haematologica
Journal of the Ferrata Storti Foundation

Selection of unrelated donors for allogeneic transplantation using post-transplant cyclophosphamide in acute lymphoblastic leukemia: an analysis by the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation

by Jaime Sanz, Allain-Thibeault Ferhat, Alexander Kulagin, Nicolaus Kröger, Montserrat Rovira, Lorenzo Lazzari, Mutlu Arat, Juan Montoro, Jurjen Versluis, Péter Reményi, Simona Sica, Didier Blaise, Muhammad Ameer Saif, Jan Vydra, Franca Fagioli, Erfan Nur, Sebastian Giebel, Zina Peric, Eolia Brissot, Arnon Nagler, Simona Piemontese, Mohamad Mohty, and Fabio Ciceri.
Collaborative Groups: ALWP of the EBMT (Acute leukemia working party European Society of Blood & Marrow Transplantation)

Received: March 3, 2025.
Accepted: July 21, 2025.

Citation: Jaime Sanz, Allain-Thibeault Ferhat, Alexander Kulagin, Nicolaus Kröger, Montserrat Rovira, Lorenzo Lazzari, Mutlu Arat, Juan Montoro, Jurjen Versluis, Péter Reményi, Simona Sica, Didier Blaise, Muhammad Ameer Saif, Jan Vydra, Franca Fagioli, Erfan Nur, Sebastian Giebel, Zina Peric, Eolia Brissot, Arnon Nagler, Simona Piemontese, Mohamad Mohty, and Fabio Ciceri. Collaborative Groups: ALWP of the EBMT (Acute leukemia working party European Society of Blood & Marrow Transplantation).
Selection of unrelated donors for allogeneic transplantation using post-transplant cyclophosphamide in acute lymphoblastic leukemia: an analysis by the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation.
Haematologica. 2025 July 31. doi: 10.3324/haematol.2025.287750 [Epub ahead of print]

Selection of unrelated donors for allogeneic transplantation using post-transplant cyclophosphamide in acute lymphoblastic leukemia: An analysis by the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation

Jaime Sanz[1], Allain-Thibeault Ferhat[2], Alexander Kulagin[3], Nicolaus Kröger[4], Montserrat Rovira[5], Lorenzo Lazzari[6], Mutlu Arat[7], Juan Montoro[1], Jurjen Versluis[8], Péter Reményi[9], Simona Sica[10], Didier Blaise[11], Muhammad Ameer Saif[12], Jan Vydra[13], Franca Fagioli[14], Erfan Nur[15], Sebastian Giebel[16], Zina Peric[17], Eolia Brissot[18], Arnon Nagler[19], Simona Piemontese[6], Mohamad Mohty[18], Fabio Ciceri[6,20]

1. Hematology Department, Hospital Universitari i Politècnic La Fe, Valencia Departament de Medicina Universitat de Valencia, CIBERONC, Instituto Carlos III, Madrid, Spain
2. EBMT Paris Office, Hospital Saint Antoine, Paris, France
3. RM Gorbacheva Research Institute, Pavlov University, Saint Petersburg, Russian Federation
4. Department for Stem Cell Transplantation , University Medical Center Hamburg/Germany
5. BMT Unit, Department of Haematology, Institute of Haematology and Oncology, IDIBAPS, Hospital clinic, University of Barcelona, Barcelona, Spain; Josep Carreras Leukaemia Research Foundation, Barcelona, Spain
6. Hematology and Bone Marrow transplant Unit, San Raffaele Scientific Institute IRCCS, Milano, Italy
7. Demiroglu Bilim University Istanbul Florence Nightingale Hospital, Istanbul, Turkey
8. Erasmus MC Cancer Institute, Rotterdam, Netherlands
9. Dél-pesti Centrumkórház, Budapest, Hungary
10. *Dipartimento di Diagnostica per Immagini, Radioterapia Oncologica ed Ematologia, Fondazione Policlinico A. Gemelli-IRCCS –Università cattolica Sacro Cuore*
11. Programme de Transplantation &Therapie Cellulaire – Marseille, France
12. Clatterbridge Cancer Centre Liverpool, Liverpool, United Kingdom
13. Institute of Hematology and Blood Transfusion, Prague, Czech Republic
14. Ospedale Infantile Regina Margherita, University of Turin, Torino, Italy
15. Amsterdam UMC, University of Amsterdam, Amsterdam, Netherlands
16. Department of Bone Marrow Transplantation and Oncohematology, Maria Sklodowska-Curie National Research Institute of Oncology, Gliwice, Poland
17. Department of hematology, University Hospital Centre Rijeka and School of Medicine, University of Rijeka, Rijeka, Croatia
18. Hôpital Saint-Antoine, Sorbonne University, INSERM UMRs 938, Paris, France
19. Division of Hematology, Sheba Medical Center, Tel Hashomer, Israel.
20. Vita-Salute San Raffaele University, Milano, Italy

Collaborative Groups: ALWP of the EBMT (Acute leukemia working party European Society of Blood & Marrow Transplantation)

Running Title: Unrelated donor selection for PTCy-HCT in ALL

Corresponding author:
Jaime Sanz
Hospital Universitari i Politècnic La Fe
Av. Fernando Abril Martorell, 106
46026 Valencia, Spain
Mail: Jaime.Sanz@uv.es

DECLARATIONS

Ethics approval and consent to participate

The scientific board of the ALWP of EBMT approved this study. All patients gave written informed consent for the use of their data.

Consent for publication

Not applicable for individual patient data. This is a pooled analysis.

Availability of data and material

The dataset supporting the conclusions of this article are available from the ALWP of the EBMT in Saint Antoine Hospital, Paris.

Competing interests

The authors declare no competing interests.

Funding

No funding

Authors' contributions

JS, SP, MM and FC: designed the study. ATF: performed the statistical analysis and helped with the interpretation of the results. JS: wrote the manuscript. AK, NK, MR, LL, MA, JM, JV, PR, SS, DB, MAS, JV, FF, EN, SG, AN: provided cases for the study. All authors reviewed and approved the manuscript.

ABSTRACT

Conflicting data exist on the impact of mismatched unrelated donor (MMUD) compared to matched unrelated donor (MUD) in hematopoietic cell transplantation (HCT) with post-transplant cyclophosphamide (PTCy), highlighting the need for disease-specific research. We conducted a retrospective analysis of donor characteristics in 350 patients with acute lymphoblastic leukemia (ALL) in complete remission (CR) who received 8/8 human leukocyte antigen (HLA)-matched MUD and 7/8 HLA-matched MMUD. The primary endpoint was leukemia-free survival (LFS). The median age was 37 years (range, 18-76), with 231 (66%) in first CR, and 280 (80%) diagnosed with B-cell ALL. The median donor age was 28 years (range, 18-57), with 237 (68%) MUD and 113 (32%) MMUD. The use of MUD or MMUD did not have a significant impact on LFS or other transplant outcomes. Among other donor-related variables, CMV-negative donor for a CMV-negative recipient was associated with improved LFS (HR 0.55; 95% CI 0.32-0.96) and overall survival (HR 0.52; 95% CI 0.28-1), while older donor age showed an increased risk of acute graft-versus-host disease (GVHD) grade III-IV (HR 1.7; 95% CI 1.1-2.64) and female donor to male recipient combination increased the risk of grade II-IV acute GvHD (HR 1.78; 95% CI 1.05-3). In conclusion, non-HLA donor characteristics rather than HLA matching should be prioritized to guide unrelated donor selection for ALL patients in the PTCy HCT setting.

Keywords: Unrelated donor transplant, stem cell donors, post-transplant cyclophosphamide, acute lymphoblastic leukemia

INTRODUCTION

Hematopoietic cell transplantation (HCT) offers potent antileukemic efficacy in acute lymphoblastic leukemia (ALL).[1] However, its use is often limited by donor availability and specific toxicities, such as graft-versus-host disease (GVHD). Over the last decades, efforts to overcome these limitations have yielded improved outcomes.[2–4]

One of the most relevant advances in the field of transplantation has been the use of post-transplant cyclophosphamide (PTCy) for GVHD prevention. Initially introduced in haploidentical transplants,[5] PTCy has since become the standard of care in the human leukocyte antigen (HLA)-matched setting, showing advantages over calcineurin inhibitor-based prophylaxis in randomized clinical trials[6] and registry data.[7] In fact, important consequences may arise in donor selection algorithms. Recent registry-based studies from both the European Society of Blood & Marrow Transplantation (EBMT)[8] and the Center for International Blood & Marrow Transplant Research (CIBMTR)[7] reported comparable outcomes for matched and mismatched unrelated donors (MUD and MMUD), potentially expanding access to HCT for patients in need. However, the Cellular Therapy and Immunobiology Working Party of the EBMT reported somewhat contradictory results, finding that HLA mismatching was associated with increased mortality in PTCy transplantation within a large cohort of patients with a variety of hematological malignancies.[9] These findings underline the need for disease specific studies. In this context, limited information is available regarding the outcomes of ALL patients receiving unrelated donor transplants with PTCy.

Our study aims to investigate key patient, disease, and transplant characteristics, particularly donor-related factors, that could impact on transplant outcomes in ALL patients receiving PTCy as GVHD prophylaxis. We analyzed data from the EBMT database with the objective of refining criteria for guiding donor selection within this specific context.

METHODS

Study design and data source

This is a retrospective, registry-based analysis conducted on behalf of the Acute Leukemia Working Party (ALWP) of the EBMT. The EBMT is a voluntary working group of more than 650 transplantation centers, all of which are required to report all consecutive HCTs and follow-up data annually. The EBMT registry maintains an internal quality control program to ensure data accuracy and consistency, with regular audits performed to address missing or incorrect data and to prompt follow-up. All transplantation centers are required to obtain written informed consent before data submission to the EBMT, in accordance with the 1975 Declaration of Helsinki. The ALWP of the EBMT group approved this study.

Patient Eligibility

The study included all adults (age ≥18 years) with ALL in first, second or subsequent complete remission (CR1 or CR≥2) reported to the EBMT database. Eligible patients underwent a first allogeneic HCT from an 8/8 MUD or a 7/8 MMUD between January 2010 and December 2021, using an unmanipulated peripheral blood graft with standard dose PTCy (50 mg/kg/day for 2 days) for GVHD prophylaxis and no *in-vivo* T-cells depletion.

Endpoints and Definitions

The primary end point was leukemia-free survival (LFS). Secondary endpoints included acute and chronic GVHD, disease relapse, non-relapse mortality (NRM), GvHD-free and relapse-free survival (GRFS), and overall survival (OS). OS was defined as the time from transplant to death. LFS was defined as survival without relapse or progression, calculated from transplant to the date of first relapse, death from any cause, or last follow-up. Relapse was defined as morphological recurrence of leukemia at any site, and NRM was defined as death from any cause without prior relapse. GVHD grading was performed according to published criteria for acute GVHD[10] and chronic GVHD (categorized as limited or extensive).[11] GRFS was defined as survival without disease relapse or severe acute or chronic extensive GvHD.[12]

Statistical Analysis

Estimations of LFS, OS and GRFS were obtained using the Kaplan-Meier method.[13] Survival probabilities are given at 2 years as percentages and 95% confidence intervals (CIs). Cumulative incidence functions were used to estimate acute GvHD, chronic GvHD, relapse incidence, and NRM.[14,15] Competing risks were death for relapse incidence and relapse for NRM, relapse or death for acute GvHD and chronic GvHD. Multivariate analyses were performed using the Cox proportional hazard.[16] The following patient, disease and transplant characteristics were included in the final model: patient´s age at transplantation, type of ALL, CR1 or CR≥2, transplantation year, conditioning regimen,[17] GvHD prophylaxis (PTCy plus one versus two additional immunosuppressive agents), performance status. The following donor and graft characteristics were also included in the final model: donor age, MUD or MMUD, donor-recipient CMV serostatus and donor-recipient gender mismatch. To take into account the heterogeneity in the effect of a characteristic or a treatment across centers, we introduced a random effect in Cox multivariate models.[18] The significance level was fixed at 0.05, and P values were two-sided. P-values for secondary endpoints should be cautiously interpreted due to multiple comparisons. Statistical analyses and adjusted survival curves were performed using the R statistical software version 4.2.3 (R Foundation for Statistical Computing, Austria, Vienna.

RESULTS

Patient and Transplant Characteristics

Patient and transplant characteristics are summarized in Table 1. A total of 350 patients were included, with a median age of 37 years (range, 18-76). Seventy patients (20%) had T-cell ALL (T-ALL), while 280 (80%) had B-cell ALL (B-ALL) of whom 101 (29%) were Philadelphia chromosome-positive (Ph+) ALL. Transplants were performed in CR1 in 231 (66%) patients. Regarding conditioning regimen, 66 (19%) patients received reduced intensity conditioning (RIC), while the remaining 284 (81%) received a myeloablative conditioning (MAC) regimen. TBI-based conditioning was administered to 181 patients

(52%), most commonly in combination with fludarabine (150 patients, 83%) or, less frequently, with cyclophosphamide (31 patients, 17%). The remaining 169 patients (48%) received chemotherapy-based regimens, with fludarabine in 162 cases (96%) and cyclophosphamide in 7 cases (4%). For GvHD prophylaxis, 56 (16%) patients received PTCy combined a calcineurin inhibitors alone, while 277 (79%) received a triple drug combination of PTCy, mycophenolate mofetil, and either a calcineurin inhibitors or sirolimus. Patient and transplant characteristics were comparable between the 7/8 and 8/8 cohorts, except for a higher proportion of male recipients and a lower use of chemotherapy-based MAC regimens in the 7/8 group. The median follow-up for surviving patients was 2 years (interquartile range [IQR], 1.4-2.3), 1.6 years (IQR, 1.4-2.7) for the 7/8 cohort and 2.1 years (IQR, 1.4-2.7) for the 8/8 cohort.

Donor Characteristics

Donor characteristics are summarized in Table 2. Considering HLA-A, -B, -C and DRB1, 237 (68%) were 8/8 MUD and 113 (32%) were 7/8 MMUD. When considering HLA-DQ matching, 219 (63%) were 10/10 allele MUD, 112 (32%) were 9/10 allele MMUD, and the remaining 9 (3%) were 8/10 allele MMUD. Other donor characteristics were comparable between the 7/8 and 8/8 cohorts, except that donors in the 7/8 group were slightly older. The median age of all donors was 28 years (range, 18-57). Among the 103 (29%) female donors, 57 (16%) donated to male recipients. CMV serostatus was negative in 164 (47%) donors, of which 60 (17%) were used for CMV-negative recipients.

Transplant Outcomes

Transplant outcomes are shown in Table 3. In the overall cohort, LFS at 2 years was 62% (95% CI 56-67). OS and GRFS were 73% (95% CI 67-78) and 48% (95% CI 42-54), respectively. The 180-day cumulative incidence of acute GvHD grade II-IV was 28% (95% CI 23-33) and grade III-IV 9% (95% CI 6-12). The 2-year cumulative incidence of chronic and chronic extensive GvHD was 28% (95% CI 23-34) and 12% (95% CI 9-17), respectively. The 2-year cumulative incidence of relapse was 24% (95% CI 19-29) and NRM 15% (95% CI 11-19).

Analysis of Risk Factors

Donor-related factors

Unadjusted univariate analysis of transplant outcomes, together with multivariable analyses by donor HLA match, are shown in Table 4. Comparisons between 8/8 MUD or 7/8 MMUD showed no significant differences in risk of NRM or relapse, nor in probabilities of LFS, OS, or GRFS (Figure 1). Similar results were obtained when comparing 10/10 MUD with 8-9/10 MMUD. The impact of 8/8 MUD compared to 7/8 MMUD on LFS was consistent across subgroups defined by patient, disease, and transplant characteristics, including conditioning intensity, GvHD prophylaxis (PTCy plus one versus two additional immunosuppressive agents) and the year in which HCT was performed (Figure 2). Risks of acute GVHD grades II-IV and III-IV, as well as any grade of chronic GVHD were similar between the groups. We observed an increased risk of chronic extensive GVHD in patients receiving 8/8 MUD (hazard ratio [HR] HR 2.9; 95% CI 1.14-7.38, p=0.03).

Regarding other donor characteristics, the multivariate analyses of non-HLA donor-related variables is shown in Table 5. Older age per 10 years was associated with increased risk of acute GVHD grades II-IV (HR 1.3; 95% CI 1-1.67) and severe acute GVHD (HR 1.66; 95% CI 1.06-2.59), female donors to male recipient combination increased the risk of grade II-IV acute GVHD (HR 1.74; 95% CI 1.03-2.94), and donor CMV-negative to CMV-negative recipient improved LFS (HR 1.8; 95% CI 1.03-3.14).

Patient, disease, and transplant factors

Patients in CR≥2 at the time of HCT had a higher risk of relapse (HR 2.13; 95% CI 1.22-3.69) and worse LFS (HR 1.84; 95% CI 1.12-2.81), OS (HR 1.74; 95% CI 1.08-2.79), and GRFS (HR 1.5; 95% CI 1.03-2.18) compared to those transplanted in CR1. Older patient age per 10 years was associated with an increased risk of NRM (HR 1.3; 95% CI 1.05-1.63) and worse GRFS (HR 1.17; 95% CI 1.03-1.33). Transplants performed more recently (per 5-year increment) showed a lower risk of chronic GVHD (HR 0.45; 95% CI 0.23-0.89).

DISCUSSION

This study shows that for ALL patients undergoing unrelated donor HCT with PTCy-based GVHD prophylaxis, HLA mismatch did not determine transplant outcomes. In contrast, older donor age and female donor to male recipient combination were associated with an increased risk of acute GVHD, while CMV-negative matching between donor and recipient improved survival. These findings may significantly influence clinical practice by expanding the availability of unrelated donors and guiding donor selection through non-HLA donor characteristics, potentially increasing access to HCT for more patients in need.

The most important finding of our study is that HLA compatibility between donor and recipient was not determinant of transplant outcomes, with the exception of an unexpectedly higher risk of chronic extensive GvHD in MUDs, the cause of which remains unclear. High-resolution HLA matching has historically been the most important criterion in unrelated donor selection, since pivotal papers have demonstrated its important impact on outcomes.[19,20] However, this paradigm has been challenged since the advent of PTCy, with its ability to mitigate the adverse effects of HLA mismatching observed in other transplant settings.[21–24] As PTCy use has increased in matched sibling donor and MUD transplants, questions remain whether HLA matching should still be prioritized over other donor characteristics in unrelated donor selection. Previous registry-based studies have explored this, producing somewhat contradictory results. The ALWP of the EBMT first reported comparable outcomes with either MUD or MMUD transplants in a large cohort of patients with acute myeloid leukemia (AML).[8] The CIBMTR later confirmed these findings in a study including AML, myelodysplastic syndrome, and ALL patients.[7] However, another report by the Cellular Therapy and Immunobiology Working Party of the EBMT found that HLA mismatching increased mortality in PTCy transplants.[9] Although this study also originates from the EBMT Registry, key methodological differences may account for the seemingly contradictory findings. The research by Arrieta-Bolaños focused on only 178 patients with ALL receiving PTCy, primarily due to a shorter inclusion period and the requirement for 6-locus high-resolution HLA typing for both donors and recipients. More importantly, the analysis encompassed a range of hematological malignancies, including acute myeloid

leukemia, non-Hodgkin lymphoma, chronic lymphocytic leukemia, chronic myeloid leukemia, Hodgkin lymphoma, multiple myeloma, and myeloproliferative neoplasms, among others. A preliminary, unpublished sub-analysis suggested that the impact of HLA mismatch might vary depending on the underlying diagnosis. These findings indicate that HLA matching, along with other non-HLA factors, could influence transplant outcomes differently based on the specific disease, highlighting the need for disease-specific analyses.

Non-HLA donor characteristics have also been shown to influence transplant outcomes and may warrant more weight to these characteristics in donor selection algorithms. For example, matching CMV-negative serostatus between donor and recipient was associated with improved survival, as previously described.[25,26] However, most patients in this cohort were transplanted before the introduction of letermovir, which seems to have reduced the impact of CMV status on HCT outcomes.[27] The role of CMV serostatus in the letermovir era will require further evaluation with more recent cohorts. Another important variable was older donor age, which was associated with a higher risk of severe acute GVHD. Younger donor age has long been recognized as beneficial, reducing the incidence of GvHD and potentially improving NRM and survival in unrelated donor HCT.[8,28–30] Although female donor to male recipient had only moderate effect on outcomes and only affected grade II acute GVHD, this finding may have practical implications, given the high representation of female donors in international registries.

This study is the largest to date involving adult ALL patients undergoing unrelated donor HCT with PTCy and confirms the safety and efficacy of the procedure.[4,31] It also confirms the adverse impact of well-established patient- and disease-related risk factors, such as more advanced disease stage and older age at transplant.[32] This study helps clarify the still-debated impact of HLA mismatch in UD-HCT with PTCy in the specific setting of ALL, while also confirming previously published findings on the influence of other donor-related variables. However, these results should be interpreted with caution due to several limitations. First, the number of cases involving this specific transplant modality remains relatively small, which may limit the statistical power and generalizability of the findings. Second, the cohort was heterogeneous,

including patients transplanted in different disease stages (CR1 and CR2), treated with varying conditioning intensities, and diverse post-transplant cyclophosphamide (PTCy) regimens. These factors could confound the observed outcomes. As the use of PTCy-based HCT continues to expand, future studies with larger, more homogeneous cohorts are needed to validate our findings and explore in greater depth the role of specific HLA mismatches and other donor-related or recipient-specific variables.

In conclusion, when selecting the most appropriate unrelated donor for ALL patients undergoing HCT with PTCy, based on this study HLA matching might not be the most important variable to consider. Other non-HLA donor characteristics, such as donor age, as well as donor/recipient sex and CMV matching, seem to play an important role. Further research is needed to refine and validate these recommendations.

REFERENCES

1. Marks DI, Clifton-Hadley L, Copland M, et al. In-vivo T-cell depleted reduced-intensity conditioned allogeneic haematopoietic stem-cell transplantation for patients with acute lymphoblastic leukaemia in first remission: results from the prospective, single-arm evaluation of the UKALL14 trial. Lancet Haematol. 2022;9(4):e276-e288.
2. Giebel S, Labopin M, Socié G, et al. Improving results of allogeneic hematopoietic cell transplantation for adults with acute lymphoblastic leukemia in first complete remission: an analysis from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation. Haematologica. 2017;102(1):139-149.
3. Nagler A, Labopin M, Arat M, et al. Posttransplant cyclophosphamide-based anti-graft-vs-host disease prophylaxis in patients with acute lymphoblastic leukemia treated in complete remission with allogeneic hematopoietic cell transplantation from human leukocyte antigen□mismatched unrelated d. Cancer. 2022;128(22):3959-3968.
4. Sanz J, Galimard J-E, Labopin M, et al. Post-transplant cyclophosphamide containing regimens after matched sibling, matched unrelated and haploidentical donor transplants in patients with acute lymphoblastic leukemia in first complete remission, a comparative study of the ALWP of the EBMT. J Hematol Oncol. 2021;14(1):84.
5. Luznik L, O'Donnell P V, Symons HJ, et al. HLA-haploidentical bone marrow transplantation for hematologic malignancies using nonmyeloablative conditioning and high-dose, posttransplantation cyclophosphamide. Biol Blood Marrow Transplant. 2008;14(6):641-650.
6. Bolaños-Meade J, Hamadani M, Wu J, et al. Post-Transplantation Cyclophosphamide-Based Graft-versus-Host Disease Prophylaxis. N Engl J Med. 2023;388(25):2338-2348.
7. Shaffer BC, Gooptu M, DeFor TE, et al. Post-Transplant Cyclophosphamide–Based Graft-Versus-Host Disease Prophylaxis Attenuates Disparity in Outcomes

Between Use of Matched or Mismatched Unrelated Donors. J Clin Oncol. 2024;42(28):3277-3286.

8. Sanz J, Labopin M, Choi G, et al. Younger unrelated donors may be preferable over HLA match in the PTCy era: a study from the ALWP of the EBMT. Blood. 2024;143(24):2534-2543.

9. Arrieta-Bolaños E, Bonneville EF, Crivello P, et al. Human Leukocyte Antigen Mismatching and Survival in Contemporary Hematopoietic Cell Transplantation for Hematologic Malignancies. J Clin Oncol. 2024;42(28):3287-3299.

10. Harris AC, Young R, Devine S, et al. International, Multicenter Standardization of Acute Graft-versus-Host Disease Clinical Data Collection: A Report from the Mount Sinai Acute GVHD International Consortium. Biol Blood Marrow Transplant. 2016;22(1):4-10.

11. Lee SJ, Vogelsang G, Flowers MED. Chronic graft-versus-host disease. Biol Blood Marrow Transplant. 2003;9(4):215-233.

12. Ruggeri A, Labopin M, Ciceri F, Mohty M, Nagler A. Definition of GvHD-free, relapse-free survival for registry-based studies: an ALWP-EBMT analysis on patients with AML in remission. Bone Marrow Transplant. 2016;51(4):610-611.

13. Kaplan EL, Meier P. Nonparametric Estimation from Incomplete Observations. J Am Stat Assoc. 1958;53(282):457-481.

14. Fine JP, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk. J Am Stat Assoc. 1999;94(446):496-.509.

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

16. Cox DR. Regression models and life tables (with discussion). J R Stat Soc B. 1972;34(2):187-220.

17. Bacigalupo A, Ballen K, Rizzo D, et al. Defining the intensity of conditioning regimens: working definitions. Biol Blood Marrow Transplant. 2009;15(12):1628-1633.

18. Biard L, Labopin M, Chevret S, Resche-Rigon M. Investigating covariate-by-centre interaction in survival data. Stat Methods Med Res. 2018;27(3):920-932.

19. Lee SJ, Klein J, Haagenson M, et al. High-resolution donor-recipient HLA matching contributes to the success of unrelated donor marrow transplantation. Blood. 2007;110(13):4576-4583.

20. Woolfrey A, Klein JP, Haagenson M, et al. HLA-C antigen mismatch is associated with worse outcome in unrelated donor peripheral blood stem cell transplantation. Biol Blood Marrow Transplant. 2011;17(6):885-892.

21. Robinson TM, Fuchs EJ, Zhang MJ, et al. Related donor transplants: has posttransplantation cyclophosphamide nullified the detrimental effect of HLA mismatch? Blood Adv. 2018;2(11):1180-1186.

22. Nagler A, Labopin M, Dholaria B, et al. Comparison of Haploidentical Bone Marrow versus Matched Unrelated Donor Peripheral Blood Stem Cell Transplantation with Posttransplant Cyclophosphamide in Patients with Acute Leukemia. Clin Cancer Res. 2021;27(3):843-851.

23. Sanz J, Galimard J-E, Labopin M, et al. Post-transplant cyclophosphamide after matched sibling, unrelated and haploidentical donor transplants in patients with acute myeloid leukemia: a comparative study of the ALWP EBMT. J Hematol Oncol. 2020;13(1):46.

24. Ambinder A, Jain T, Tsai HL, Horowitz MM, Jones RJ, Varadhan R. HLA-matching with PTCy: a reanalysis of a CIBMTR dataset with propensity score matching and donor age. Blood Adv. 2022;6(14):4335-4346.

25. Ljungman P. The role of cytomegalovirus serostatus on outcome of hematopoietic stem cell transplantation. Curr Opin Hematol. 2014;21(6):466-469.

26. Shaw BE, Mayor NP, Szydlo RM, et al. Recipient/donor HLA and CMV matching in recipients of T-cell-depleted unrelated donor haematopoietic cell transplants. Bone Marrow Transplant. 2017;52(5):717-725.

27. Marty FM, Ljungman P, Chemaly RF, et al. Letermovir Prophylaxis for Cytomegalovirus in Hematopoietic-Cell Transplantation. N Engl J Med. 2017;377(25):2433-2444.

28. Kollman C, Howe CWS, Anasetti C, et al. Donor characteristics as risk factors in recipients after transplantation of bone marrow from unrelated donors: the effect of donor age. Blood. 2001;98(7):2043-2051.

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

30. Wang Y, Wu DP, Liu QF, et al. Donor and recipient age, gender and ABO incompatibility regardless of donor source: validated criteria for donor selection for haematopoietic transplants. Leukemia. 2018;32(2):492-498.

31. Giebel S, Labopin M, Salmenniemi U, et al. Posttransplant cyclophosphamide versus antithymocyte globulin in patients with acute lymphoblastic leukemia treated with allogeneic hematopoietic cell transplantation from matched unrelated donors: A study from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation. Cancer. 2023;129(23):3735-3745.

32. DeFilipp Z, Advani AS, Bachanova V, et al. Hematopoietic Cell Transplantation in the Treatment of Adult Acute Lymphoblastic Leukemia: Updated 2019 Evidence-Based Review from the American Society for Transplantation and Cellular Therapy. Biol Blood Marrow Transplant. 2019;25(11):2113-2123.

Table 1. Patient, disease and transplant characteristics

	Type of donor			
Variable	Overall	UD 7/8	UD 8/8	P value*
No. of patients	350	113	237	
Age in years, median (range)	37 (18-76)	40 (18-68)	35 (18-76)	0.18
Sex, n (%)				0.04
Male	202 (58)	74 (65)	128 (54)	
Female	148 (42)	39 (35)	109 (46)	
CMV serologic status, n (%)				0.24
Positive	255 (74)	88 (78)	167 (72)	
Negative	90 (26)	25 (22)	65 (28)	
Missing	5	0	5	
Karnofsky score at HCT, n (%)				0.63
≥ 90	233 (70)	80 (72)	153 (70)	
< 90	98 (30)	31 (28)	67 (30)	
Missing	19	2	17	
HCT-CI, n (%)				0.41
0	182 (57)	51 (53)	131 (59)	
1-2	77 (24)	28 (29)	49 (22)	
≥ 3	60 (19)	18 (19)	42 (19)	
Type of ALL, n (%)				0.06
T-ALL	70 (20)	25 (22)	45 (19)	
B-ALL Ph+	101 (29)	36 (32)	65 (27)	
B-ALL Ph-	109 (31)	39 (35)	70 (30)	
B-ALL Ph unknown	70 (20)	15 (12)	57 (24)	
Disease status at HCT, n (%)				0.39
CR1	231 (66)	71 (63)	160 (68)	
CR≥2	119 (34)	42 (37)	77 (32)	
Measurable residual disease, n (%)				0.68
Positive	56 (29)	20 (31)	36 (28)	
Negative	138 (71)	45 (69)	93 (72)	
Missing	156			
Year of HCT, median (IQR)	2019 (2017-2020)	2019 (2017-2021)	2019 (2017-2020)	0.45
Conditioning, n (%)				0.003
Reduced intensity	66 (19)	26 (23)	40 (17)	
TBI myeloablative	191 (55)	70 (62)	121 (51)	
Chemotherapy myeloablative	93 (27)	17 (15)	76 (32)	
GVHD prophylaxis, n (%)				0.07
PTCy + CNI + MMF	250 (71)	90 (80)	160 (67)	
PTCy + CNI	56 (16)	12 (11)	44 (19)	
PTCy + sirolimus + MMF	27 (8)	5 (4)	22 (9)	
PTCy + other	17 (5)	6 (5)	11 (5)	

Abbreviations: UD, unrelated donor; HCT, hematopoietic cell transplant; CMV, cytomegalovirus; HCT-CI, hematopoietic cell transplant-specific comorbidity index; ALL, acute lymphocytic leukemia; Ph, Philadelphia chromosome; CR, complete remission; GvHD, graft-versus-host disease; PTCy, post-transplant cyclophosphamide; CNI, calcineurin inhibitor; MMF, mycophenolate mofetil; IQR, interquartile range; TBI, total body irradiation
* Wilcoxon rank sum test; Fisher's exact test

Table 2. Donor characteristics

	Type of donor			
Variable	Overall	UD 7/8 n = 113	UD 8/8 n = 237	p value*
Age in years, median (range)	28 (18-57)	29 (18-57)	28 (18-54)	0.04
Age group, n (%)				0.13
18-25	113 (32)	33 (29)	80 (34)	
25-33	129 (37)	37 (33)	92 (39)	
33-58	108 (31)	43 (38)	65 (27)	
Sex, n (%)				0.5
Male	247 (71)	74 (65)	128 (54)	
Female	103 (29)	39 (35)	109 (46)	
Donor/recipient sex, n (%)				0.15
Female / male recipient	57 (16)	23 (20)	34 (14)	
Other	293 (84)	90 (80)	203 (86)	
CMV serologic status, n (%)				0.11
Negative	164 (47)	46 (41)	118 (50)	
Positive	186 (53)	67 (59)	119 (50)	
Donor/recipient CMV serology, n (%)				0.18
Donor and recipient negative	60 (17)	13 (12)	47 (20)	
Other	285 (83)	100 (88)	185 (80)	
Missing	5	0	5	
Donor/recipient HLA match, n (%)				
Considering HLA-A, -B, -C, DR, DQ				0.001
10/10 MUD	219 (63)	0 (0)	219 (92)	
9/10 MMUD	112 (32)	102 (90)	10 (4)	
8/10 MMUD	9 (3)	9 (8)	0 (0)	
Locus mismatch				
HLA-A	66 (19)	66 (58)	0 (0)	
HLA-B	18 (5)	18 (16)	0 (0)	
HLA-C	22 (6)	22 (19)	0 (0)	
HLA-DR	7 (2)	7 (6)	0 (0)	
HLA-DQ	19 (5)	9 (8)	10 (4)	

Abbreviations: UD, unrelated donor; MUD, matched unrelated donor; MMUD, mismatched unrelated donor; CMV, cytomegalovirus; HLA, human leukocyte antigen

Table 3. Transplant outcomes of the entire cohort

Outcome*	% (95% CI)
Acute graft-versus-host disease*	
Grade II-IV	28 (23-33)
Grade III-IV	9 (6-12)
Chronic graft-versus-host disease[#]	
Overall	28 (23-34)
Extensive	12 (9-17)
Non-relapse mortality[#]	15 (11-19)
Relapse incidence [#]	24 (19-29)
Leukemia-free survival[&]	62 (56-67)
Overall survival[&]	73 (67-78)
Graft-versus-host disease-free and relapse-free survival[&]	48 (42-54)

*180-day cumulative incidence; [#]cumulative incidence at 2 years; [&]survival probability at 2 years.

Table 4. Transplantation Outcomes according to the donor's HLA match

	Univariate analysis*		Multivariate analysis[x]	
Outcome	**8/8 MUD**	**7/8 MMUD**	**HR (95% CI)**	**p-value**
aGVHD grades II–IV	30 (24 - 36)	24 (16 - 33)	1.28 (0.78 – 2.12)	0.3
aGVHD grades III–IV	9 (6 - 13)	8 (4 - 15)	1.1 (0.45 - 2.66)	0.83
cGVHD any grade	27 (21 - 34)	30 (20 - 40)	1 (0.59 - 1.68)	1
cGVHD extensive	15 (10 - 21)	6 (2 - 13)	**2.9 (1.14 – 7.38)**	**0.03**
NRM	14 (9 - 19)	17 (10 - 26)	0.79 (0.42 – 1.5)	0.47
Relapse	23 (17 - 29)	25 (17 - 35)	0.91 (0.54 - 1.54)	0.74
Overall survival	74 (67 - 80)	69 (58 - 78)	0.85 (0.54 – 1.36)	0.51
Disease-free survival	64 (56 - 70)	58 (46 - 67)	0.84 (0.56 – 1.26)	0.4
GRFS	48 (40 - 54)	50 (39 - 60)	1.02 (0.71 – 1.46)	0.92

* Cumulative incidence probability (95% confidence interval) of myeloid engraftment at 40 days, platelet engraftment at 180 days, acute graft-versus-host disease (aGVHD) at 150 days, chronic graft-versus-host disease (cGVHD), non-relapse mortality (NRM) and relapse at 3 years. Probability of overall survival, disease-free survival and graft-versus-host disease and relapse-free survival (GRFS) (95% confidence interval) at 3 years.

[x] 7/8 MMUD donors was the reference group.

Table 5. Multivariate analysis of transplant outcomes according to non-HLA donor-related variables

	Donor age[1]		D/R Sex[2]		D/R CMV[3]	
Outcome	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
aGVHD grades II–IV	**1.3 (1-1.67)**	**0.047**	**1.74 (1.03-2.94)**	**0.04**	0.9 (0.51-1.58)	0.71
aGVHD grades III–IV	**1.66 (1.06-2.59)**	**0.026**	1.46 (0.56-3.8)	0.43	2.34 (0.53-10.28)	0.26
cGVHD any grade	1.15 (0.87-1.51)	0.33	1.7 (0.93-3.11)	0.09	0.92 (0.51-1.66)	0.78
cGVHD extensive	1.24 (0.82-1.89)	0.31	2.09 (0.85-5.13)	0.11	0.6 (0.26-1.38)	0.23
NRM	1.03 (0.72-1.45)	0.89	0.76 (0.31-1.85)	0.54	2.46 (0.86-7.05)	0.09
Relapse	1 (0.75-1.32)	0.99	1.5 (0.85-2.67)	0.16	1.49 (0.77-2.9)	0.24
OS	0.95 (0.73 – 1.22)	0.67	0.87 (0.49 - 1.56)	0.64	1.88 (0.99-3.58)	0.055
LFS	1 (0.81-1.24)	0.98	1.16 (0.72-1.87)	0.53	**1.8 (1.03-3.14)**	**0.038**
GRFS	1.18 (0.97-1.44)	0.09	1.43 (0.94-2.18)	0.09	1.44 (0.9-2.31)	0.13

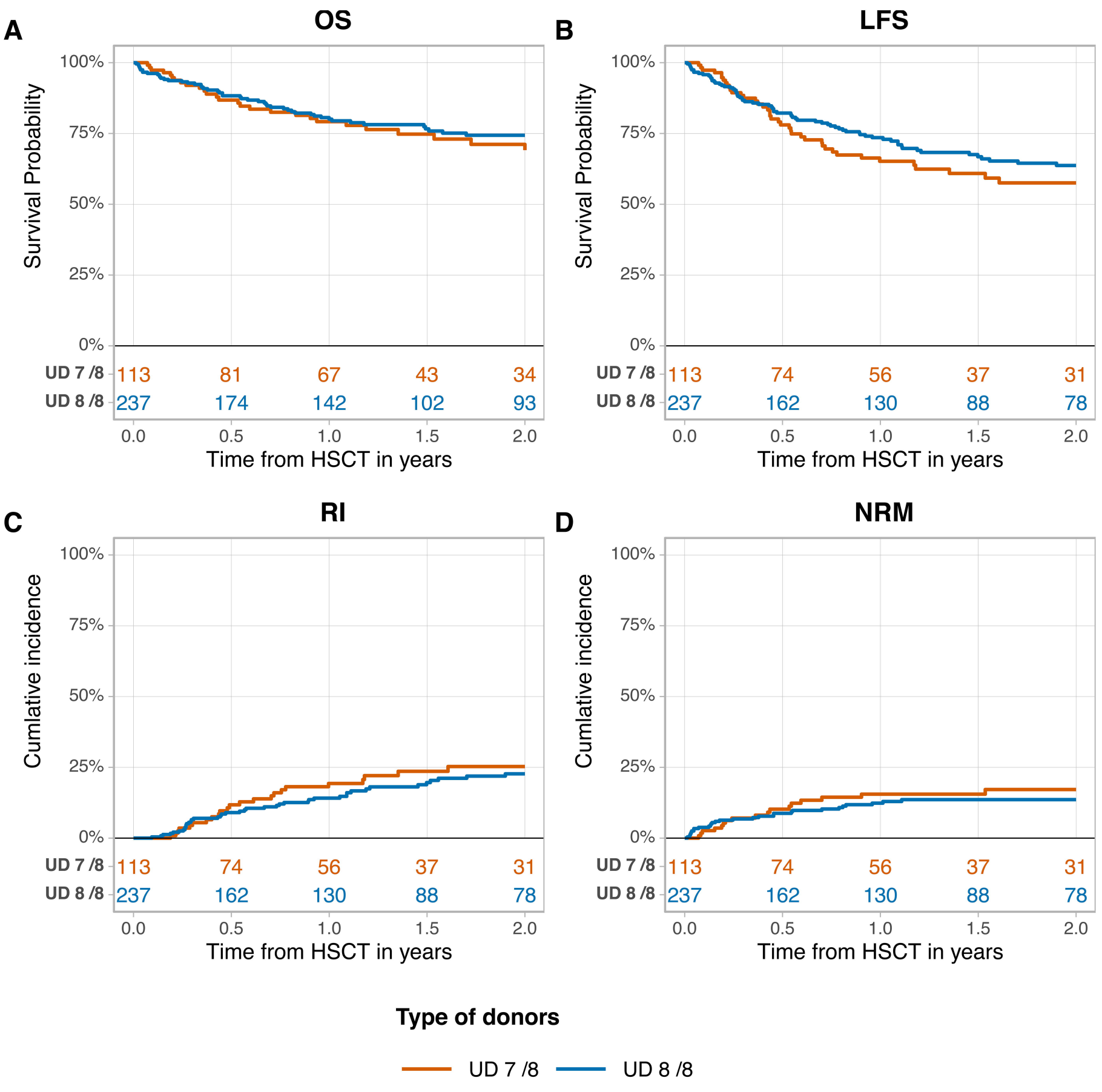
Abbreviations: GvHD, graft-versus-host disease; aGvHD, acute GvHD; cGvHD, chronic GvHD; NRM, non-relapse mortality; LFS, leukemia-free survival; OS, overall survival; GRFS, graft-versus-host disease and relapse-free survival; HR, hazard ratio; CI, confidence interval; D/R, donor/recipient

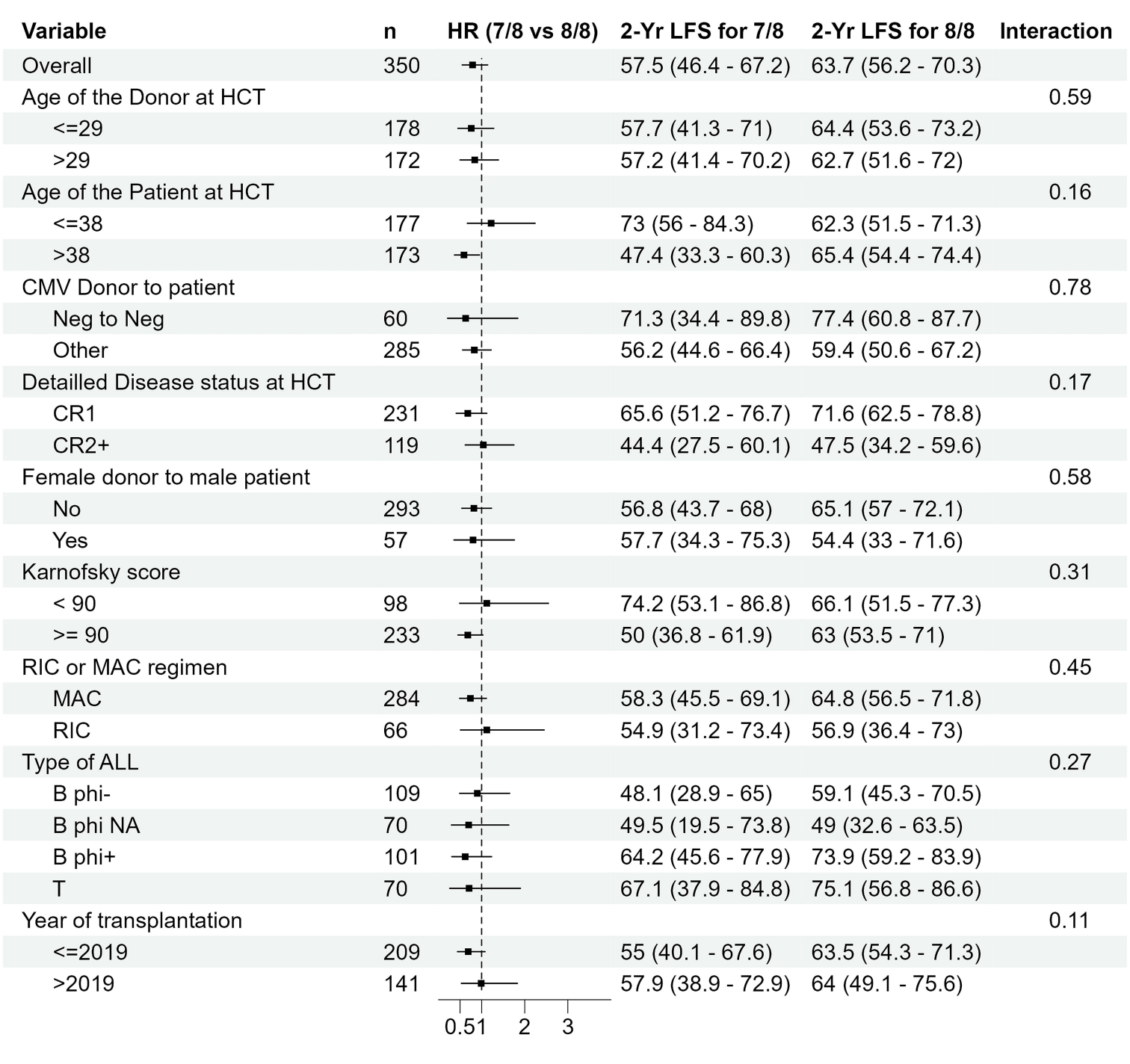
1. Continuous variable
2. Other combination different from female donor to male patient was used as reference group.
3. CMV negative donor to CMV negative patient was used as reference group.

Figure legends

Figure 1. Adjusted transplant outcomes for 8/8 matched or 7/8 mismatched unrelated donors; A: Probability of overall survival (OS); B: Probability of leukemia-free survival (LFS); C: Cumulative incidence of relapse (RI); D: Cumulative incidence non-relapse mortality (NRM).

Figure 2. Forest plot of leukemia-free survival (LFS) for 8/8 matched or 7/8 mismatched unrelated donors within subgroups of patient, disease or transplant characteristics.


A
OS
Survival Probability
100%
75%
50%
25%
0%
UD 7 /8 113 81 67 43 34
UD 8 /8 237 174 142 102 93
0.0 0.5 1.0 1.5 2.0
Time from HSCT in years
B
LFS
Survival Probability
100%
75%
50%
25%
0%
UD 7 /8 113 74 56 37 31
UD 8 /8 237 162 130 88 78
0.0 0.5 1.0 1.5 2.0
Time from HSCT in years
C
RI
Cumlative incidence
100%
75%
50%
25%
0%
UD 7 /8 113 74 56 37 31
UD 8 /8 237 162 130 88 78
0.0 0.5 1.0 1.5 2.0
Time from HSCT in years
D
NRM
Cumlative incidence
100%
75%
50%
25%
0%
UD 7 /8 113 74 56 37 31
UD 8 /8 237 162 130 88 78
0.0 0.5 1.0 1.5 2.0
Time from HSCT in years
Type of donors
UD 7 /8
UD 8 /8


Variable
n
HR (7/8 vs 8/8)
2-Yr LFS for 7/8
2-Yr LFS for 8/8
Interaction
Overall
350
57.5 (46.4 - 67.2)
63.7 (56.2 - 70.3)
Age of the Donor at HCT
0.59
<=29
178
57.7 (41.3 - 71)
64.4 (53.6 - 73.2)
>29
172
57.2 (41.4 - 70.2)
62.7 (51.6 - 72)
Age of the Patient at HCT
0.16
<=38
177
73 (56 - 84.3)
62.3 (51.5 - 71.3)
>38
173
47.4 (33.3 - 60.3)
65.4 (54.4 - 74.4)
CMV Donor to patient
0.78
Neg to Neg
60
71.3 (34.4 - 89.8)
77.4 (60.8 - 87.7)
Other
285
56.2 (44.6 - 66.4)
59.4 (50.6 - 67.2)
Detailled Disease status at HCT
0.17
CR1
231
65.6 (51.2 - 76.7)
71.6 (62.5 - 78.8)
CR2+
119
44.4 (27.5 - 60.1)
47.5 (34.2 - 59.6)
Female donor to male patient
0.58
No
293
56.8 (43.7 - 68)
65.1 (57 - 72.1)
Yes
57
57.7 (34.3 - 75.3)
54.4 (33 - 71.6)
Karnofsky score
0.31
< 90
98
74.2 (53.1 - 86.8)
66.1 (51.5 - 77.3)
>= 90
233
50 (36.8 - 61.9)
63 (53.5 - 71)
RIC or MAC regimen
0.45
MAC
284
58.3 (45.5 - 69.1)
64.8 (56.5 - 71.8)
RIC
66
54.9 (31.2 - 73.4)
56.9 (36.4 - 73)
Type of ALL
0.27
B phi-
109
48.1 (28.9 - 65)
59.1 (45.3 - 70.5)
B phi NA
70
49.5 (19.5 - 73.8)
49 (32.6 - 63.5)
B phi+
101
64.2 (45.6 - 77.9)
73.9 (59.2 - 83.9)
T
70
67.1 (37.9 - 84.8)
75.1 (56.8 - 86.6)
Year of transplantation
0.11
<=2019
209
55 (40.1 - 67.6)
63.5 (54.3 - 71.3)
>2019
141
57.9 (38.9 - 72.9)
64 (49.1 - 75.6)
0.5
1
2
3