438	0.835	0.794	0.536	0.580	0.354	0.125	0.446	0.205
Graft Source of 2nd Tx (BM+PB vs Other)	0.467	0.063	0.244	0.031	0.764	0.678	9.610	0.079	0.157	0.024	0.247	0.048
Infused MNCs (＜Median vs ≥Median)	1.180	0.720	3.115	0.044	0.762	0.674	1.433	0.697	1.880	0.373	2.183	0.258
Infused CD34 cells (＜Median vs ≥Median)	1.070	0.877	0.686	0.802	0.611	0.446	2.308	0.367	1.916	0.359	2.222	0.248
GVHD Prophylaxis for 2nd Tx (Non-intensified vs Intensified)	3.667	0.043	0.148	3.627	2.778	0.333	2.371	0.709	5.848	0.015	4.566	0.027

Supplementary Table 8. Univariate analysis for 2nd transplant outcomes in primary GF patients with positive DSA (group A).

Abbreviations: Tx, transplantation; DSA, Donor specific antibody; FC, fludarabine/cyclophosphamide; BM, bone marrow; PB, peripheral blood; MNCs, mononucleated cells; GVHD, graft versus host disease.

Outcomes / Variables	ANC Engraftment				Platelet Engraftment				aGVHD				cGVHD				TRM				OS			
	Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate	
	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*
Recipient Gender (Male vs Female)	0.913	0.669			0.769	0.284			0.905	0.755			1.004	0.994			1.175	0.599			0.954	0.868		
Recipient Age (＜Median vs ≥Median)	0.773	0.228			0.581	0.026			0.630	0.152			0.837	0.776			0.470	0.016			0.452	0.007		
Disease (AA vs Other)	0.761	0.215			0.526	0.009			1.073	0.831			1.399	0.594			0.522	0.062			0.430	0.014	0.179	0.007
1st Donor Type (CB vs Other)	0.718	0.119			0.687	0.121			1.368	0.327			0.734	0.625			0.801	0.465			0.831	0.515		
Chimerism (Mixed vs Full recipient)	1.188	0.414			1.602	0.055			1.554	0.178			0.278	0.058			1.439	0.230			1.200	0.517		
Time from 1st Tx to 2nd Tx (＜Median vs ≥Median)	0.794	0.277			0.746	0.225			0.789	0.454			2.431	0.190			0.917	0.773			0.792	0.418		
DSA prior to 2nd Tx (Neg. vs Pos.)	0.707	0.633			0.289	0.220			0.045	0.437			0.047	0.809			0.366	0.180			0.260	0.032		
Change donor (No vs Yes)	2.211	0.003	2.683	0.002	2.662	0.004	2.387	0.033	0.849	0.653			0.709	0.611			1.953	0.033			1.767	0.047		
2nd Donor Age (＜Median vs ⩾Median)	0.730	0.180			0.928	0.782			1.602	0.164			1.587	0.546			0.538	0.065			0.631	0.133		
2nd Donor Gender (Male vs Female)	0.746	0.181			0.800	0.371			0.968	0.920			0.879	0.838			0.670	0.185			0.841	0.545		
2nd Donor Type																								
MRD	1.000				1.000				1.000				1.000				1.000				1.000			
URD	3.623	0.044	4.065	0.006	0.665	0.58			6.594	0.934							1.484	0.693			1.466	0.702		
CB	6.289	0.001	8.696	0.001	1.543	0.493			5.428	0.935			8.970	0.952			1.763	0.513			1.811	0.493		
Haplo	2.849	0.011	3.663	0.008	0.833	0.695			7.192	0.934			3.070	0.956			1.614	0.510			1.888	0.380		
ABO of 2nd Tx (Matched/Minor mismatched vs Major/Bidirectional mismatched)	0.898	0.557			0.516	0.287			0.887	0.223			1.245	0.625			1.342	0.692			1.297	0.521		
Conditioning Regimen of 2nd Tx (FC vs Other)	1.231	0.368			1.240	0.419			2.070	0.069			1.836	0.442			1.739	0.072			1.534	0.141		
Graft Source of 2nd Tx																								
PB+BM	1.000				1.000				1.000				1.000				1.000				1.000			
PB	2.165	0.002			1.595	0.089			0.685	0.308			1.169	0.825			1.278	0.453			1.147	0.658		
CB	3.165	0.008			2.169	0.102			0.747	0.631			3.577	0.124			1.231	0.700			1.055	0.920		
Infused MNCs (＜Median vs ≥Median)	2.327	<0.001	1.998	0.011	2.419	<0.001	1.817	0.048	0.818	0.538			0.966	0.954			2.392	0.006			1.862	0.032		
Infused CD34 cells (＜Median vs ≥Median)	1.528	0.057			1.720	0.034			0.969	0.923			1.657	0.421			1.572	0.153			1.815	0.047		
GVHD Prophylaxis for 2nd Tx (Non-intensified vs Intensified)	1.524	0.166			1.384	0.327			1.133	0.778			0.939	0.936			0.943	0.889			0.803	0.591		

Supplementary Table 9. Univariate and multivariate analysis for 2nd transplant outcomes in primary GF patients with negative DSA and full recipient or mixed chimerism (group B).

Abbreviations: AA, aplastic anemia; GF, graft failure; MRD, matched related donor; URD, unrelated donor; CB, cord blood; Haplo, haploidentical transplantation; Tx, transplantation; DSA, Donor specific antibody; CR, complete remission; FC, fludarabine/cyclophosphamide; BM, bone marrow; PB, peripheral blood; MNCs, mononucleated cells; GVHD, graft versus host disease.

Outcomes / Variables	ANC Engraftment				Platelet Engraftment				aGVHD				cGVHD				TRM				OS			
	Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate	
	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*
Recipient Gender (Male vs Female)	2.151	0.048			1.948	0.187			0.812	0.648			5.747	0.325			2.208	0.073			2.299	0.058		
Recipient Age (＜Median vs ≥Median)	1.190	0.650			0.780	0.621			1.761	0.210			6.449	0.112			0.637	0.246			0.670	0.293		
Disease (AA vs Other)	1.064	0.893			0.613	0.365			0.753	0.562			3.495	0.447			0.795	0.622			0.761	0.554		
1st Donor Type (CB vs Other)	1.305	0.349			0.961	0.906			0.875	0.710			5.826	0.300			1.014	0.962			0.957	0.887		
Time from 1st Tx to 2nd Tx (＜Median vs ≥Median)	0.855	0.680			0.646	0.408			0.809	0.639			4.847	0.173			0.510	0.088			0.469	0.052		
Change donor (No vs Yes)	2.125	0.067			5.970	0.019			0.558	0.207			2.611	0.623			3.745	0.001			3.534	0.002		
2nd Donor Age (＜Median vs ≥Median)	0.632	0.246			0.582	0.308			0.838	0.709			1.545	0.665			0.846	0.677			0.788	0.546		
2nd Donor Gender (Male vs Female)	0.502	0.101			0.650	0.426			0.589	0.280			1.714	0.592			0.792	0.553			0.728	0.408		
ABO of 2nd Tx (Matched/Minor mismatched vs Major/Bidirectional mismatched)	0.614	0.321			0.524	0.723			0.504	0.741			0.837	0.729			1.704	0.456			1.433	0.579		
Conditioning Regimen of 2nd Tx (FC vs Other)	0.356	0.014			0.337	0.031			0.817	0.666			0.013	0.291			0.407	0.071			0.489	0.122		
Graft Source of 2nd Tx																								
PB+BM	1.000				1.000				1.000				1.000				1.000				1.000			
PB	2.358	0.037			4.444	0.022			2.035	0.135			0.026	0.571			3.411	0.004			3.166	0.005		
CB	2.342	0.260			2.899	0.307			0.786	0.819			0.027	0.566			0.723	0.758			0.599	0.626		
Infused MNCs (＜Median vs ≥Median)	2.047	0.077			4.474	0.007			1.344	0.513			2.748	0.383			1.859	0.143			1.953	0.111		
Infused CD34 cells (＜Median vs ≥Median)	2.395	0.048			3.775	0.017			1.126	0.820			2.067	0.532			1.626	0.330			1.718	0.269		
GVHD Prophylaxis for 2nd Tx (Non-intensified vs Intensified)	3.428	0.003			9.100	0.004			1.185	0.712			3.831	0.413			3.413	0.003			3.058	0.005		

Supplementary Table 10. Univariate and multivariate analysis for 2nd transplant outcomes in primary GF patients with negative DSA and full donor chimerism (group C).

Abbreviations: AA, aplastic anemia; GF, graft failure; MRD, matched related donor; URD, unrelated donor; CB, cord blood; Haplo, haploidentical transplantation; Tx, transplantation; DSA, Donor specific antibody; CR, complete remission; FC, fludarabine/cyclophosphamide; BM, bone marrow; PB, peripheral blood; MNCs, mononucleated cells; GVHD, graft versus host disease.

Variables \ Outcomes	ANC Engraftment				Platelet Engraftment				aGVHD				cGVHD				TRM				OS			
	Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate	
	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*
Recipient Gender (Male vs Female)	0.831	0.482			0.976	0.934			0.624	0.311			0.497	0.279			0.761	0.519			0.923	0.843		
Recipient Age (＜Median vs ≥Median)	0.691	0.129			0.599	0.058	0.388	0.007	0.794	0.557			3.994	0.018	3.470	0.037	0.614	0.242			0.685	0.332		
Disease (AA vs Other)	0.900	0.674			1.706	0.786			1.689	0.236			3.118	0.084			0.901	0.805			0.716	0.416		
1st Donor Type																								
MRD	1.000				1.000		1.000		1.000				1.000				1.000				1.000			
URD	1.684	0.278			4.167	0.006	6.289	0.007	2.954	0.126			1.020	0.995			4.125	0.036			3.676	0.042		
CB	0.999	0.999			0.866	0.847	1.580	0.569	1.020	0.980			1.558	0.683			2.397	0.435			1.930	0.549		
Haplo	1.642	0.085			3.003	<0.001	2.623	0.023	2.312	0.130			0.765	0.635			1.964	0.237			1.886	0.219		
Chimerism																								
Full donor	1.000				1.000				1.000				1.000				1.000				1.000			
Mixed	1.060	0.824			1.004	0.989			0.811	0.624			0.727	0.591			0.835	0.695			0.819	0.649		
Full recipient	0.664	0.256			0.695	0.342			1.029	0.960			1.205	0.789			1.143	0.821			1.243	0.687		
Time from 1st Tx to 2nd Tx (＜Median vs ≥Median)	0.909	0.693			1.265	0.379			0.674	0.329			0.581	0.309			0.840	0.670			0.959	0.914		
DSA prior to 2nd Tx (Neg. vs Pos.)	0.642	0.320			0.775	0.633			0.749	0.701			0.038	0.433			2.058	0.490			2.058	0.490		
Disease Status prior to 2nd Tx (Relapse vs CR)	0.918	0.832			1.245	0.635			1.791	0.410			0.031	0.275			1.996	0.519			1.122	0.884		
Change donor (No vs Yes)	1.246	0.385			1.361	0.274			2.038	0.126			0.718	0.525			1.527	0.303			1.364	0. 426		
2nd Donor Age (＜Median vs ≥Median)	0.756	0.263			0.631	0.495			1.937	0.117			1.213	0.712			0.722	0.453			0.565	0.171		
2nd Donor Gender (Male vs Female)	1.275	0.323			0.797	0.406			1.320	0.489			1.871	0.236			0.735	0.467			0.605	0.214		
2nd Donor Type																								
MRD	1.000				1.000				1.000				1.000				1.000				1.000			
URD	0.838	0.701			1.387	0.481			6.170	0.929			0.656	0.718			1.067	0.944			0.857	0.860		
CB	2.732	0.201			12.65	0.156			1.063	0.926			0.000	0.990			3.017	0.345			2.655	0.389		
Haplo	1.458	0.289			2.660	0.008			8.505	0.927			1.109	0.876			1.495	0.525			1.304	0.633		
ABO of 2nd Tx (Matched/Minor mismatched vs Major/Bidirectional mismatched)	0.753	0.214			0.325	0.186			0.634	0.589			1.023	0.541			0.475	0.315			0.606	0.427		
Conditioning Regimen of 2nd Tx (FC vs Other)	0.641	0.143			1.328	0.400			0.578	0.216			1.556	0.565			1.404	0.477			1.595	0.296		
Graft Source of 2nd Tx																								
PB+BM	1.000				1.000				1.000				1.000				1.000				1.000			
PB	1.145	0.582			0.847	0.541			0.545	0.130			1.582	0.404			0.698	0.390			0.744	0.451		
CB	2.203	0.283			2.632	0.345			1.122	0.912			0.000	0.990			1.822	0.567			1.880	0.546		
Infused MNCs (＜Median vs ≥Median)	0.769	0.275			1.020	0.783			1.652	0.219			1.150	0.795			0.838	0.666			0.788	0.538		
Infused CD34 cells (＜Median vs ≥Median)	1.153	0.584			2.098	0.012			0.616	0.375			1.584	0.449			0.878	0.778			1.015	0.973		
GVHD Prophylaxis for 2nd Tx (Other vs Intensified)	0.930	0.793			1.208	0.691			1.133	0.095			0.944	0.930			1.637	0.278			1.938	0.110		

Supplementary Table 11. Univariate and multivariate analysis for 2nd transplant outcomes in patients with secondary GF.

Abbreviations: AA, aplastic anemia; GF, graft failure; MRD, matched related donor; URD, unrelated donor; CB, cord blood; Haplo, haploidentical transplantation; Tx, transplantation; DSA, Donor specific antibody; CR, complete remission; FC, fludarabine/cyclophosphamide; BM, bone marrow; PB, peripheral blood; MNCs, mononucleated cells; GVHD, graft versus host disease.

Outcomes / Variables	ANC Engraftment				Platelet Engraftment				aGVHD				cGVHD				TRM				OS			
	Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate	
	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*
Recipient Gender (Male vs Female)	0.838	0.479			0.626	0.093			0.754	0.429			1.345	0.676			1.460	0.339			1.099	0.783		
Recipient Age (＜Median vs ≥Median)	0.555	0.021			0.488	0.009			0.799	0.521			6.560	0.022			0.359	0.012			0.375	0.006		
Disease (AA vs Other)	0.702	0.172			0.471	0.009			1.958	0.099			3.249	0.151			0.248	0.010			0.175	0.001	0.122	0.049
1st Donor Type																								
MRD	1.000				1.000				1.000				1.000				1.000				1.000			
URD	0.870	0.850			0.349	0.232			1.172	0.889			0.183	0.246			0.000	0.976			0.238	0.242		
CB	1.218	0.745			0.840	0.812			7.499	0.894			0.030	0.042			2.066	0.346			0.607	0.509		
Haplo	2.387	0.158			1.238	0.774			1.089	0.890			0.347	0.355			1.160	0.844			1.015	0.994		
GF Type (Primary vs Secondary)	1.250	0.503			1.702	0.129			0.747	0.585			3.507	0.086			1.052	0.926			1.092	0.855		
Time from 1st Tx to 2nd Tx (＜Median vs ≥Median)	0.907	0.694			0.919	0.754			0.953	0.889			2.517	0.258			1.280	0.515			1.074	0.834		
DSA prior to 2nd Tx (Neg. vs Pos.)	0.587	0.263			0.708	0.512			0.660	0.574			3.755	0.255			0.855	0.836			0.552	0.282		
Disease Status prior to 2nd Tx (Relapse vs CR)	0.045	0.356			0.047	0.566			0.048	0.729							0.087	0.029			0.087	0.029		
Change donor (No vs Yes)	2.390	0.018			2.937	0.022	3.045	0.049	2.107	0.219			0.086	＜0.001	0.058	0.033	2.865	0.010			2.101	0.056		
2nd Donor Age (＜Median vs ⩾Median)	0.937	0.808			1.152	0.626			1.862	0.102			1.918	0.397			0.460	0.074			0.468	0.044		
2nd Donor Gender (Male vs Female)	0.830	0.486			0.943	0.839			0.960	0.913			0.261	0.209			0.716	0.388			0.880	0.718		
2nd Donor Type																								
MRD	1.000				1.000				1.000				1.000				1.000				1.000			
URD	2.141	0.322			0.678	0.673			3.406	0.913			0.000	0.991			0.637	0.713			0.639	0.715		
CB	5.344	0.020			5.405	0.065			2.294	0.917			1.428	0.802			1.555	0.611			1.696	0.543		
Haplo	1.715	0.302			1.026	0.966			2.522	0.916			0.344	0.327			0.777	0.734			1.048	0.949		
ABO of 2nd Tx (Matched/Minor mismatched vs Major/Bidirectional mismatched)	0.566	0.248			0.458	0.213			0.756	0.598			0.775	0.631			0.689	0.347			0.613	0.498		
Conditioning Regimen of 2nd Tx (FC vs Other)	1.181	0.544			1.224	0.505			1.433	0.376			2.653	0.361			1.205	0.645			1.364	0.384		
Graft Source of 2nd Tx																								
PB+BM	1.000		1.000		1.000		1.000		1.000				1.000		1.000		1.000				1.000			
PB	2.545	0.003	1.866	0.076	1.980	0.052	1.332	0.454	1.010	0.980			4.354	0.055	1.795	0.043	3.057	0.007			2.060	0.055		
CB	4.348	0.006	3.846	0.034	6.329	0.011	5.917	0.015	0.979	0.973			6.025	0.112	2.552	0.943	2.879	0.066			2.035	0.198		
Infused MNCs (＜Median vs ≥Median)	2.020	0.008			2.047	0.013			0.842	0.634			0.497	0.339			1.736	0.155			1.330	0.401		
Infused CD34 cells (＜Median vs ≥Median)	1.562	0.090			1.353	0.278			1.370	0.383			1.655	0.491			1.416	0.381			1.873	0.083		
GVHD Prophylaxis for 2nd Tx (Other vs Intensified)	2.202	0.039			1.951	0.123			2.156	0.205			0.312	0.155			2.577	0.024			1.938	0.101		

Supplementary Table 12. Univariate and multivariate analysis for 2nd transplant outcomes in patients with full recipient chimerisms.

Abbreviations: AA, aplastic anemia; GF, graft failure; MRD, matched related donor; URD, unrelated donor; CB, cord blood; Haplo, haploidentical transplantation; Tx, transplantation; DSA, Donor specific antibody; CR, complete remission; FC, fludarabine/cyclophosphamide; BM, bone marrow; PB, peripheral blood; MNCs, mononucleated cells; GVHD, graft versus host disease.

Outcomes / Variables	ANC Engraftment				Platelet Engraftment				aGVHD				cGVHD				TRM				OS			
	Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate	
	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*
Recipient Gender (Male vs Female)	1.802	0.025			1.567	0.152			0.688	0.299			1.769	0.363			1.534	0.205			1.626	0.144		
Recipient Age (＜Median vs ≥Median)	1.213	0.462			0.869	0.653			1.071	0.847			4.939	0.020	4.581	0.039	0.729	0.334			0.722	0.307		
Disease (AA vs Other)	0.814	0.474			0.989	0.974			0.849	0.669			6.218	0.084			0.735	0.422			0.670	0.292		
1st Donor Type																								
MRD	1.000				1.000				1.000				1.000				1.000		1.000		1.000		1.000	
URD	3.448	0.248			4.049	0.193			1.805	0.630							10.29	0.007	14.38	0.012	7.534	0.009	1.180	0.831
CB	1.178	0.746			2.959	0.056			2.244	0.334							2.192	0.337	1.020	0.985	1.471	0.585	13.19	0.001
Haplo	0.965	0.931			2.591	0.027			2.588	0.197			1.050	0.589			2.153	0.210	0.801	0.775	1.823	0.325	0.938	0.927
GF Type (Primary vs Secondary)	1.250	0.400			2.285	0.009			0.623	0.204			0.849	0.788			2.545	0.012			2.500	0.010		
Time from 1st Tx to 2nd Tx (＜Median vs ≥Median)	0.955	0.86			1.348	0.342			0.503	0.060			0.967	0.958			1.041	0.902			1.073	0.825		
DSA prior to 2nd Tx (Neg. vs Pos.)	0.908	0.846			1.053	0.933			1.684	0.194			0.742	0.782			1.792	0.58			1.792	0.580		
Disease Status prior to 2nd Tx (Relapse vs CR)	1.187	0.817			2.277	0.431			0.044	0.532			0.042	0.653			1.094	0.931			1.094	0.931		
Change donor (No vs Yes)	1.591	0.079			2.032	0.032	2.317	0.032	0.927	0.831			0.724	0.597			2.146	0.022			2.058	0.026	3.125	0.036
2nd Donor Age (＜Median vs ⩾Median)	0.758	0.307			0.817	0.535			1.258	0.543			0.720	0.589			1.002	0.995			0.917	0.796		
2nd Donor Gender (Male vs Female)	0.571	0.054			0.501	0.053			1.188	0.640			3.698	0.037			0.673	0.231			0.608	0.120		
2nd Donor Type																								
MRD	1.000				1.000				1.000				1.000				1.000				1.000			
URD	0.437	0.205			0.492	0.28			1.894	0.602														
CB	1.377	0.676			2.941	0.215			3.548	0.303							1.259	0.818			0.849	0.858		
Haplo	0.824	0.712			2.075	0.176			3.107	0.266			1.243	0.836			1.651	0.491			1.201	0.761		
ABO of 2nd Tx (Matched/Minor mismatched vs Major/Bidirectional mismatched)	0.724	0.452			0.889	0.515			0.855	0.679			1.012	0.623			0.895	0.442			0.750	0.323		
Conditioning Regimen of 2nd Tx (FC vs Other)	0.401	0.002	0.393	0.049	0.661	0.203			0.579	0.136			0.272	0.043			0.649	0.258			0.717	0.365		
Graft Source of 2nd Tx																								
PB+BM	1.000				1.000				1.000				1.000				1.000				1.000			
PB	1.639	0.066			1.667	0.113			0.958	0.907			0.841	0.779			1.666	0.144			1.567	0.186		
CB	2.299	0.173			2.188	0.291			1.237	0.780							1.178	0.829			1.044	0.955		
Infused MNCs (＜Median vs ≥Median)	1.686	0.051			1.999	0.03			1.003	0.994			2.270	0.252			1.351	0.359			1.164	0.634		
Infused CD34 cells (＜Median vs ≥Median)	2.292	0.007			4.180	＜0.001	3.265	0.018	0.692	0.381			2.175	0.344			2.475	0.035			2.611	0.025		
GVHD Prophylaxis for 2nd Tx (Other vs Intensified)	2.150	0.006			3.778	＜0.001	4.262	0.027	1.426	0.341			1.555	0.574			3.021	＜0.001	4.717	0.008	2.959	＜0.001	4.184	0.014

Supplementary Table 13. Univariate and multivariate analysis for 2nd transplant outcomes in patients with full donor chimerisms.

Abbreviations: AA, aplastic anemia; GF, graft failure; MRD, matched related donor; URD, unrelated donor; CB, cord blood; Haplo, haploidentical transplantation; Tx, transplantation; DSA, Donor specific antibody; CR, complete remission; FC, fludarabine/cyclophosphamide; BM, bone marrow; PB, peripheral blood; MNCs, mononucleated cells; GVHD, graft versus host disease.

Variables \ Outcomes	ANC Engraftment				Platelet Engraftment				aGVHD				cGVHD				TRM				OS			
	Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate	
	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*
Recipient Gender (Male vs Female)	0.837	0.428			0.794	0.378			1.176	0.661			0.900	0.841			0.926	0.817			0.917	0.787		
Recipient Age (＜Median vs ≥Median)	0.813	0.348			0.697	0.160			0.958	0.906			0.905	0.848			0.768	0.427			0.784	0.451		
Disease (AA vs Other)	0.930	0.757			0.644	0.096			1.183	0.673			1.453	0.523			1.182	0.624			1.089	0.799		
1st Donor Type																								
MRD	1.000				1.000				1.000				1.000				1.000				1.000			
URD	1.019	0.965			1.859	0.202			2.605	0.191			1.024	0.985			3.108	0.121			3.174	0.115		
CB	1.524	0.271			1.653	0.241			0.888	0.885			4.724	0.058			3.380	0.069			3.458	0.064		
Haplo	2.203	0.015			1.992	0.050			2.005	0.263			1.286	0.759			2.400	0.159			2.695	0.109		
GF Type (Primary vs Secondary)	0.939	0.781			1.737	0.036			0.838	0.641			0.819	0.716			1.689	0.159			1.605	0.186		
Time from 1st Tx to 2nd Tx (＜Median vs ≥Median)	1.134	0.571			1.855	0.021			0.511	0.075			0.612	0.345			1.832	0.077			1.815	0.073		
DSA prior to 2nd Tx (Neg. vs Pos.)	0.482	0.077			0.341	0.042			0.636	0.547			0.039	0.405			0.525	0.207			0.539	0.232		
Disease Status prior to 2nd Tx (Relapse vs CR)	1.081	0.841			1.366	0.488			1.050	0.940			0.036	0.456			1.642	0.508			1.232	0.741		
Change donor (No vs Yes)	1.583	0.073			1.552	0.151			1.002	0.996			2.657	0, 198			1.425	0.304			1.477	0.242		
2nd Donor Age (＜Median vs ≥Median)	0.667	0.090			0.636	0.104			1.194	0.645			1.264	0.690			0.913	0.795			0.930	0.831		
2nd Donor Gender (Male vs Female)	1.285	0.256			1.285	0.330			1.123	0.751			0.944	0.911			0.949	0.874			0.968	0.920		
2nd Donor Type																								
MRD	1.000				1.000				1.000				1.000				1.000				1.000			
URD	1.996	0.244			1.458	0.532			3.679	0.934			1.480	0.948			3.087	0.171			3.214	0.157		
CB	3.021	0.066			2.101	0.267			5.03	0.932			1.347	0.948			1.063	0.958			1.096	0.937		
Haplo	2.331	0.015			2.004	0.058			8.219	0.929			0.756	0.957			1.595	0.443			1.707	0.378		
ABO of 2nd Tx (Matched/Minor mismatched vs Major/Bidirectional mismatched)	0.823	0.379			0.563	0.488			0.889	0.420			0.753	0.369			0.562	0.236			0.723	0.412		
Conditioning Regimen of 2nd Tx (FC vs Other)	1.144	0.566			1.417	0.211			1.099	0.817			1.256	0.700			1.603	0.165			1.490	0.232		
Graft Source of 2nd Tx																								
PB+BM	1.000				1.000				1.000				1.000				1.000				1.000			
PB	1.550	0.053			0.840	0.507			0.434	0.033			0.747	0.590			0.645	0.200			0.746	0.373		
CB	1.761	0.282			1.059	0.925			0.513	0.516			1.742	0.602			0.549	0.558			0.565	0.578		
Infused MNCs (＜Median vs ≥Median)	1.135	0.564			1.288	0.325			1.175	0.662			2.058	0.188			1.616	0.152			1.572	0.165		
Infused CD34 cells (＜Median vs ≥Median)	1.100	0.674			1.504	0.130			0.595	0.169			1.256	0.660			1.935	0.597			1.297	0.436		
GVHD Prophylaxis for 2nd Tx (Other vs Intensified)	1.155	0.626			1.048	0.898			1.805	0.332			3.763	0.201			0.579	0.303			0.686	0.433		

Supplementary Table 14. Univariate and multivariate analysis for 2nd transplant outcomes in patients with mixed chimerisms.

Abbreviations: AA, aplastic anemia; GF, graft failure; MRD, matched related donor; URD, unrelated donor; CB, cord blood; Haplo, haploidentical transplantation; Tx, transplantation; DSA, Donor specific antibody; CR, complete remission; FC, fludarabine/cyclophosphamide; BM, bone marrow; PB, peripheral blood; MNCs, mononucleated cells; GVHD, graft versus host disease.

Variables \ Outcomes	ANC Engraftment				Platelet Engraftment				aGVHD				cGVHD				TRM				OS			
	Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate	
	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*
Recipient Gender (Male vs Female)	0.957	0.856			1.015	0.957			0.680	0.306			13.895	0.012	11.030	0.023	1.269	0.490			1.350	0.363		
Recipient Age (＜Median vs ≥Median)	0.950	0.835			0.589	0.069			1.228	0.584			2.013	0.236			0.726	0.354			0.710	0.296		
Disease (AA vs Other)	0.958	0.888			1.057	0.877			2.532	0.128			3.279	0.221			0.851	0.721			0.736	0.491		
1st Donor Type																								
MRD	1.000				1.000				1.000				1.000				1.000				1.000			
URD	0.980	0.977			0.846	0.827			2.130	0.915							1.350	0.765			2.061	0.429		
CB	1.464	0.482			0.464	0.249			1.644	0.917			3.349	0.964			1.349	0.721			1.341	0.726		
Haplo	2.119	0.117			0.938	0.916			2.958	0.912			1.084	0.960			1.545	0.555			1.805	0.421		
GF Type (Primary vs Secondary)	1.300	0.393			1.256	0.507			1.346	0.494			0.635	0.559			1.263	0.604			1.203	0.658		
Chimerism																								
Full donor	1.000				1.000				1.000				1.000				1.000				1.000			
Mixed	1.770	0.060	2.865	0.015	1.381	0.350			0.421	0.051			0.461	0.217			1.272	0.565			1.115	0.789		
Full recipient	1.692	0.109	1.934	0.170	1.066	0.861			0.546	0.187			0.151	0.077			1.034	0.943			1.212	0.654		
Time from 1st Tx to 2nd Tx (＜Median vs ≥Median)	1.891	0.013			1.322	0.334			1.141	0.725			1.366	0.612			1.927	0.063	0.204	0.028	1.637	0.134		
DSA prior to 2nd Tx (Neg. vs Pos.)	0.492	0.072			0.595	0.244			1.693	0.318			0.940	0.938			1.789	0.445			1.534	0.497		
Disease Status prior to 2nd Tx (Relapse vs CR)	0.048	0.907			0.047	0.588			0.047	0.838							0.089	0.036			0.808	0.036		
Change donor (No vs Yes)	1.692	0.065			1.780	0.105			1.077	0.858			0.949	0.938			2.421	0.010	0.373	0.006	1.988	0.037	2.179	0.034
2nd Donor Age (＜Median vs ≥Median)	0.871	0.592			0.719	0.275			1.940	0.105			0.856	0.798			0.807	0.552			0.645	0.208		
2nd Donor Gender (Male vs Female)	1.014	0.954			0.744	0.304			0.877	0.723			1.154	0.807			0.733	0.737			0.768	0.423		
2nd Donor Type																								
MRD	1.000				1.000				1.000				1.000				1.000				1.000			
URD	1.812	0.418	1.282	0.073	0.773	0.755			3.874	0.945							2.264	0.417			2.461	0.371		
CB	3.891	0.066	4.167	0.012	1.353	0.741			4.058	0.945			3.055	0.957			2.170	0.442			2.414	0.382		
Haplo	1.805	0.211	1.064	0.064	0.817	0.736			7.662	0.942			8.532	0.961			1.437	0.621			1.684	0.475		
ABO of 2nd Tx (Matched/Minor mismatched vs Major/Bidirectional mismatched)	0.889	0.457			0.647	0.236			0.995	0.675			1.104	0.744			0.614	0.522			0.852	0.324		
Graft Source of 2nd Tx																								
PB+BM	1.000				1.000				1.000				1.000				1.000				1.000			
PB	1.838	0.025			1.894	0.046			1.754	0.179			0.725	0.635			1.484	0.267			1.191	0.606		
CB	2.890	0.078			2.075	0.317			1.992	0.502			3.713	0.238			1.782	0.443			1.556	0.554		
Infused MNCs (＜Median vs ≥Median)	1.462	0.124			1.657	0.081	1.895	0.037	0.970	0.937			1.007	0.990			1.385	0.347			1.458	0.253		
Infused CD34 cells (＜Median vs ≥Median)	1.234	0.403			1.437	0.214			0.527	0.112			2.722	0.139			1.637	0.187			1.957	0.062	2.208	0.031
GVHD Prophylaxis for 2nd Tx (Other vs intensified)	3.788	0.025			5.902	0.079			2.304	0.285			2.141	0.642			3.922	0.001			3.472	0.003		

Supplementary Table 15. Univariate and multivariate analysis for 2nd transplant outcomes in patients receving FC-based conditioning regimens.

Abbreviations: AA, aplastic anemia; GF, graft failure; MRD, matched related donor; URD, unrelated donor; CB, cord blood; Haplo, haploidentical transplantation; Tx, transplantation; DSA, Donor specific antibody; CR, complete remission; FC, fludarabine/cyclophosphamide; BM, bone marrow; PB, peripheral blood; MNCs, mononucleated cells; GVHD, graft versus host disease.

Variables \ Outcomes	ANC Engraftment				Platelet Engraftment				aGVHD				cGVHD				TRM				OS			
	Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate	
	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*
Recipient Gender (Male vs Female)	1.528	0.189			0.811	0.595			0.832	0.718			0.294	0.275			1.852	0.199			1.605	0.297		
Recipient Age (＜Median vs ≥Median)	0.788	0.452			0.438	0.034			1.467	0.437			2.560	0.303			0.421	0.052			0.470	0.079	0.757	0.019
Disease (AA vs Other)	0.999	0.991			1.026	0.799			1.122	0.402			0.921	0.731			1.174	0.209			1.189	0.169		
1st Donor Type																								
MRD	1.000				1.000				1.000				1.000				1.000				1.000			
URD	6.579	0.051			3.726	0.262			7.029	0.927							5.600	0.922			5.292	0.918		
CB	5.882	0.027			1.553	0.671			7.084	0.927			0.290	0.314			5.782	0.922			6.251	0.917		
Haplo	9.804	0.005			1.692	0.618			1.167	0.923			0.332	0.369			1.734	0.912			1.609	0.908		
GF Type (Primary vs Secondary)	0.946	0.884			1.171	0.731			0.219	0.141			5.083	0.076			1.610	0.443			1.712	0.386		
Chimerism																								
Full donor	1.000				1.000				1.000				1.000				1.000				1.000			
Mixed	0.371	0.022			0.189	0.012			1.001	0.999			0.740	0.763			0.311	0.047			0.308	0.045		
Full recipient	0.460	0.062			0.181	0.008			1.093	0.883			0.246	0.255			0.253	0.012			0.302	0.019		
Time from 1st Tx to 2nd Tx (＜Median vs ≥Median)	0.478	0.021			0.568	0.140			0.590	0.285			2.197	0.390			0.452	0.074			0.508	0.114		
DSA prior to 2nd Tx (Neg. vs Pos.)	0.993	0.994			0.040	0.373			0.046	0.656							0.107	0.069			0.107	0.069		
Change donor (No vs Yes)	1.810	0.075			3.422	0.008	0.180	0.027	1.204	0.715			0.282	0.166			2.551	0.029			2.315	0.045	6.358	0.025
2nd Donor Age (＜Median vs ≥Median)	0.756	0.407			1.102	0.808			1.089	0.864			0.014	0.303			1.287	0.595			0.861	0.745		
2nd Donor Gender (Male vs Female)	0.699	0.279			1.008	0.984			1.413	0.485			0.401	0.417			0.898	0.808			0.979	0.962		
2nd Donor Type																								
MRD	1.000				1.000				1.000				1.000				1.000				1.000			
URD	4.348	0.112			1.922	0.468																		
CB	3.125	＜0.001			11.63	0.030			3.238	0.959							6.111	0.952			6.032	0.950		
Haplo	6.803	0.002			3.058	0.044			8.952	0.955			0.613	0.663			8.145	0.950			8.249	0.949		
ABO of 2nd Tx (Matched/Minor mismatched vs Major/Bidirectional mismatched)	0.723	0.557			0.679	0.231			0.782	0.431			1.064	0.894			0.623	0.246			0.741	0.356		
Graft Source of 2nd Tx																								
PB+BM	1.000				1.000				1.000				1.000				1.000				1.000			
PB	3.205	0.001			2.857	0.013			0.596	0.318			3.115	0.213			3.215	0.013			2.817	0.022		
CB	11.23	0.002			6.803	0.062			0.350	0.317							1.627	0.545			1.461	0.632		
Infused MNCs (＜Median vs ≥Median)	3.012	0.002			4.552	0.001	3.871	0.042	0.904	0.840			1.198	0.843			2.801	0.025			0.405	0.039		
Infused CD34 cells (＜Median vs ≥Median)	2.973	0.006			3.291	0.007			1.400	0.546			0.810	0.833			2.532	0.094			2.950	0.049	7.874	0.048
GVHD Prophylaxis for 2nd Tx (Other vs intensified)	2.370	0.009			5.123	＜0.001	2.013	＜0.001	1.359	0.529			1.386	0.772			2.045	0.108			2.183	0.075	6.098	0.029

Supplementary Table 16. Univariate and multivariate analysis for 2nd transplant outcomes in patients receving TBI-based conditioning regimens.

Abbreviations: AA, aplastic anemia; GF, graft failure; MRD, matched related donor; URD, unrelated donor; CB, cord blood; Haplo, haploidentical transplantation; Tx, transplantation; DSA, Donor specific antibody; CR, complete remission; FC, fludarabine/cyclophosphamide; BM, bone marrow; PB, peripheral blood; MNCs, mononucleated cells; GVHD, graft versus host disease.