Haploidentical Hematopoietic Cell Transplantation Using Post-transplant Cyclophosphamide for Children With Non-malignant Diseases

Hasan Hashem (hasankamalhashem@yahoo.com)
King Hussein Cancer Center (KHCC) https://orcid.org/0000-0002-4681-4726
Rula Najjar
King Hussein Cancer Center
Mayada Abu Shanap
Division of Pediatric Hematology and Oncology and Bone Marrow Transplantation, King Hussein Cancer Center
Eman Khattab
Division of Pediatric Hematology and Oncology and Bone Marrow Transplantation, King Hussein Cancer Center
Rawad Rihani
Division of Pediatric Hematology and Oncology and Bone Marrow Transplantation, King Hussein Cancer Center
Abdelghani Tbakhi
King Hussein Cancer Center
Iyad Sultan
Division of Pediatric Hematology and Oncology and Bone Marrow Transplantation, King Hussein Cancer Center

Research Article

Keywords: Haploidentical, non-malignant diseases, Hematopoietic cell transplantation, HSCT, Primary immunodeficiency, Post-transplant cyclophosphamide

Posted Date: May 17th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-513679/v1

Version of Record: A version of this preprint was published at Journal of Clinical Immunology on August 6th, 2021. See the published version at https://doi.org/10.1007/s10875-021-01113-4.

Abstract

Haploidentical hematopoietic cell transplantation (HCT) is a valuable curative option for children with non-malignant diseases. Haploidentical HCT using post-transplant cyclophosphamide (PTCy) is a readily available option in the absence of an HLA- matched donor. We conducted a retrospective single-center study on the outcome of haploidentical HCT in children with non-malignant diseases. We gathered data from 44 patients underwent HCT in the period 2015 to 2020. The indications for HCT were bone marrow failure, primary immunodeficiency, metabolic disorders, and hemoglobinopathy. Median age at HCT was 4 years (range 0.7-20).The conditioning regimens were myeloablative (n=16), or reduced intensity (n=26). After a median follow-up of 20 months (range 4-71), 2-year overall survival was 89% and 2 year GvHD-free relapse-free survival (GRFS) was 66%. Incidence of primary graft failure was 13.6%. Cumulative incidence of grade II-IV acute and moderate/severe chronic GvHD were 20% and 6.4%, respectively. Younger age at HCT (<5 years) and primary immunodeficiency were significantly associated with better GRFS (p <0.05). In conclusion, haploidentical HCT using PTCy is feasible and curative in children with non-malignant diseases lacking an HLA-matched donor. Early diagnosis and referral in addition to timely treatment can further improve outcomes.

Introduction:

Allogeneic hematopoietic cell transplantation (HCT) is curative for a variety of non-malignant diseases, including primary immunodeficiency (PID), bone marrow failure (BMF), and metabolic disorders.[1–5] However, finding a donor can be a barrier for HCT; as many patients do not have a suitable HLA-matched related donor. Moreover, the chance of finding an HLA-matched unrelated donor for some ethnic groups remains low (http://bethematch.org).[6]

Haploidentical HCT has become an alternative donor source for patients who do not have an HLA-matched donor that is readily available for almost all patients. Nevertheless, graft failure (GF) and graft-versus-host-disease (GvHD) are the main barriers for haploidentical HCT.[7,8] In more recent years, T-cell replete haploidentical HCT using post-transplant cyclophosphamide (PTCy) has emerged as a promising strategy, and is being used more frequently due to availability, safety profile, and low cost of the procedure.[9] This approach relies on cyclophosphamide to eliminate both donor and host alloreactive T-cells to reduce the risk of both GF and GvHD.[10,11] Moreover, hematopoietic stem cells are protected from the cytotoxic effects of PTCy due to higher amounts of aldehyde dehydrogenase, an enzyme responsible for metabolizing the drug.[12,13]

Over the last decade, haploidentical HCT with PTCy has been increasingly used for patients with non-malignant diseases with variable outcomes.[14–22] This increase is attributed to improvement in diagnostic testing including genetic testing, the increased use of reduced toxicity regimens, improvement in supportive care, and donor pool expansion. Here, we describe patient and transplant characteristics and outcomes after haploidentical HCT with PTCy in 44 children with non-malignant diseases.

Patients And Methods:

Patients:

This retrospective study included 44 patients < 21 years of age who underwent haploidentical hematopoietic cell transplantation (HCT) using post-transplant cyclophosphamide (PTCy) at our center between January 2015 and December 2020. The study was approved by the institutional review board of our institution. Indications for HCT were a variety of non-malignant diseases (Table 1). All patients received mycophenolate mofetil and tacrolimus or cyclosporine A starting day + 5 post HCT as GvHD prophylaxis. All HCTs were supported with granulocyte-colony-stimulating factor (G-CSF) starting from day + 5 post HCT.

Table 1
Indications for hematopoietic cell transplantation

Indication for transplant, n (%)	N = 44 (100%)
Primary immunodeficiency	16/44 (36.3%)
Chronic granulomatous disease	4/44 (9%)
Severe combined immunodeficiency	3/44 (6.9%)
Leukocyte adhesion deficiency	2/44 (4.5%)
Severe congenital neutropenia	2/44 (4.5%)
Hyper IgM syndrome	2/44 (4.5%)
Autoimmune lymphoproliferative syndrome	1/44 (2.2%)
Hyper IgE syndrome	1/44 (2.2%)
Griscelli syndrome	1/44 (2.2%)
Severe aplastic anemia	14/44 (32%)
Inherited bone marrow failure	8/44 (18.2%)
Fanconi anemia	5/44 (11.1%)
Congenital amegakaryocytic thrombocytopenia	3/44 (6.9%)
Metabolic disorder	4/44 (9%)
Cerebral adrenal leukodystrophy	2/44 (4.5%)
Mucopolysaccharidosis type II	1/44 (2.2%)
Osteopetrosis	1/44 (2.2%)
Hemoglobinopathy	2/44 (4.5%)
Beta-Thalassemia major	1/44 (2.2%)
Sickle cell disease	1/44 (2.2%)

Definitions and outcomes:

Endpoints studied included neutrophil and platelet recovery, graft failure, acute and chronic GvHD, GvHD-free relapse-free survival (GRFS) and overall survival. Neutrophil recovery was defined as achieving an absolute neutrophil count (ANC) $\geq 0.5 \times 10^9$/L for three consecutive days. Platelet recovery was defined as achieving platelets $\geq 20 \times 10^9$/L, unsupported for 7 days. The diagnosis and grading of acute and chronic GVHD were based on international standard criteria.[23,24] Graft failure (GF) was defined as either

failure to show neutrophil recovery or whole blood donor chimerism < 5% beyond day 30 after HCT (primary GF) or complete loss of donor cells (< 5% donor cells) after initial engraftment (secondary GF). Preparative regimens were classified as myeloablative (MAC) or reduced intensity (RIC) if the dose of alkylating agents or TBI is reduced by at least 30% from a MAC approach.[25,26]

Statistical analysis:

Kaplan–Meier curves were plotted for overall survival (OS), GvHD-free relapse-free survival (GRFS), and *p* values were obtained for Mantel-Cox log-rank tests performed using R; version 4.0.3. Values of $p < 0.05$ were considered statistically significant. GRFS was calculated as the time from first HCT until the first occurrence of any of the following events: GF, disease relapse, death, grade 3–4 aGvHD or moderate/severe cGvHD. Cox regression model was built to examine for factors associated with GRFS and OS. Variables tested included age at HCT (< 5 years versus > 5 years), conditioning regimen intensity (MAC versus RIC), serotherapy use, thiotepa use, CD34 stem cell dose, CD3 cell dose, type of disease (PID versus others), stem cell source (bone marrow versus peripheral blood), ABO matching, gender matching, and donor age. The cumulative incidence of GvHD were also calculated using competing risk analysis, using R; version 4.0.3.

Results:

Patient and transplant characteristics

The characteristics of 44 patients studied including transplant characteristics are depicted in Table 2. Median age at HCT was 4 years (range 0.7–20). MAC regimens were used in 17/44 (39%) patients and RIC in 27/44 (61%) patients. Fludarabine, cyclophosphamide and TBI 2–4 Gy with or without thiotepa +/- antithymocyte globulin (ATG) was the predominant regimen in 18 patients (41%). Bone marrow was used as stem cell source in 18/44 (41%) patients and peripheral blood in 26/44 (59%) patients. Serotherapy was used in 37/44 (84%) patients (35 patients received rabbit ATG and 2 received alemtuzumab). The median follow-up in surviving patients was 20 months (range 4–71).

Table 2
Summary of patients and transplant characteristics

	All patients / all HCT procedures	Died	Graft failure
Number of patients	44	5	8
Number of HCT/procedures	47		
Median age at HCT, years (range)	4 (0.7–20)	9 (0.75-17)	4 (0.75-13)
M:F	1.6:1	0.66:1	1.6:1
Underlying disease			
Primary immunodeficiency	16/44 (36%)		
Severe aplastic anemia	14/44 (32%)	3/14 (21%)	5/14 (36%)
Inherited bone marrow failure	8/44 (18%)	1/8 (12.5%)	1/8 (12.5%)
Metabolic disorder	4/44 (9%)	1/4 (25%)	2/4 (50%)
Hemoglobinopathy	2/44 (5%)		
Donor relationship			
Parent	33/44 (75%)	3/33 (9%)	6/33 (18%)
Sibling	11/44 (25%)	2/11 (18%)	2/11 (18%)
Median donor age (y) (range)	25.5 (3–55)	20 (13–42)	31.5 (3–50)
ABO compatibility			
Yes	29/44 (66%)	5/29 (17%)	6/29 (20%)
No	15/44 (34%)		2/15 (13%)
Stem cell source			
PB	26/44 (59%)	4/26 (15%)	4/26 (15%)

ATG: anti-thymocyte globulin; BM: bone marrow; Bu: busulfan; Cy: cyclophosphamide; F: female; Flu: fludarabine; HCT: hematopoietic stem cell transplantation; M: male; Mel: melphalan; PB: peripheral blood; TBI: total body irradiation; TT: thiotepa

	All patients / all HCT procedures	Died	Graft failure
BM	18/44 (41%)	1/18 (6%)	4/18 (22%)
Median CD34 + cell dose *10^6/kg (n = 44) (range)	10.3 (3.8–24.3)	10 (7-15.9)	11.9 (7-15.9)
Conditioning regimen			
Flu – Mel	2/44 (5%)		
Flu – Mel - TBI	10/44 (23%)		
Flu – Mel - TT	2/44 (5%)		1/2 (50%)
Flu – TBI	5/44 (11%)	1/5 (20%)	
Flu – Cy - TBI	9/44 (20%)	1/9 (11%)	4/9 (44%)
Flu – Cy – TT - TBI	9/44 (20%)	2/9 (22%)	1/9 (11%)
Flu - Bu	1/44 (2%)		1/1 (100%)
Flu – Bu - TT	6/44 (14%)	1/6 (17%)	1/6 (16%)
Serotherapy			
ATG	35/44 (80%)	3/35 (9%)	7/35 (20%)
Alemtuzumab	2/44 (5%)		
None	7/44 (15%)	2/7 (29%)	1/7 (14%)
Sex matching			
Match sex	27/44 (61%)	2/27 (7%)	4/27 (15%)
M - F	8/44 (18%)	1/8 (13%)	2/8 (25%)
F - M	9/44 (21%)	2/9 (22%)	2/9 (22%)

ATG: anti-thymocyte globulin; BM: bone marrow; Bu: busulfan; Cy: cyclophosphamide; F: female; Flu: fludarabine; HCT: hematopoietic stem cell transplantation; M: male; Mel: melphalan; PB: peripheral blood; TBI: total body irradiation; TT: thiotepa

Engraftment and graft failure

Median time to neutrophil engraftment was on day + 12 (range 10–26) and for platelet engraftment was on day + 18 (range 12–52). Full donor chimerism was confirmed in 36/42 evaluable patients (86%). Two patients died before chimerism evaluation (SAA x 1, and osteopetrosis x 1). Primary graft failure (GF) was observed in 6 patients (13.6%) and secondary GF in 2 patients. Six of the 8 patients with GF had severe aplastic anemia (SAA) and 3 out of these (50%) had strong donor-specific antibodies. Four of the 8 patients with GF underwent a second HCT. All surviving patients had full donor chimerism at last follow-up except for 5 patients with mixed donor chimerism (SCID x 3, CGD x 1, and thalassemia x 1).

Overall survival and GvHD-free relapse-free survival

After a median follow-up of 20 months (range 4–71), 39 of the 44 patients are alive and disease-free. The causes of death for the 5 patients (11%) were sepsis in 3 patients, intracranial hemorrhage in 1 patient and diffuse alveolar hemorrhage in another patient. Three of the 5 deaths were related to primary GF. The 2-year overall survival for the whole cohort was 89% and the 2-year GRFS was 66% (Fig. 1a). The analysis of factors associated with GRFS showed that younger age at HCT (< 5 years, $p = 0.01$) and primary immunodeficiency ($p = 0.048$) were associated with less events. There was a trend toward improved OS with younger age (p = 0.076) and PID (p = 0.07) but did not reach statistical significance (Fig. 2).

Post-transplant complications

Four patients (9%) developed moderate hepatic sinusoidal obstruction syndrome (SOS) and all were treated with defibrotide. There was no severe SOS. Acute GvHD grade 2–4 was observed in 9/44 (20%) patients. Most cases of aGvHD were mild (grade 2: n = 7, grade 3: n = 2) and most of these were skin aGvHD except for the 2 patients with grade 3 aGvHD in skin and gut (Fig. 1b). Chronic GvHD was observed in 10/44 (22%) patients. cGvHD was mild in 8 patients, moderate in 1 and severe in 1 patient (Fig. 1b). The cumulative incidences of systemic CMV reactivation, BK hemorrhagic cystitis, and EBV viremia were 55%, 20%, and 16%, respectively. All infections were treated successfully with no long-term complications. There was no CMV disease. Only 2 of 7 patients with EBV viremia required antiviral therapy and none required rituximab. No patients had developed EBV-related lymphoproliferative disease (PTLD).

Discussion:

We show here that haploidentical HCT using PTCy is feasible and effective in treating non-malignant diseases, after a median follow-up of 20 months (range 4–71). The 2-year OS for patients with a variety of non-malignant diseases, including PID, inherited BMF syndromes, SAA, metabolic disorders, and hemoglobinopathy, was 89%. The 2-year GRFS in our cohort of 44 patients was 66%.

Our data compares favorably to the published literature on haploidentical HCT for children with non-malignant diseases. There are 4 relatively recent publications with more than 10 patients describing

outcomes of haploidentical HCT in children with a variety of non-malignant diseases. In the study by Uppuluri and colleagues, 16 patients underwent haploidentical HCT for PID, at a median follow-up of 23.3 months, OS was 62.5% and grade II-IV was 50%.[20] Benedicte et al. have reported the outcomes of haploidentical HCT for 27 patients with OS of 77% and grade II-IV aGvHD of 46% at a median follow-up of 25.6 months.[19] Malhi and colleagues have reported the results of 23 patients using haploidentical HCT. After a median follow-up of 2.5 years, OS and EFS were 91% and 78%, respectively. Grade II-IV aGvHD was 78%.[21] Olaya M et al. have reported outcomes of 47 patients with inborn errors of immunity using different donors. Nineteen patients underwent haploidentical HCT with an OS of 72%.[15]

In a univariate analysis model, the only factors associated with a better GRFS were transplantation at an age younger than 5 years and PID as an indication for HCT.[27] This could reflect that early recognition and diagnosis of these diseases leads to less severe post-HCT complications with better survival outcomes. Active infections at the time of HCT have been known to be associated with poor survival in patients with PID. Moreover, we show that particularly patients with PID had 100% overall survival compared to other non-malignant diseases in our cohort. Although we did not find a significant improvement in survival over time, this could relate to allowing patients with more severe diseases to have access to transplant.

Eight patients developed GF. Four of the 8 patients proceeded to second HCT and are alive. Only age at HCT (after 5 years) showed a significant association with higher incidence of graft failure. Most patients with GF were transplanted for SAA (n = 6). This could be attributed to the risk of transfusion-induced sensitization to the HLA-haploidentical grafts.[28,29] Interestingly, 3 out the 6 patients with SAA and GF had strong donor-specific antibodies and despite desensitization with intravenous immunoglobulins (IVIG), rituximab and plasmapheresis, they succumbed to GF. The limited sample size does not allow us to derive definitive recommendation on transplant conditioning regimen. The desire to lower toxicity and end organ damage is highly desirable when HCT is offered to children with non-malignant diseases. We did not show that RIC is associated with more GF. Hence, using RIC in patients with certain non-malignant diseases such as PID should be further investigated in prospective manner.

There is a general agreement that the incidence of acute and chronic GvHD must be kept to a minimum for HCT for non-malignant diseases. We observed an acceptable rates of GvHD as most of the patients had only grade 1 aGvHD and mild chronic GvHD. Haploidentical HCT using PTCy along with using serotherapy contributed to the low rates of GvHD in our cohort with no mortality from viral infections. The near universal approach in our center of using *in vivo* T-cell depletion prevented us from studying this further.

One limitation of our study is the retrospective design. Second, non-malignant diseases are a heterogeneous group with a diverse pathophysiology, making it difficult to select the best conditioning regimen for each disease.

In conclusion, our data show that in resource limited settings, and when HLA-identical donors are not available, haploidentical HCT using PTCy, is feasible and effective in curing children with various non-

malignant diseases with acceptable rates of GvHD. GF remains an obstacle especially when anti-HLA antibodies are strongly present due to transfusion-induced sensitization, despite using desensitization techniques. With the expansion of HCT in children with non-malignant diseases and the improved outcomes and long-term survival, conditioning regimens can be further modified so as to ensure intact survival and low rates of GF. Reduced intensity conditioning needs to be further studied prospectively especially in patients with primary immunodeficiency.

Declarations:

Acknowledgements: we thank the patients and their families.

Funding: none

Conflict of interest statement: the authors declare no conflict of interest

Data availability: The data that support the findings of this study are available upon request from the corresponding author

Authors' contributions: HH and IS collected, analyzed, and interpreted data, and wrote the manuscript; HH, RN, MA, EK, RR, AT, IS reviewed and edited the manuscript. All authors edited and approved the final version of the manuscript.

Ethical approval: institutional review board at our institution approved the current study

References:

1. Steward CG. Hematopoietic stem cell transplantation for osteopetrosis. *Pediatr Clin North Am*. 2010;57(1):171–180. doi:10.1016/j.pcl.2009.11.006.
2. Shenoy S, Boelens JJ. Advances in unrelated and alternative donor hematopoietic cell transplantation for nonmalignant disorders. *Curr Opin Pediatr*. 2015;27(1):9–17. doi:10.1097/MOP.0000000000000179.
3. Bertaina A, Pitisci A, Sinibaldi M, Algeri M. T Cell-Depleted and T Cell-Replete HLA-Haploidentical Stem Cell Transplantation for Non-malignant Disorders. *Curr Hematol Malig Rep*. 2017;12(1):68–78. doi:10.1007/s11899-017-0364-3.
4. Alter BP. Inherited bone marrow failure syndromes: Considerations pre- and posttransplant. *Hematology*. 2017;2017(1):88–95. doi:10.1182/asheducation-2017.1.88.
5. Gennery AR, Albert MH, Slatter MA, Lankester A. Hematopoietic Stem Cell Transplantation for Primary Immunodeficiencies. *Front Pediatr*. 2019;7(October):7–10. doi:10.3389/fped.2019.00445.
6. Gragert L, Eapen M, Williams E, et al. HLA Match Likelihoods for Hematopoietic Stem-Cell Grafts in the U.S. Registry. *N Engl J Med*. 2014;371(4):339–348. doi:10.1056/nejmsa1311707.

7. Brodsky RA, Luznik L, Bolaños-Meade J, Leffell MS, Jones RJ, Fuchs EJ. Reduced intensity HLA-haploidentical BMT with post transplantation cyclophosphamide in nonmalignant hematologic diseases. *Bone Marrow Transplant*. 2008;42(8):523–527. doi:10.1038/bmt.2008.203.
8. Gennery AR, Slatter MA, Grandin L, et al. Transplantation of hematopoietic stem cells and long-term survival for primary immunodeficiencies in Europe: Entering a new century, do we do better? *J Allergy Clin Immunol*. 2010;126(3). doi:10.1016/j.jaci.2010.06.015.
9. Mussetti A, Greco R, Peccatori J, Corradini P. Post-transplant cyclophosphamide, a promising anti-graft versus host disease prophylaxis: where do we stand? *Expert Rev Hematol*. 2017;10(5):479–492. doi:10.1080/17474086.2017.1318054.
10. Luznik L, O P V, Fuchs Ephraim J. Post-transplantation cyclophosphamide for tolerance induction in HLA-haploidentical BMT Graft failure, graft-versus-host disease, and infection: the Devil's Triangle. 2013;39(6):1–16. doi:10.1053/j.seminoncol.2012.09.005.Post-transplantation.
11. Al-Homsi AS, Roy TS, Cole K, Feng Y, Duffner U. Post-transplant high-dose cyclophosphamide for the prevention of graft-versus-host disease. *Biol Blood Marrow Transplant*. 2015;21(4):604–611. doi:10.1016/j.bbmt.2014.08.014.
12. Luznik L, Jalla S, Engstrom LW, Lannone R, Fuchs EJ. Durable engraftment of major histocompatibility complex-incompatible cells after nonmyeloablative conditioning with fludarabine, low-dose total body irradiation, and posttransplantation cyclophosphamide. *Blood*. 2001;98(12):3456–3464. doi:10.1182/blood.V98.12.3456.
13. Kanakry CG, Ganguly S, Zahurak M, et al. Aldehyde dehydrogenase expression drives human regulatory T cell resistance to posttransplantation cyclophosphamide. *Sci Transl Med*. 2013;5(211). doi:10.1126/scitranslmed.3006960.
14. Bahr TL, Lund T, Sando NM, Orchard PJ, Miller WP. Haploidentical transplantation with post-transplant cyclophosphamide following reduced-intensity conditioning for osteopetrosis: Outcomes in three children. *Bone Marrow Transplant*. 2016;51(11):1546–1548. doi:10.1038/bmt.2016.180.
15. Olaya M, Franco A, Chaparro M, et al. Hematopoietic Stem Cell Transplantation in Children with Inborn Errors of Immunity: a Multi-center Experience in Colombia. *J Clin Immunol*. 2020;40(8):1116–1123. doi:10.1007/s10875-020-00856-w.
16. Kurzay M, Hauck F, Schmid I, et al. T-cell replete haploidentical bone marrow transplantation and post-transplant cyclophosphamide for patients with inborn errors. *Haematologica*. 2019;104(10):E478–E482. doi:10.3324/haematol.2018.215285.
17. Klein OR, Chen AR, Gamper C, et al. Alternative-Donor Hematopoietic Stem Cell Transplantation with Post-Transplantation Cyclophosphamide for Nonmalignant Disorders. *Biol Blood Marrow Transplant*. 2016;22(5):895–901. doi:10.1016/j.bbmt.2016.02.001.
18. Rastogi N, Katewa S, Thakkar D, Kohli S, Nivargi S, Yadav SP. Reduced-toxicity alternate-donor stem cell transplantation with posttransplant cyclophosphamide for primary immunodeficiency disorders. *Pediatr Blood Cancer*. 2018;65(1):2–5. doi:10.1002/pbc.26783.

19. Neven B, Diana JS, Castelle M, et al. Haploidentical Hematopoietic Stem Cell Transplantation with Post-Transplant Cyclophosphamide for Primary Immunodeficiencies and Inherited Disorders in Children. *Biol Blood Marrow Transplant*. 2019;25(7):1363–1373. doi:10.1016/j.bbmt.2019.03.009.
20. Uppuluri R, Sivasankaran M, Patel S, et al. Haploidentical Stem Cell Transplantation with Post-Transplant Cyclophosphamide for Primary Immune Deficiency Disorders in Children: Challenges and Outcome from a Tertiary Care Center in South India. *J Clin Immunol*. 2019;39(2):182–187. doi:10.1007/s10875-019-00600-z.
21. Mallhi KK, Srikanthan MA, Baker KK, et al. HLA-Haploidentical Hematopoietic Cell Transplantation for Treatment of Nonmalignant Diseases Using Nonmyeloablative Conditioning and Post-Transplant Cyclophosphamide. *Biol Blood Marrow Transplant*. 2020;26(7):1332–1341. doi:10.1016/j.bbmt.2020.03.018.
22. Even-Or E, NaserEddin A, Dinur Schejter Y, Shadur B, Zaidman I, Stepensky P. Haploidentical stem cell transplantation with post-transplant cyclophosphamide for osteopetrosis and other nonmalignant diseases. *Bone Marrow Transplant*. 2021;56(2):434–441. doi:10.1038/s41409-020-01040-9.
23. Rowlings PA, Przepiorka D, Klein JP, et al. IBMTR Severity Index for grading acute graft-versus-host disease: Retrospective comparison with Glucksberg grade. *Br J Haematol*. 1997;97(4):855–864. doi:10.1046/j.1365-2141.1997.1112925.x.
24. Lee SJ. Classification systems for chronic graft-versus-host disease. *Blood*. 2017;129(1):30–37. doi:10.1182/blood-2016-07-686642.
25. Bacigalupo A, Ballen K, Rizzo D, et al. Defining the intensity of conditioning regimens: working definitions. *Biol Blood Marrow Transplant*. 2009;15(12):1628–33. doi:10.1016/j.bbmt.2009.07.004.
26. Gyurkocza B, Sandmaier BM. Conditioning regimens for hematopoietic cell transplantation: One size does not fit all. *Blood*. 2014;124(3):344–353. doi:10.1182/blood-2014-02-514778.
27. Slatter MA, Gennery AR. Hematopoietic cell transplantation in primary immunodeficiency–conventional and emerging indications. *Expert Rev Clin Immunol*. 2018;14(2):103–114. doi:10.1080/1744666X.2018.1424627.
28. Ciurea SO, De Lima M, Cano P, et al. High risk of graft failure in patients with anti-hla antibodies undergoing haploidentical stem-cell transplantation. *Transplantation*. 2009;88(8):1019–1024. doi:10.1097/TP.0b013e3181b9d710.
29. Ciurea SO, Cao K, Fernadez-Vina M, et al. The European Society for Blood and Marrow Transplantation (EBMT) Consensus Guidelines for the Detection and Treatment of Donor-specific Anti-HLA Antibodies (DSA) in Haploidentical Hematopoietic Cell Transplantation. *Bone Marrow Transplant*. 2018;53(5):521–534. doi:10.1038/s41409-017-0062-8.

Figures

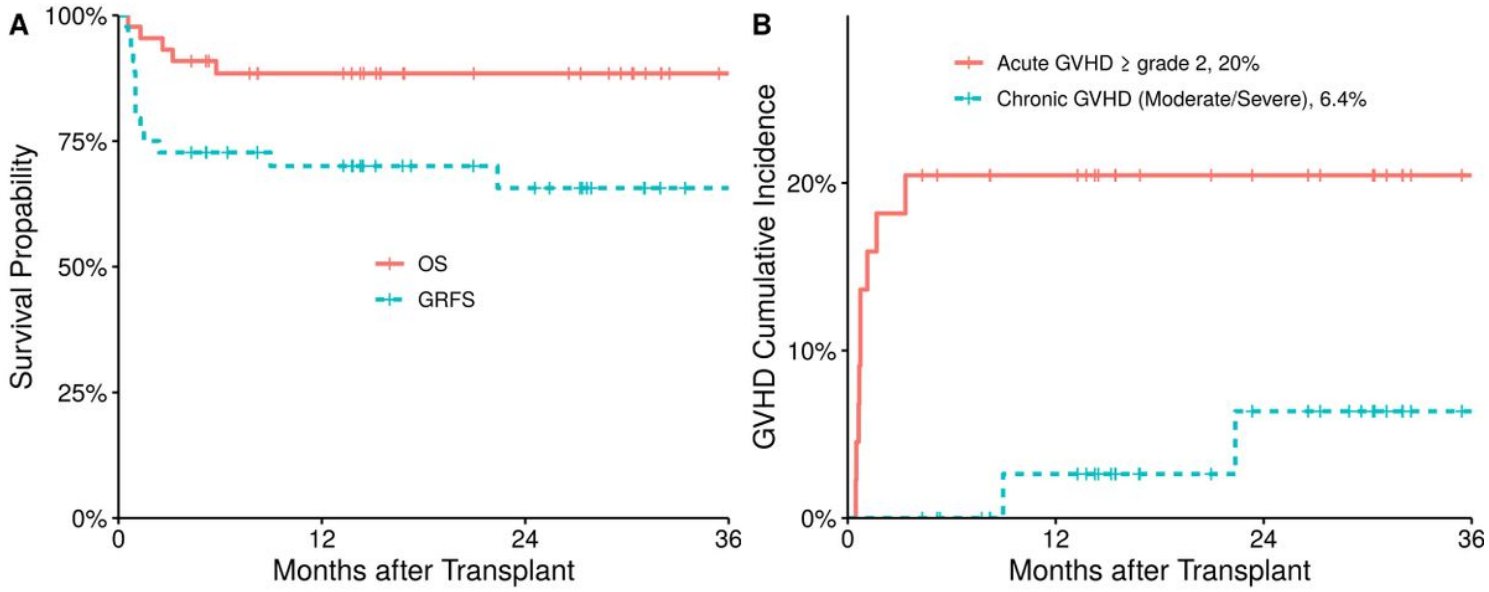

Figure 1

Kaplan-Meier survival curve analysis representing: A) overall survival of 89% and GvHD-free relapse-free survival (GRFS) of 66%. Events are defined as death, graft failure, disease relapse, acute GvHD grade III-IV, chronic GvHD moderate or severe; B) Cumulative incidence of grade II-IV acute GvHD and moderate/severe GvHD

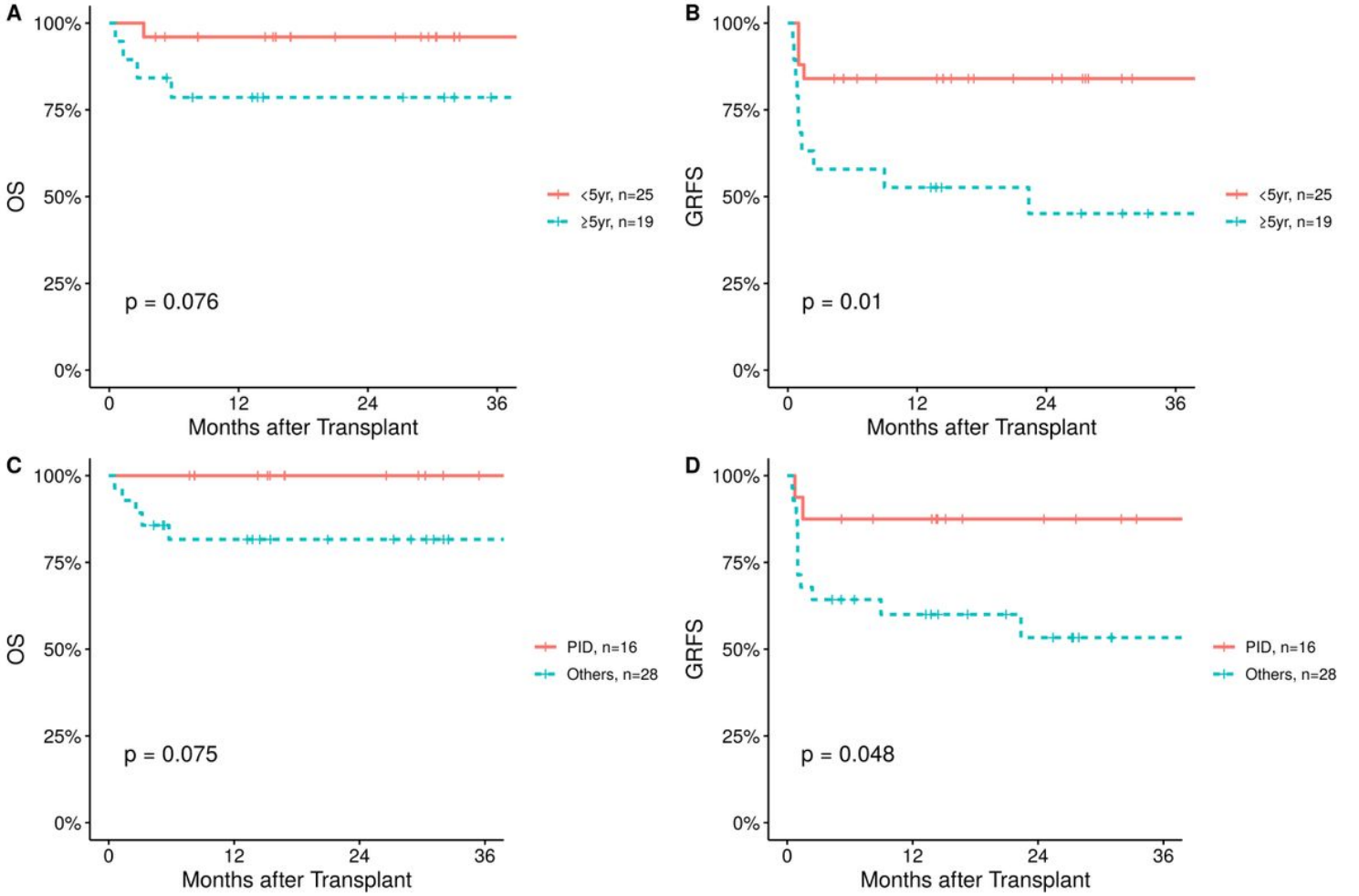

Figure 2

Kaplan-Meier survival curve analysis representing: A) overall survival (OS) by age (<5 years vs > 5 years); B) GvHD-free relapse-free survival (GRFS) by age; C) OS by indication for HCT (PID versus others); D) GRFS by indication for HCT