Transplantation Publish Ahead of Print

DOI: 10.1097/TP.0000000000003342

Comparable Outcomes Between Unrelated and Haploidentical Stem Cell Transplantation in Adult Patients With Severe Aplastic Anemia

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Financial Disclosure: The authors declare no funding was received for this study.

Disclaimer: The authors declare no conflicts of interest.

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List of abbreviations

SAA, severe aplastic anemia

SCT, stem cell transplantation

MSD, matched sibling donor

IST, immunosuppressive therapy

URD, unrelated donor

HAPLO, haploidentical related donor

WM-URD, well matched-unrelated donor

OS, overall survival

MM-URD, mismatched-unrelated donor

BM, bone marrow

G-CSF, granulocyte colony-stimulating factor

PB, peripheral blood

VSAA, very severe aplastic anemia

TBI, total body irradiation

GVHD, graft-versus-host disease

ATG, antithymocyte globulin

ANC, absolute neutrophil count

SOS, sinusoidal obstructive syndrome

GF, graft failure

IFD, invasive fungal disease

CMV, cytomegalovirus,

FFS, failure-free survival

TRM, transplant-related mortality

HR, hazard ratio

Abstract

Backgrounds: Regarding patients with severe aplastic anemia (SAA) who fail immunosuppressive therapy and lack an HLA-matched sibling donor (MSD), the best alternative donor including unrelated (URD) and haploidentical (HAPLO) donors for allogeneic stem cell transplantation (SCT) remains to be established.

Methods: We analyzed the comprehensive outcomes of 153 consecutive adult SAA patients treated with SCT from alternative donors: 73 HLA-well matched (8/8) URDs (WM-URDs), 34 mismatched (6-7/8) URDs (MM-URDs), and 46 HAPLOs.

Results: Neutrophil/platelet engraftments were achieved at a median of 11/15 days for WM-URDs, 13/16.5 days for MM-URDs, and 12/14 days for HAPLOs, respectively. The 3-year overall survival (OS), failure-free survival, cumulative incidence of graft-failure, and transplant-related mortality were statistically not different among the 3 groups: 90.3%, 87.5%, 2.7%, and 9.8% for WM-URDs; 85.3%, 81.7%, 0%, and 14.7% for MM-URDs, and 84.4%, 82.3%, 6.5%, and 11.2% for HAPLOs, respectively. The rates of other complications, including graft-versus-host disease, cytomegalovirus DNAemia, hemorrhagic cystitis, invasive fungal disease, secondary malignancies, and sinusoidal obstruction syndrome, were also statistically not different. Subgroup analysis of the MM-URD group showed that the 3-year OS of patients receiving SCTs from 6/8-URDs were worse than those receiving SCTs from 7/8-URDs (75.0% vs. 94.4%, p=0.26).

Conclusion: There was no significant difference in the SCT outcomes with WM-URDs, MM-URDs, or HAPLO donors. The clinician can make the best choice among these alternative donor sources based on the host/donor features and the urgency of the need for SCT. However, the selection of 6/8-URDs should be avoided due to inferior survival outcomes.

Introduction

Severe aplastic anemia (SAA) is a hematopoietic stem cell disorder characterized by pancytopenia and hypocellular bone marrow. It can be life-threatening because of fatal infections and/or hemorrhage related to the disease course. The standard treatments for SAA include allogeneic hematopoietic stem cell transplantation (SCT) from an HLA-matched sibling donor (MSD) or immunosuppressive therapy (IST).[1,2] SCT from an alternative donor, including an unrelated (URD) or haploidentical related donor (HAPLO), is considered a treatment option for patients who fail to respond to IST and who lack an MSD.[2,3]

In accordance with the classic principle that HLA compatibility is a major factor determining the outcomes of SCT, a well-matched (WM)-URD has been suggested as an alternative donor choice for SCT for various hematological diseases.[4] Even with specific cohort of SAA patients, the superiority of the use of HLA-matched donors over that of HLA-mismatched donors has been reported in several previous studies.[5] However, the search for a WM-URD can be time-consuming, and the probability of finding a WM-URD is approximately 50%.[6] Unlike URD SCT, HAPLO SCT could be a favorable option because of the ready availability of a related donor for SCT without the need to search for a donor and the subsequent use of adoptive cellular immunotherapy.[7] Moreover, the current results of HAPLO SCT are promising. A European group reported an average 1-year survival rate of approximately 74%.[2] Our previous study also demonstrated good outcomes, as indicated by an 88.2% 1-year overall survival (OS) rate in a prospectively designed study.[8] Nevertheless, HAPLO SCTs are still regarded as experimental owing to the relatively limited number of studies and uncertain long-term outcomes.[9]

Considering the increased ease in securing a HAPLO donor than a URD, the technological advances in HAPLO SCTs, and the classical importance of HLA compatibility, a study identifying optimal alternative donors needs to be performed. Thus, to compare and

investigate the most optimal alternative donors among WM-URDs, mismatched (MM)-URDs, and HAPLOs for adult patients with acquired SAA, we conducted a retrospective cohort study.

Materials and Methods

Patient selection

Among 338 consecutive adult patients with SAA who received allogeneic SCTs between March 2002 and May 2018 at our center, 153 patients who received SCTs from alternative donors were enrolled in the study cohort: 73 with WM-URDs, 34 with MM-URDs, and 46 with HAPLOs. The data were analyzed in May 2019. This study was approved by the Institutional Review Board of the Catholic University of Korea (KC18RESI0765) and was conducted in accordance with the Declaration of Helsinki.

The alternative donor types and stem cell sources for the SCTs in the current study were selected according to the strategy used at our center as follows.[3,8,10] (i) All patients had failed IST prior to SCT and did not have a suitable MSD. (ii) A URD was first considered as the alternative donor according to a policy of the Korean Network for Organ Sharing. URDs with antigen mismatches at the level of HLA-A, B, or DR and the combined mismatch of the HLA-C antigen plus 2 alleles were strictly excluded as alternative SCT donors.[10,11] (iii) Although bone marrow (BM) was our preferred graft source for URD SCTs, the choice of the stem cell source between BM and granulocyte colony-stimulating factor (G-CSF)-mobilized peripheral blood (PB) stem cells was solely determined according to the potential URD donor.[10] (iv) For SCT with MM-URD and HAPLO SCT, all patients had been evaluated for the presence of donor specific HLA antibodies (DSA) since July 2013. We have excluded HLA-mismatched donor whose HLA presented strong results for DSA since September 2013 (see Definitions). (v) HAPLO was allowed as a first-line treatment in cases requiring an urgent SCT, including those presented as very severe aplastic anemia (VSAA) with no MSD or potential URD donors.[8] (vi) All HAPLO SCTs used T-cell-replete PB stem cells as a graft source.

Transplantation procedure, GVHD prophylaxis, and supportive care

For patients receiving URD SCTs, a conditioning regimen consisting of total body irradiation (TBI, fractionated 800 or 600 cGy during D-4 and D-5) and cyclophosphamide (50-60 mg/kg/day for 2 days on D-3 and D-2) was used for all patients. Based on our previous study[10] and experience with de-escalating the conditioning intensity, the dose of cyclophosphamide was reduced from 120 mg/kg to 100 mg/kg in January 2010, and the TBI dose was also changed from 800 cGy to 600 cGy in December 2014. All patients who received HAPLO SCTs were administered a conditioning regimen with TBI (fractionated 800 or 600 cGy during D-7 and D-8) and fludarabine (30 mg/m^2/day for 5 days, on D-6, D-5, D-4, D-3, and D-2). The TBI dose in these patients was reduced from 800 cGy to 600 cGy in October 2014 based on the results of our previous trial.[8]

For graft-versus-host disease (GVHD) prophylaxis, tacrolimus was administered starting on D-1 in combination with a short-term course of methotrexate (5 mg/m^2 IV bolus on days +1, +3, +6, and +11). During conditioning, antithymocyte globulin (ATG, Thymoglobulin®, Sanofi Genzyme, Lyon, France) at various doses was infused intravenously into all patients who received HAPLO SCTs (5-10 mg/kg) and a subset of patients who received URD SCTs (2.5-5 mg/kg). The use of ATG and the ATG dose were selected based on previous reports.[8,10,11] During the transplantation procedures, all patients were treated in a designated room with laminar airflow isolation and received identical supportive treatments, including G-CSF (5 μg/kg per day) that was administered subcutaneously from day +7 until an absolute neutrophil count (ANC) >3.0 x 10^9/L was reached, prostaglandin E1 and ursodeoxycholic acid, which were administered for the prophylaxis of sinusoidal obstructive syndrome (SOS), and prophylactic ciprofloxacin, itraconazole oral solution and intravenous acyclovir starting from the initiation of conditioning until engraftment was achieved. Prophylaxis against pneumonia caused by *Pneumocystis jiroveci* was performed by administering cotrimoxazole (Bactrim,

Roche, Basel, Switzerland) after engraftment until the end of post-SCT 1 year.

Definitions

The diagnosis of SAA was based on criteria proposed by previous reports.[2,12] VSAA was diagnosed as SAA with a neutrophil count less than 0.2 x 10^9/L.[13] DSA were measured by using a Luminex 200 system (Luminex Corp., Austin, TX): Beads with median fluorescence intensity (MFI) of greater than 1000 were defined as positive. DSA status were defined as weak (MFI 1000-3000), weak-moderate (MFI 3000-5000), moderate (MFI 5000–10 000), and strong (MFI >10 000) as described in our previous reports.[8,14] The hematopoietic cell transplantation-comorbidity index was assessed according to the method outlined by Sorror et al.[15] Neutrophil engraftment was indicated by an ANC ≥ 0.5 x 10^9/L during the first 3 consecutive days. Platelet engraftment was indicated by a platelet count ≥ 20 x 10^9/L without transfusion support during the first 5 consecutive days. Primary GF was defined as the failure to achieve hematopoietic recovery of the ANC (≥ 0.5 x 10^9/L). Secondary GF was indicated by an ANC < 0.5 x 10^9/L despite prior hematopoietic recovery of the ANC.[16] Nonhematological toxicity during transplantation was assessed according to the NCI Common Terminology Criteria for adverse events.[17] Invasive fungal disease (IFD) was diagnosed based on the criteria outlined by the European Organization for the Research and Treatment of Cancer/Mycoses Study Group.[18] Acute and chronic GVHD were diagnosed and graded according to the most recent consensus criteria.[19,20]

Statistics

All categorical variables were assessed with chi-squared tests. The continuous variables among the 3 groups treated with WM-URDs, MM-URDs, and HAPLOs were compared by 1-way ANOVA. The cumulative incidences of neutrophil and platelet engraftment, acute and chronic GVHD, cytomegalovirus (CMV) DNAemia, grade II-IV hemorrhagic cystitis, IFD, secondary malignancies, posttransplant lymphoproliferative

diseases, and SOS were calculated by considering both GF and death by other causes as competing risks. The OS rate represents the proportion of patients who were alive at the specified time after the date of transplantation and was associated with death due to any cause. The failure-free survival (FFS) rate was indicated as the proportion of patients who were alive without primary or secondary GF or death from any cause after SCT. The OS and FFS rates were calculated using Kaplan–Meier survival analysis. The probability of GF and the transplant-related mortality (TRM) rate were calculated by cumulative incidence estimation by considering the competing risks, including treatment-related deaths and GF, respectively. The cumulative incidences of the abovementioned outcomes were compared using the Gray test with univariate analysis. Variables with $p < 0.2$ according to the univariate analyses were included in multivariate models, with the exception of factors related to donor type (WM-URD, MM-URD, and HAPLO). Finally, variables with $p < 0.2$ or those related to donor type regardless of the p-value were included in the multivariate models, which were generated based on the Fine and Gray regression model with a backward stepwise selection. All statistical analyses were performed using R statistical software (ver. 3.6.1, R Foundation for Statistical Computing, Vienna, Austria, 2019-07-05). Statistical significance was indicated at p-values < 0.05.

Results

Baseline and transplant-related characteristics

The pretransplantation characteristics were well balanced among the 3 groups, except for the patient and donor ages and variables related to specific considerations linked to donor choice, i.e., severity at diagnosis, HLA incompatibility, stem cell source, the content of the graft cells, and the use of ATG. The proportion of VSAA patients, the HLA mismatch level, patients who received transplant since 2012, TBI dose (800 vs. 600 cGy), use of ATG, use of PB stem cells, and dosages of CD34+ and CD3+ graft cells obtained from the PB stem cell sources were

significantly higher in HAPLO than in either WM-URD or MM-URD (all p<0.001). The median patient age at SCT in the HAPLO (33.5 years, range, 18 - 59) cohort was greater than that of the WM-URD (29 years, range, 18 - 59) or MM-URD cohorts (31 years, range 18 - 54) (p=0.038). The median age of the donor was also significantly older for the HAPLOs (40 years, range, 13 - 66) than the respective WM-URDs (28 years, range, 19 - 42) or MM-URDs (28 years, range 20 - 46) (p < 0.001). Other details regarding the patient characteristics are shown in Table 1.

Hematopoietic recovery, graft failure, and survival outcomes

In terms of platelet engraftment, 1 patient in the WM-URD group, who died of sepsis 6 weeks post-SCT, and 1 surviving patient in the HAPLO group did not achieve platelet engraftment until the last follow-up at 18.8 months. Neutrophil and platelet engraftment in 1 patient in the MM-URD group could not be confirmed because he died of sepsis 1 week post-SCT. The cumulative incidences of patients who achieved neutrophil and platelet engraftments showed no statistically significant intergroup differences (p = 0.611 for neutrophil engraftment and p = 0.269 for platelet engraftment) at medians of 11 (range, 8-30) and 15 (range, 8-230) days for the WM-URDs, 13 (range 9-21) and 16.5 (range 6-102) days for the MM-URDs, and 12 (range 10-22) and 14 (range, 5-182) days for the HAPLOs, respectively (Figure 1).

At corresponding median follow-up times of 70.8 (range, 0.9 - 173.2) months in the WM-URD patients, 75.3 months (range, 1.2 - 174.1) in the MM-URD patients, and 29.9 months (range, 1.1 - 81.8) in the HAPLO patients, both the 3-year OS rates and FFS rates were not statistically different between the 3 groups. The 3-year OS rates were 90.3% (95% CI: 80.6-95.2) for the WM-URDs, 85.3% (95% CI: 68.2-93.6) for the MM-URDs, and 84.4% (95% CI: 70.0 - 92.3) for the HAPLOs (p = 0.659, Figure 2A). The 3-year FFS rates were 87.5% (95% CI: 77.3 – 93.3) for WM-URDs, 85.3% (95% CI: 68.2 – 93.6) for MM-URDs, and 82.3% (95% CI: 67.6 - 90.7) for HAPLOs (p = 0.8, Figure 2B).

The cumulative incidences of both GF and TRM were also not statistically different among the 3 groups. The 3-year cumulative incidence of GF was 2.7% (95% CI: 0.5 - 8.6) for WM-URDs, 0% for MM-URDs, and 6.5% (95% CI: 1.7 - 16.2) for HAPLOs (p = 0.253, Figure 2C). The 3-year cumulative incidence of TRM was 9.8% (95% CI: 4.3 – 18.0) for WM-URDs, 14.7% (95% CI: 5.3 – 28.7) for MM-URDs, and 11.2% (95% CI: 4.0 - 22.5) for HAPLOs (p = 0.655, Figure 2D).

Comparison of the incidence of GVHD and major complications

The cumulative incidences of acute and chronic GVHD according to the donor type is shown in Figure 3. The 180-day cumulative incidence of grade II-IV acute GVHD showed a trend toward a higher rate in the MM-URD group than in the other groups (35.6%, 95% CI: 24.8 - 46.6 for WM-URDs; 52.9%, 95% CI: 34.7 - 68.3 for MM-URDs; and 30.4%, 95% CI: 17.8 - 44.0 for HAPLOs; p = 0.076, Figure 3A). Similarly, the 3-year cumulative incidence of moderate-to-severe chronic GVHD for MM-URDs was higher than that for either WM-URDs or HAPLOs (23.3%, 95% CI: 14.3 – 33.6 for WM-URDs; 32.5%, 95% CI: 17.4 – 48.6 for MM-URDs; and 11.2%, 95% CI: 4.0 -22.6) for HAPLOs; p = 0.072, Figure 3D). According to the post hoc analyses of grade II-IV acute GVHD and moderate-to-severe chronic GVHD, the respective incidences were significantly higher for MM-URDs than HAPLOs (p = 0.032 for grade II-IV acute GVHD and p = 0.022 for moderate-to-severe chronic GVHD) (Figure 3A and 3D). However, the donor type was not significantly associated with the development of grade II-IV acute GVHD and moderate-to-severe chronic GVHD in the multivariate analyses. ATG use was identified as the significant factor affecting the occurrence of grade II-IV acute GVHD (hazard ratio (HR) = 0.521, 95% CI: 0.314 - 0.866, p = 0.012, Table S1, SDC, http://links.lww.com/TP/B953), whereas the factor of transplant year significantly associated with development of moderate-to-severe chronic GVHD (HR = 0.307, 95% CI: 0.15 - 0.628, p = 0.001, Table S2, SDC, http://links.lww.com/TP/B953).

In contrast, the cumulative incidence of either grade III-IV acute GVHD or mild-to-severe chronic GVHD was not significantly different among the 3 groups. The 180-day incidence of acute GVHD III-IV was 12.3% (95% CI: 6.0 - 21.0) for WM-URDs, 23.5% (95% CI: 10.9 - 38.9) for MM-URDs, and 15.2% (95% CI: 6.6 - 27.1) for HAPLOs (p = 0.308, Figure 3B). The 3-year rate of mild-to-severe chronic GVHD was 41.1% (95% CI: 29.7 - 52.2) for WM-URDs, 41.2% (95% CI: 24.4 - 57.2) for MM-URDs, and 28.5% (95% CI: 16.2 - 42.2) for HAPLOs, (p = 0.425, Figure 3C).

We compared the incidences of other major complications, including CMV DNAemia, posttransplant lymphoproliferative disease, IFD, secondary malignancies, grade II-IV hemorrhagic cystitis, and SOS, among the 3 groups. The incidences of these complications were not different among the 3 groups (Table 2 and Figure S1, SDC, http://links.lww.com/TP/B953).

Subgroup analysis of mismatched unrelated donors

The MM-URD patients were subgrouped according to the level of HLA mismatch, resulting in an MM-URD group with 7/8-HLA matches (1 allele MM-URD, n = 18) and a 6/8-URD group including 2 mismatched alleles, and 1 mismatched HLA-C antigen with/without a 1 allele mismatch (n = 16). The cumulative incidences of grade II-IV acute GVHD [55.6% (95% CI: 29.3-75.4) vs. 50.0% (95% CI: 23.3-71.9), p=0.724], grade III-IV acute GVHD [22.2% (95% CI: 6.6-43.6) vs. 25.0% (95% CI: 7.3-48.0), p=0.891], mild-to-severe chronic GVHD [44.4% (95% CI: 20.7-65.9) vs. 37.5% (95% CI: 14.4-60.8), p=0.664], and moderate-to-severe chronic GVHD [27.8% (95% CI: 9.6-49.6) vs. 38.4% (14.6-62.1), p=0.912] showed no differences between the 7/8-URD and 6/8-URD groups (Figure S2, SDC, http://links.lww.com/TP/B953). Both the 3-year OS rates and the 3-year cumulative incidences of TRM were more favorable in the 7/8-URD group than in the 6/8-URD group [94.4% (95% CI: 66.6-99.2) vs. 75.0% (95 CI: 46.3-89.8) for OS, Figure 4A; 12.3% (95% CI: 1.8-33.3) vs.

25.0% (95% CI: 7.3-48.0) for TRM, Figure 4B], although the differences did not reach statistical significance (p=0.26 for OS, p=0.263 for TRM).

Discussion

In the current study, we comprehensively compared the major transplant outcomes in adult patients with acquired SAA who received grafts from MM-URDs, WM-URDs, and HAPLOs. To the best of our knowledge, this is the first report comparing the outcomes of SCT from the 3 different types of alternative donors. All outcomes compared in the current study did not show significant differences. However, subgroup analysis of the MM-URD group revealed that SCTs from 6/8-URDs, who had 2 mismatched alleles or 1 mismatched HLA-C antigen with/without a 1 allele mismatch, produced inferior survival outcomes and higher incidences of TRM compared to SCTs from 7/8-URDs. One major problem with our results was the unbalanced transplant characteristics that resulted from either the use of different selection criteria for the donor type or differences in the transplant procedures due to the donor type (i.e., severity at diagnosis, HLA incompatibility, follow-up times, TBI dose, ATG dose, stem cell type, and graft cell contents). Apart from the acceptable differences in terms of the baseline characteristics according to the donor type, there were significant differences in the 3 factors, including patient age, donor age, and disease severity, among the WM-URD, MM-URD, and HAPLO groups; both the patient and donor ages were greater in the HAPLO group than in the other 2 groups, and the disease severity was greater in the HAPLO group than in the WM-URD or MM-URD groups. Interestingly, all 3 factors that showed increases in the HAPLO groups have been well known to be adverse prognostic factors related to either a higher incidence of GVHD or poor survival outcomes.[2,21-23] Therefore, we believe that the comparable SCT outcomes of the HAPLO group compared to those of the WM-URD or MM-URD groups may still be valid despite concern about potential selection bias associated with the unbalanced characteristics related to these 3 factors.

Regarding the clear advantages in terms of donor availability, the lack of the need for a donor search, and the decreased costs associated with HAPLOs compared to URDs,[7] ongoing research is underway to demonstrate the effectiveness of HAPLO SCTs compared to URD SCTs, which have traditionally been considered the first alternative option for patients without MSDs. The results of recent studies have shown encouraging survival outcomes with acceptable levels of engraftment after HAPLO SCTs despite the small sample sizes.[24-27] Nevertheless, data comparing HAPLO and URD SCTs for acquired SAA are scarce, and it remains unclear whether HAPLO SCTs could fully replace URD SCTs. There has only been 1 recent comparison report. Lu et al. observed no significant difference between HAPLO SCTs and WM-URD SCTs (median age of cohort: 11 years) after using uniform non–TBI-based conditioning regimens consisting of cyclophosphamide, fludarabine, and ATG (OS 80.3% vs. 89.6%, FFS 76.4% vs. 89.4%, and GVHD-free failure-free survival 79% vs. 71.6%).[28] In the current study, TBI plus cyclophosphamide for URD SCTs and TBI plus fludarabine for HAPLO SCTs were used as conditioning regimens for patients with a median age of 31 years. No optimal conditioning regimen has been established for either URD or HAPLO SCTs. Both URD and HAPLO SCTs produced acceptable outcomes with excellent engraftment compared to those in prior reports, which indicated survival rates of 49 - 85% for URD SCTs[29] and 74% for HAPLO SCTs.[2] Based upon the current data and the findings of Lu et al., we suggest that HAPLO SCTs should be considered a salvage option of a value equal to that of URD SCTs for acquired SAA patients who failed at least 1 course of IST and lack an MSD.

Because recent results of HAPLO SCTs showed similar outcomes upon comparison not only to WM-URD SCTs but also to MSD SCTs for SAA,[28,30] patients or clinicians might avoid choosing an MM-URD as an alternative donor. However, growing clinical evidence has indicated that 7/8-URDs produce SCT outcomes comparable to those of WM-URDs and significant superior impact on survival compared to 6/8-URDs in SAA.[31,32] This was the first

report comparing the outcomes of consecutive patients undergoing HAPLO SCTs to those of patients undergoing MM-URD SCTs. As expected, SCTs with either WM-URDs or 7/8-URDs resulted in favorable impacts on survival outcomes and TRM compared to those with 6/8-URDs in the current study. It was shown that HAPLO SCT produced superior survival outcomes compared to 6/8-URD SCT. We suggest that 6/8-URDs are the worst choice as alternative donors among WM-URDs, MM-URDs, and HAPLOs.

This study had several limitations. The relatively small sample size and retrospective study design are important shortcomings. Because the patients of HAPLO group were transplanted more recently, the follow-up duration of HAPLO was shorter than those of the other groups. We were not able to compare the long-term clinical outcomes in HAPLO to those of other groups. In addition, another well-known alternative donor type (cord blood) was not included in the comparison of alternative donors.[2] Thus, the most optimal alternative donor among URDs, HAPLOs, and cord blood has yet to be determined for SAA patients, although comparable transplant outcomes were identified among WM-URDs, 7/8-URDs, and HAPLOs in the current study.

Despite these limitations, our data indicated that the host/donor features and urgency of the need for transplant should be considered by physicians when choosing the best alternative donor for adult patients with SAA who do not have an available MSD. However, the selection of 6/8-URDs is not recommended due to inferior survival outcomes.

Acknowledgments

The authors acknowledge all employees at Seoul St. Mary's Hospital, Seoul, Korea, particularly the house staff and nurses, for providing excellent care to the patients.

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board (IRB) of The Catholic University of Korea (KC18RESI0765) and was conducted in accordance with the Declaration of Helsinki. Our study was a retrospective study with a relatively large cohort. The IRB waived informed consent for this study due to its retrospective nature.

Consent for publication

Not applicable

References

1. Killick SB, Bown N, Cavenagh J, et al. Guidelines for the diagnosis and management of adult aplastic anaemia. *Br J Haematol.* 2016;172(2):187–207. doi:10.1111/bjh.13853

2. Bacigalupo A. How I treat acquired aplastic anemia. *Blood.* 2017;129(11):1428–1436. doi:10.1182/blood-2016-08-693481

3. Shin SH, Lee SE, Lee JW. Recent advances in treatment of aplastic anemia. *Korean J Intern Med.* 2014;29(6):713–726. doi:10.3904/kjim.2014.29.6.713

4. 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. doi:10.1182/blood-2007-06-097386

5. Bacigalupo A, Socie G, Lanino E, et al; Severe Aplastic Anemia Working Party of the European Group for Blood and Marrow Transplantation. Fludarabine, cyclophosphamide, antithymocyte globulin, with or without low dose total body irradiation, for alternative donor transplants, in acquired severe aplastic anemia: a retrospective study from the EBMT-SAA Working Party. *Haematologica.* 2010;95(6):976–982. doi: 10.3324/haematol.2009.018267

6. Weisdorf D, Spellman S, Haagenson M, et al. Classification of HLA-matching for retrospective analysis of unrelated donor transplantation: revised definitions to predict survival. *Biol Blood Marrow Transplant.* 2008;14(7):748–758. doi:10.1016/j.bbmt.2008.04.003

7. Ballen KK, Koreth J, Chen YB, et al. Selection of optimal alternative graft source: mismatched unrelated donor, umbilical cord blood, or haploidentical transplant. *Blood.* 2012;119(9):1972–1980. doi:10.1182/blood-2011-11-354563

8. Lee SE, Park SS, Jeon YW, et al. Optimal conditioning regimen for haplo-identical stem cell transplantation in adult patients with acquired severe aplastic anemia: prospective de-escalation study of TBI and ATG dose. *Am J Hematol.* 2018;93(11):1368–1375. doi:10.1002/ajh.25257

9. Young NS. Aplastic anemia. *N Engl J Med.* 2018;379(17):1643–1656. doi:10.1056/NEJMra1413485

10. Park SS, Kwak DH, Jeon YW, et al. Beneficial role of low-dose antithymocyte globulin in unrelated stem cell transplantation for adult patients with acquired severe aplastic anemia: reduction of graft-versus-host disease and improvement of graft-versus-host disease-free, failure-free survival rate. *Biol Blood Marrow Transplant.* 2017;23(9):1498–1508. doi:10.1016/j.bbmt.2017.05.026

11. Lee JW, Cho BS, Lee SE, et al. The outcome of unrelated hematopoietic stem cell transplants with total body irradiation (800 cGy) and cyclophosphamide (120 mg/kg) in adult patients with acquired severe aplastic anemia. *Biol Blood Marrow Transplant.* 2011;17(1):101–108. doi:10.1016/j.bbmt.2010.06.014

12. Camitta BM, Thomas ED, Nathan DG, et al. Severe aplastic anemia: a prospective study of the effect of early marrow transplantation on acute mortality. *Blood.* 1976;48(1):63–70.

13. Bacigalupo A, Passweg J. Diagnosis and treatment of acquired aplastic anemia. *Hematol Oncol Clin North Am.* 2009;23(2):159–170. doi:10.1016/j.hoc.2009.01.005

14. Lee H, Min JW, Kim JI, et al. Clinical significance of HLA-DQ antibodies in the development of chronic antibody-mediated rejection and allograft failure in kidney transplant recipients. *Medicine (Baltimore).* 2016;95(11):e3094. doi:10.1097/MD.0000000000003094

15. Sorror ML, Maris MB, Storb R, et al. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. *Blood.* 2005;106(8):2912–2919. doi:10.1182/blood-2005-05-2004

16. Champlin RE, Horowitz MM, van Bekkum DW, et al. Graft failure following bone marrow transplantation for severe aplastic anemia: risk factors and treatment results. *Blood.* 1989;73(2):606–613.

17. U.S. Department of Health and Human Services. Common terminology criteria for adverse events (CTCAE) version 4.0. *National Institutes of Health, National Cancer Institute.* 2009;4(03).

18. De Pauw B, Walsh TJ, Donnelly JP, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. *Clin Infect Dis.* 2008;46(12):1813–1821. doi:10.1086/588660

19. 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. doi:10.1016/j.bbmt.2015.09.001

20. Pavletic SZ, Vogelsang GB, Lee SJ. 2014 National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: preface to the series. *Biol Blood Marrow Transplant.* 2015;21(3):387–388. doi:10.1016/j.bbmt.2014.12.035

21. Przepiorka D, Smith TL, Folloder J, et al. Risk factors for acute graft-versus-host disease after allogeneic blood stem cell transplantation. *Blood.* 1999;94(4):1465–1470.

22. Urbano-Ispizua A, Rozman C, Pimentel P, et al. Risk factors for acute graft-versus-host disease in patients undergoing transplantation with CD34+ selected blood cells from HLA-identical siblings. *Blood.* 2002;100(2):724–727. doi:10.1182/blood-2001-11-0057

23. Kollman C, Howe CW, 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. doi:10.1182/blood.v98.7.2043

24. Xu LP, Wang SQ, Wu DP, et al. Haplo-identical transplantation for acquired severe aplastic anaemia in a multicentre prospective study. *Br J Haematol.* 2016;175(2):265–274. doi:10.1111/bjh.14225

25. Clay J, Kulasekararaj AG, Potter V, et al. Nonmyeloablative peripheral blood haploidentical stem cell transplantation for refractory severe aplastic anemia. *Biol Blood Marrow Transplant.* 2014;20(11):1711–1716. doi:10.1016/j.bbmt.2014.06.028

26. Gao L, Li Y, Zhang Y, et al. Long-term outcome of HLA-haploidentical hematopoietic SCT without in vitro T-cell depletion for adult severe aplastic anemia after modified conditioning and supportive therapy. *Bone Marrow Transplant.* 2014;49(4):519–524. doi:10.1038/bmt.2013.224

27. Esteves I, Bonfim C, Pasquini R, et al. Haploidentical BMT and post-transplant Cy for severe aplastic anemia: a multicenter retrospective study. *Bone Marrow Transplant.* 2015;50(5):685–689. doi:10.1038/bmt.2015.20

28. Lu Y, Sun RJ, Zhao YL, et al. Unmanipulated haploidentical hematopoietic stem cell transplantation achieved outcomes comparable with matched unrelated donor transplantation in young acquired severe aplastic anemia. *Biol Blood Marrow Transplant.* 2018;24(9):1881–1887. doi:10.1016/j.bbmt.2018.05.015

29. Arai Y, Kondo T, Yamazaki H, et al. Allogeneic unrelated bone marrow transplantation from older donors results in worse prognosis in recipients with aplastic anemia. *Haematologica.* 2016;101(5):644–652. doi:10.3324/haematol.2015.139469

30. Xu LP, Jin S, Wang SQ, et al. Upfront haploidentical transplant for acquired severe aplastic anemia: registry-based comparison with matched related transplant. *J Hematol Oncol.* 2017;10(1):25. doi:10.1186/s13045-017-0398-y

31. Devillier R, Dalle JH, Kulasekararaj A, et al. Unrelated alternative donor transplantation for severe acquired aplastic anemia: a study from the French Society of Bone Marrow Transplantation and Cell Therapies and the EBMT Severe Aplastic Anemia Working Party. *Haematologica.* 2016;101(7):884–890. doi:10.3324/haematol.2015.138727

32. Yagasaki H, Kojima S, Yabe H, et al. Acceptable HLA-mismatching in unrelated donor bone marrow transplantation for patients with acquired severe aplastic anemia. *Blood.* 2011;118(11):3186–3190. doi:10.1182/blood-2011-04-349316

Figure legends

Figure 1. Cumulative incidences of (A) Neutrophil and (B) Platelet engraftment according to donor types.

Figure 2. Transplant outcomes according to donor types. (A) Overall survival, (B) Failure-free survival, (C) Cumulative incidence of graft failure, and (D) Cumulative incidence of transplant-related mortality.

Figure 3. Cumulative incidences of acute and chronic GVHD according to donor types. (A) Grade II-IV acute GVHD, (B) Grade III-IV acute GVHD, (C) Mild-to-severe chronic GVHD, and (D) Moderate-to-severe chronic GVHD. * indicates statistical significance ($p<0.05$).

Figure 4. Comparison of outcomes between 7/8-unrelated donors (URDs) and 6/8-URDs. (A) Overall survival, (B) Cumulative incidence of transplant-related mortality. * The 6/8-URD group included 2 mismatched alleles, and 1 mismatched HLA-C antigen with/without a 1 allele mismatch.

Table 1. Pretransplant patient characteristics

Variables	WM-URD (n=73)	MM-URD (n=34)	HAPLO (n=46)	*P* (*<0.05)
Patient age (years) (median, range)	29 (18-59)	31 (18-54)	33.5 (18-59)	0.038*
Donor age (years) (median, range)	28 (19-42)	28 (20-46)	40 (13-66)	<0.001*
Sex				0.979
Male (n, %)	36 (49.3%)	17 (50.0%)	22 (47.8%)	
Severity at diagnosis				<0.001*
Severe (n, %)	51 (69.9%)	27 (79.4%)	20 (43.4%)	
Very severe (n, %)	22 (30.1%)	7 (20.6%)	26 (56.5%)	
Pre-SCT IST				0.324
ATG-cyclosporine (n, %)	34 (46.6%)	21 (61.8%)	25 (54.3%)	
Others (n, %)	39 (53.4%)	13 (38.2%)	21 (45.7%)	
Time from diagnosis to SCT (months) (median, range)	51.6 (2.1-335)	50.5 (3.2-250)	63.0 (1.6-503)	0.637
Comorbidities (HCT-CI)				0.283
0-2 (n, %)	56 (76.7%)	28 (82.4%)	31 (67.4%)	
≥3 (n, %)	17 (23.3%)	6 (17.6%)	15 (32.6%)	
Sex incompatibility				0.542
Female to male (n, %)	9 (12.3%)	2 (5.9%)	6 (13.0%)	
ABO-match				0.462
Identical (n, %)	30 (41.1%)	10 (29.4%)	19 (41.3%)	
Mismatch (n, %)	43 (58.9%)	24 (70.6%)	27 (58.7%)	
HLA incompatibility				<0.001*
8/8 fully matched (n, %)	73 (100%)	0 (0%)	0 (0%)	
Mismatch (n, %)				
1 allele (n, %)	0 (0%)	18 (52.9%)	0 (0%)	
2 alleles (n, %)	0 (0%)	1 (2.9%)	0 (0%)	
1 antigen (n, %)	0 (0%)	10 (29.4%)	0 (0%)	
1 antigen and 1 allele (n, %)	0 (0%)	5 (14.7%)	0 (0%)	
≥ 2 antigens (n, %)	0 (0%)	0 (0%)	46 (100%)	
Donor-specific HLA antibody[a]				-
Negative (n, %)	-	6 (17.6%)	29 (63.0%)	
Positive (n, %)[a]	-	0 (0%)	11 (23.9%)	
Weak (n, %)	-	0 (0%)	6 (13.0%)	
Weak-moderate (n, %)	-	0 (0%)	2 (4.3%)	
Moderate (n, %)	-	0 (0%))	2 (4.3%)	
Strong (n, %)	-	0 (0%)	1 (2.2%)	
Unknown (n, %)	-	28 (82.4%)	6 (13.0%)	
Transplant year[b]				<0.001*
2002~2011	49 (67.1%)	23 (67.6%)	0	
2012~2018	24 (32.9%)	11 (32.4%)	46 (100%)	
TBI dose				<0.001*
800 cGy (n, %)	59 (80.8%)	33 (97.1%)	10 (21.7%)	
600 cGy (n, %)	14 (19.2%)	1 (2.9%)	36 (78.3%)	
ATG for conditioning				<0.001*
None (n, %)	41 (56.2%)	16 (47.1%)	0 (0%)	
2.5 mg/kg (n, %)	32 (43.8%)	17 (50.0%)	0 (0%)	
5.0 mg/kg (n, %)	0	1 (2.9%)	37 (80.4%)	
7.5 mg/kg (n, %)	0	0	4 (8.7%)	
10.0 mg/kg (n, %)	0	0	5 (10.9%)	
Stem cell type				<0.001*
BM (n, %)	34 (46.6%)	17 (50.0%)	0 (0%)	
PB (n, %)	39 (53.4%)	17 (50.0%)	46 (100%)	

Graft cell content (median, range)				
$CD34^+$ cells ($x10^6$/kg)	5.0 (0.6-11.4)	4.4 (0.9-14.4)	5.8 (1.4-17.0)	<0.001*
$CD3^+$ cells ($x10^6$/kg)	144.5 (3.2-665.9)	94.3 (4.6-515.3)	411.4(117.8-870.8)	<0.001*

WM-URD, well-matched unrelated donor; MM-URD, mismatched unrelated donor; HAPLO, haploidentical related donor; IST, immunosuppressive treatment; SCT, stem cell transplantation; HCT-CI, hematopoietic cell transplantation-comorbidity index; TBI, total body irradiation; ATG, anti-thymocyte globulin; BM, bone marrow; PB, peripheral blood (G-CSF mobilized);

[a]Positivity of donor specific HLA antibody (DSA) was classified according to degree of median fluorescence intensity (MFI); weak (MFI 1000-3000), weak-moderate (MFI 3000-5000), moderate (MFI 5000-10 000) and strong (MFI >10 000). DSA test has been performed since July 2013. We have excluded HAPLO donor presenting strong DSA since September 2013.

[b]HAPLO SCT started since June 2012

Table 2. The cumulative incidence of posttransplant complications according to the donor-type groups

Complications	WM-URD (n=73)	MM-URD (n=34)	HAPLO (n=46)	*P*
	Cumulative incidence at 3 years (95% CI)			
CMV DNAemia	41.1% (29.7-52.1)	52.9% (34.7-68.2)	45.7% (30.7-59.4)	0.337
PTLD	1.4% (0.1-6.6)	0.0%	4.3% (0.8-13.2)	0.336
Invasive fungal disease	9.6% (4.2-17.7)	8.8% (2.2-21.4)	10.9% (3.9-21.8)	0.94
Secondary malignancy	5.5% (1.8-12.5)	0.0%	2.2% (0.2-10.1)	0.105
Hemorrhagic cystitis (≥ grade II)	9.6% (4.2-17.7)	14.7% (5.3-28.7)	13.1% (5.2-24.6)	0.751
Sinusoidal obstruction syndrome	2.7% (0.5-8.6)	0.0%	2.2% (0.2-10.1)	0.632

CI, confidence interval; WM-URD, well-matched unrelated donor; MM-URD, mismatched unrelated donor; HAPLO, haploidentical related donor; CMV, cytomegalovirus; PTLD, posttransplant lymphoproliferative disease

Figure 1

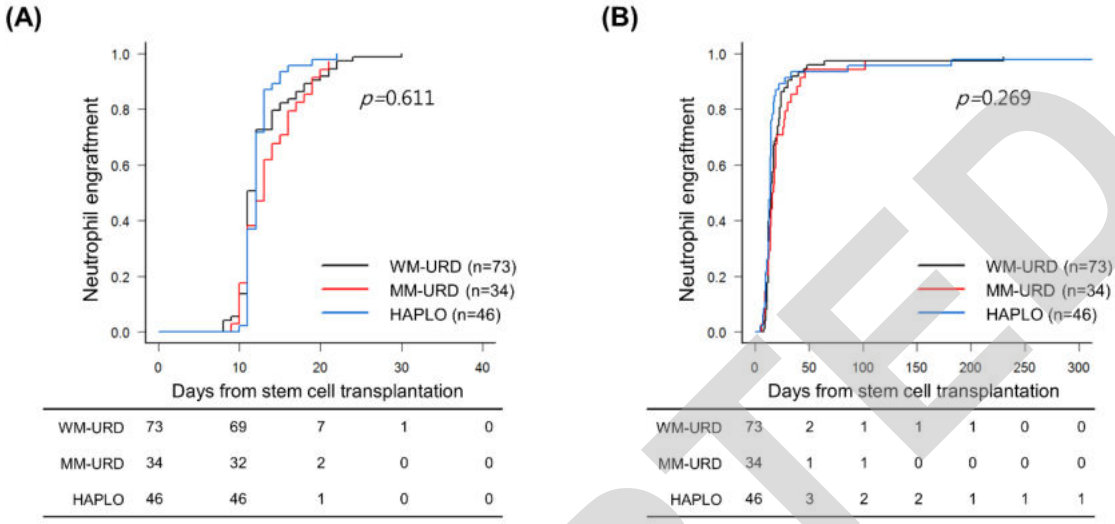

Figure 2

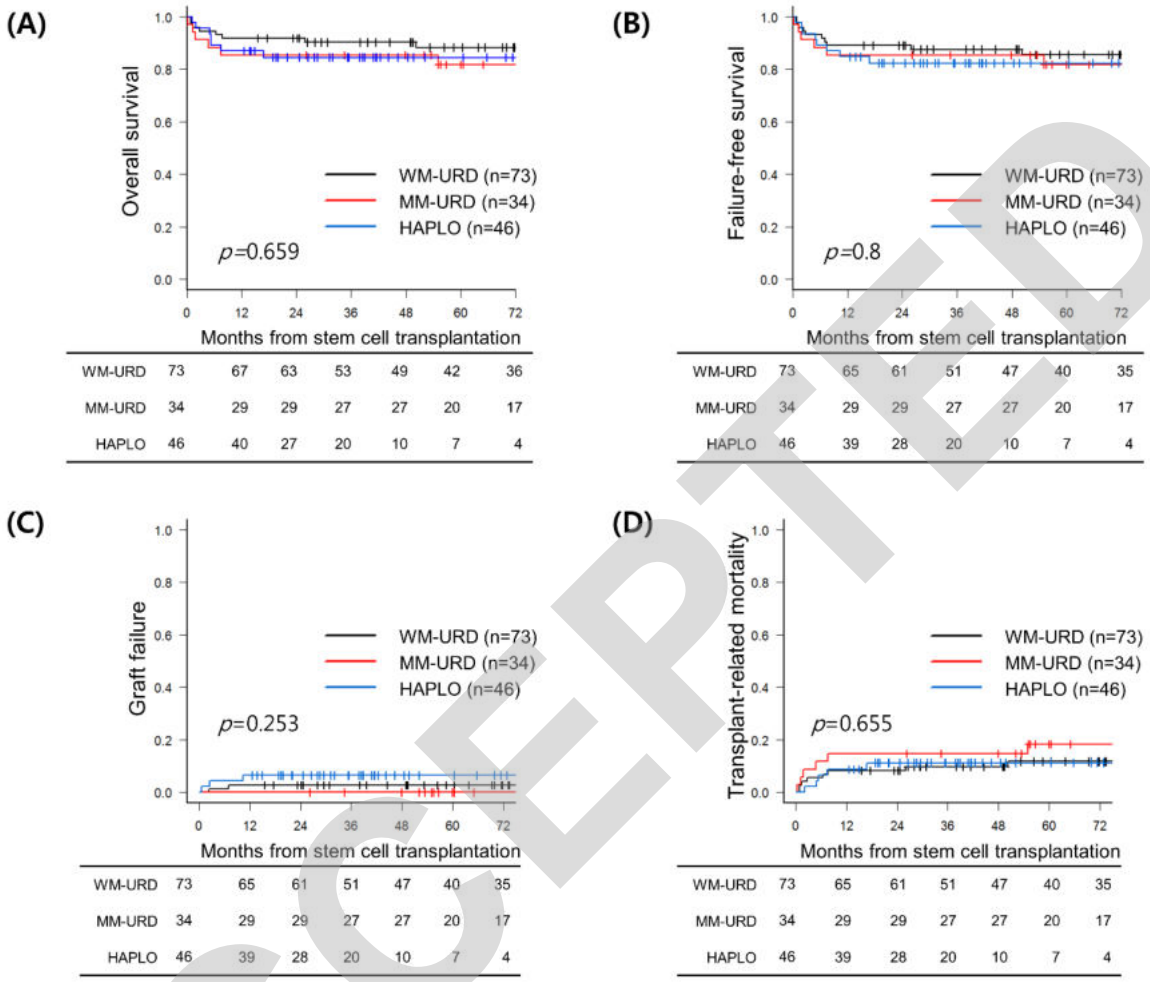

Figure 3

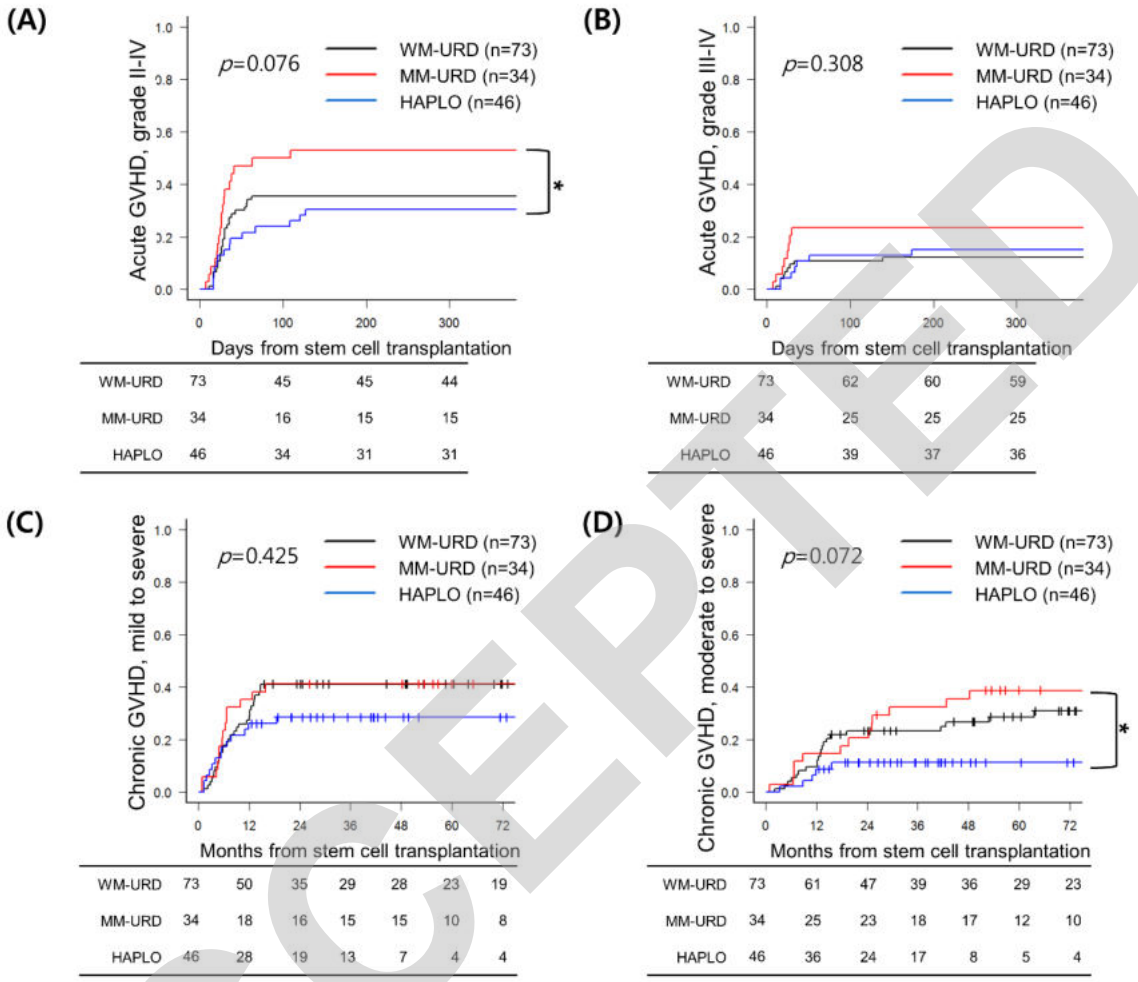

Figure 4