Comparable long-term outcomes between upfront haploidentical and identical sibling donor transplant in aplastic anemia: a national registry-based study

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Abstract

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) remains a curative option for severe aplastic anemia (SAA), and transplantation from identical sibling donors (ISD) has been recommended as a first-line treatment. Haploidentical donor (HID) transplantation for SAA has made great advances; thus, an increased role of HID-SCT in SAA should be considered. We performed a national registry-based analysis comparing long-term outcomes in the upfront HID or upfront ISD SCT setting. A total of 342 SAA patients were enrolled, with 183 patients receiving HID SCT and 159 receiving ISD SCT. The estimated 9-year overall survival and failure-free survival were 87.1±2.5% and 89.3±3.7% (P=0.173) and 86.5±2.6% *versus* 88.1±3.8% (P=0.257) for patients in the HID and ISD SCT groups, respectively. Transplantation from HID or ISD SCT has greatly improved quality of life (QoL) levels post-HSCT compared to pre-HSCT. The occurrence of chronic graft-*versus*-host disease was the only identified adverse factor affecting each subscale of QoL. Physical and mental component summaries in adults as well as physical, mental, social, and role well-being in children were all similar between HID and ISD SCT at 5-year time points. At the last follow-up, the proportion of returning to society was comparable between the HID and ISD groups, showing 78.0% *versus* 84.6% among children and 74.6% *versus* 81.2% among adults. These data suggest that haploidentical transplant can be considered a potential therapeutic option in the upfront setting for SAA patients in the absence of an HLA-identical related or unrelated donor.

Introduction

Severe aplastic anemia (SAA) is a potentially fatal bone marrow failure disorder characterized by pancytopenia, transfusion dependency, and susceptibility to various infections.[1] Allogeneic hematopoietic stem cell transplantation (allo-HSCT) and immunosuppressive therapy (IST) are two effective treatment options in SAA.[2] In consideration of long-term recovery following treatment, allo-HSCT has the advantage of rapid complete hematopoietic recovery, better health-related quality of life, while virtually eliminating the risk of relapse and secondary clonal disease.[3-5] Transplantation from identical sibling donors (ISD) has produced a long-term survival of approximately 90% and has been recommended as a first-line choice among younger patients according to the current treatment algorithm.[2,6] The recent outcomes of upfront matched unrelated donor (MUD) transplants are also similar with ISD especially in children and adolescents with SAA.[7] However, rapid donor availability remains an issue for certain patients.

During the last decade, the results of allo-HSCT for SAA with a haploidentical donor (HID) have improved remark-

ably.[8] HID transplantation (haplo-SCT) has achieved similar overall survival (OS) as ISD-SCT (89% *vs*. 91%) as salvage therapy for SAA.[9] Due to the improved results of allo-HSCT with HID, it is considered whether this treatment should be given an increased role among SAA patients in the absence of HLA-identical sibling donors.[10] Based on a previous registry-based comparison, haplo-SCT as upfront therapy has been indicated to be comparable to upfront ISD-SCT, showing an estimated 3-year OS of 86% and 91% with a median follow-up of 21.4 and 26.0 months.[11] However, the long-term outcomes of upfront haplo-SCT and the comparison with upfront ISD-SCT in SAA have not been evaluated.

For long-term evaluation, survival is a vital indicator but not the only goal for SAA patients receiving allo-HSCT. For such a non-malignant disease, the major concern for long-term survivors also includes hematologic recovery, health-related quality of life (QoL), and return to society. The current study aimed to compare the long-term efficacy of SAA patients who received an upfront transplant from HID or ISD, focusing on survival, late complications, QoL including psychological status and physical function, and the return to work or school. This analysis will provide evidence in favor of haplo-SCT as a therapeutic option in the upfront setting for SAA patients in the absence of an HLA-identical donor.

Methods

Study design

This was a multi-center retrospective study based on data from the Chinese Blood and Marrow Transplantation Registry Group (CBMTRG). The data were collected from 11 transplantation centers. The study was approved by the Institutional Review Board at the 11 participating centers. Written informed consent was obtained from each patient in accordance with the Declaration of Helsinki.

Patients

Patients with SAA who received upfront allo-HSCT from HID or ISD during the period from January 2012 to December 2018 were included. None of the patients had been previously treated with antithymocyte globulin (ATG)-based immunosuppressive therapy. All enrolled patients underwent upfront allo-HSCT within 4 months after the definite diagnosis of SAA. A total of 158 patients were reported in the published study[11] and outcomes were updated with extended follow-up.

Transplantation protocol

The conditioning regimen was uniform in haploidentical transplantation, which consisted of the following: 3.2 mg/kg/day intravenous (i.v.) busulfan (Bu) on days -7 and -6; 50 mg/kg/day i.v. cyclophosphamide (Cy) and 2.5 mg/kg/day i.v. rabbit ATG (r-ATG) from day -5 to day -2.[12] In ISD SCT cohort, the applied regimens included the following: Cy (200 mg/kg) + r-ATG (10-12 mg/kg), Flu (120 mg/m^2) + Cy (100-200 mg/kg) + r-ATG (10-12.5 mg/kg), and Bu (6.4 mg/kg) + Cy (160 mg/kg) + r-ATG (10 mg/kg).

Graft-*versus*-host disease (GVHD) prophylaxis consisted of ciclosporin (CsA), mycophenolate mofetil (MMF), and short-term methotrexate (MTX). CsA at 3 mg/kg/day in divided doses was started from day -9, and was continued for up to 1 year post-SCT. Mycophenolate mofetil (MMF) was administered orally (0.5 g every 12 hours in adults and 0.25 g every 12 hours in children) from day −9 and the dose was halved on day +30 and then stopped on day +60 in HID cohort. In the ISD cohort, MMF was tapered upon engraftment. MTX was administered at a dose of 15 mg/m^2 on day +1 and at a dose of 10 mg/m^2 on days +3, +5, and +11 in HID cohort (MTX +1, +3, and +6 in ISD cohort).

In both HID and ISD cohorts, unmanipulated G-CSF mobilized bone marrow (BM) or G-CSF mobilized peripheral blood stem cells (PBSC) or combination of BM with PB were infused as grafts. The other details of transplantation were performed as described previously.[11]

Definitions and assessments

The following outcomes were examined in the present study: chronic GVHD (cGVHD), hematologic reconstitution, OS, failure-free survival (FFS), GVHD-free failure-free survival (GFFS), QoL and social status (returning to work or school). cGVHD was assessed according to the National Institutes of Health Consensus Criteria.[13] The definition of mixed chimerism or graft failure has previously been reported in detail.[14] FFS was defined as survival with a response to therapy which meant transfusion independence and no longer meeting the criteria for severe disease. Death, primary or secondary graft failure and relapse were considered treatment failure. GFFS was defined as survival without grades III–IV acute GVHD (aGVHD), extensive cGVHD, and treatment failures. All outcomes were assessed at the time of last contact.

Late complications and fertility

Late complications requiring treatment were evaluated at the last follow-up. The late complications included second malignancy, cardiovascular, respiratory, kidney, and skeletal complications. Besides, the successful fertility data post-SCT was also collected in the two cohorts.

Health-related quality of life evaluation

For SAA recipients, the participating transplant centers were required to report their evaluation of QoL to the CBMTRG pre-HSCT, at 3 years and 5 years post-HSCT. The SF-36 questionnaire reflects eight subscales in adults: physical functioning (PF), role-physical (RP), bodily pain

(BP), general health (GH), vitality (VT), social functioning (SF), role-emotional (RE), and mental health (MH). Furthermore, PF, RP, BP, and GH were aggregated to form a physical component summary (PCS) scale, and VT, SF, RE, and MH were aggregated to form a mental component summary (MCS) scale.[15] The PedsQL 4.0 questionnaire contains subscales that assess four QoL domains in children, involving physical, emotional, social, and role status.[16]

Statistical analysis

Comparisons of patient characteristics between the groups were performed using the Mann–Whitney U test for continuous variables and χ^2 and Fisher's exact tests for categorical data. The probabilities of survival were calculated using the Kaplan–Meier estimator. Cumulative incidences were estimated for engraftment and GVHD to accommodate competing risks, with death as the competing event. Variables with *P*<0.1 in univariate analysis (*Online Supplementary Table S1*) and donor source were included in Cox proportional hazards regression. The level of significance was set at *P*<0.05. SPSS 16.0 (Mathsoft, Seattle, WA, USA) and the R software package (version 3.6.2; http://www.r-project.org) were used for data analyses.

Results

Basic characteristics

A total of 342 consecutive patients who received upfront allo-HSCT were enrolled in the present study. The baseline characteristics are summarized in Table 1. There were no statistically significant differences between the HID (n=183) and ISD (n=159) groups with regard to sex, Eastern Cooperative Oncology Group scale (ECOG), or donor-recipient blood type. As indicated in Table 1, the median age at transplant was 21 (range, 1-51) and 32 (range, 7-61) years in the HID and ISD groups, respectively (*P*<0.001). A higher proportion of BM plus peripheral blood (PB) grafts was infused in the HID group (91.3% *vs*. 79.2% in the ISD group, *P*<0.001). Patients receiving HID-SCT had a longer interval between disease diagnosis and transplant, with a median of 2.0 months, than patients receiving ISD-SCT who were transplanted within a median of 1.5 months after diagnosis.

Early-phase outcomes

As the sample size was enlarged, early-phase outcomes were updated and presented briefly. The cumulative incidences (CI) of 28-day neutrophils (97.3±0.1% *vs*. 97.5±0.1%, *P*=0.328; *Online Supplementary Figure S1A*) and 100-day platelet engraftment (95.6±0.1% *vs*. 96.2±0.1%, *P*=0.275; *Online Supplementary Figure S1B*) were similar between the HID and ISD groups. As indicated in Table 1, the median time to achieve neutrophil engraftment was 1 day shorter (*P*=0.039) after ISD-HSCT, whereas that of platelet engraftment was 2 days shorter after ISD-HSCT (*P*=0.010). Haploidentical donors were associated with a significantly higher incidence of grade II-IV aGVHD and III-IV aGVHD of 31.3±0.1% and 8.9±0.1%, respectively, compared to 4.5±0.1% and 1.9±0.1% in the ISD group (*P*<0.001, *P*=0.005; *Online Supplementary Figure S2*).

Chronic graft-*versus*-host disease

The cumulative 5-year incidence of overall cGVHD in the HID group (29.3±0.1%) was significantly higher than that in the ISD group (10.4±0.1%, *P* < 0.001). The cumulative incidence of moderate to severe cGVHD seemed to be higher in patients receiving HID-SCT (7.0±0.1%) with close to statistical difference, when compared to 2.6±0.1% in the ISD-SCT group (*P*=0.065; *Online Supplementary Figure S3*).

Survival outcomes

The median follow-up for surviving patients was 75.5 months (range, 37.1-117.7) and 70.3 months (range, 39.9-115.6) in the HID and ISD groups, respectively. The estimated 9-year probabilities of OS were 87.1±2.5% and 89.3±3.7% among HID and ISD patients, respectively (Figure 1A, *P*=0.173). The FFS at 9 years was 86.5±2.6% in the HID group and 88.1±3.8% in the ISD group (Figure 1B, *P*=0.257). No differences in terms of either OS or FFS were found according to patient age (children *vs*. adults). The estimated 9-year OS and FFS were 88.8±3.6% *versus* 87.7±2.7% (*P*=0.963) and 87.7±3.8% *versus* 87.0±2.8% (*P*=0.974) in the child and adult cohorts, respectively. The GFFS at 9 years was 82.0±2.8% *versus* 87.3±3.9% in the HID and ISD groups (*P*=0.028).

We also calculated the survival outcomes among adults stratified by age. The estimated 9-year OS were 88.0±3.4% and 86.4±4.5% among adults aged 18-39 and those aged 40 years or older (*P*=0.394). Similarly, the 9-year OS were 87.6±3.3% *versus* 85.7±9.4% in the HID group, and 88.7±5.6% *versus* 86.7±5.1% in the ISD group among adults 18-39 years and those aged 40 years or older.

In the multivariate analyses (Table 2), significant factors influencing overall survival included SAA course (>2 months or not, hazard ratio [HR] =2.138, *P*=0.044) and ECOG score (>1 or not, HR=2.291, *P*=0.017). In addition, a longer SAA course (>2 months or not, HR=2.093, *P*=0.040) and a higher ECOG score (>1 or not, HR=2.370, *P*=0.009) were also identified risk factors for inferior FFS.

A total of 23 patients in the HID group and 13 patients in the ISD group experienced transplant-related mortality (TRM), which occurred at a median of 96 days (range, 1-1,811 days) and 106 days (range, 2-2,893 days) after HID or ISD-SCT. Death was mainly attributable to infections (65.2% *vs*. 69.2%), followed by GVHD (21.7% *vs*. 15.4%) in the HID and ISD groups, respectively. The detailed description of TRM is summarized in Table 3.

Table 1. Patient and graft characteristics.

Variable	Haplo-identical N=183	Identical sibling N=159	*P*
Age in years, median (range)	21 (1-51)	32 (7-61)	< 0.001
Children, N (%)	72 (39.3)	16 (10.1)	
Adult, N (%)	111 (60.7)	143 (89.9)	
Male/Female, N	111/72	93/66	0.684
Disease course, mth, median (range)			
Interval from SAA diagnosis to SCT	2.0 (0.5-4.0)	1.5 (0.5-4.0)	0.012
Previous transfusion			
Median units of RBC (range)	8 (0-60)	7.5 (0-92)	0.091
Median units of PLT (range)	12 (1-160)	10 (1-130)	0.004
#ECOG pre-SCT, median, (range)	1 (0-3)	1 (0-3)	0.682
Donor-patient sex match, N (%)			< 0.001
Male-male	81 (44.3)	35 (22.0)	
Male-female	50 (27.3)	36 (22.6)	
Female-male	33 (18.0)	57 (35.8)	
Female-female	19 (10.4)	31 (19.5)	
ABO match, N (%)			0.256
Matched	95 (51.9)	96 (60.4)	
Minor mismatched	36 (19.7)	25 (15.7)	
Major mismatched	38 (20.8)	23 (14.5)	
Different	14 (7.7)	15 (9.4)	
Graft type, N (%)			< 0.001
BM+PB	167 (91.3)	126 (79.2)	
BM only	10 (5.5)	5 (3.1)	
PB only	6 (3.3)	28 (17.6)	
Median MNC, $\times 10^8$/kg (range)	10.1 (3.4-34.8)	10.5 (4.6-26.4)	0.728
Median $CD34^+$ count, $\times 10^6$/kg (range)	3.8 (0.1-18.8)	4.0 (1.0-14.6)	0.252
Median $CD3^+$ count, $\times 10^8$/kg (range)	2.2 (0.1-14.5)	2.0 (0.2-7.7)	0.033
Median $CD4^+$ count, $\times 10^8$/kg (range)	1.3 (0.1-7.4)	1.1 (0.1-5.0)	0.011
Median $CD8^+$ count, $\times 10^8$/kg (range)	0.8 (0.1-7.7)	0.7 (0.1-2.7)	0.135
Median follow-up among alive patients, months (range)	75.5 (37.1-117.7)	70.3 (39.9-115.6)	0.718
Neutrophil engraftment, median (range)	12 (9-26)	11 (6-23)	0.039
Platelet engraftment, median (range)	15 (5-91)	13 (7-40)	0.010

ECOG (Eastern Cooperative Oncology Group scale) is used to evaluate patients' performance status. SAA: severe aplastic anemia; SCT: stem cell transplantation; RBC: red blood cell count; PLT: platelet; BM: bone marrow; PB: peripheral blood; MNC: mononuclear cell count.

Hematologic recovery

Primary graft failure (PGF) occurred in three cases from the HID group. Two patients underwent a second transplant from an unrelated donor or an original donor. The remaining patient experienced hematologic recovery with complete recipient chimerism. One patient from the HID group and one from the ISD group developed secondary graft failure (SGF) at 2.5 months and 1.5 months post-transplantation, and both died of viral infection. Mixed chimerism occurred more frequently in the ISD group than in the HID group. Five cases in the HID group and 29 cases in the ISD group suffered mixed chimerism, with median occurrences of 2 months (range, 1-2) and 3 months (range, 1-18).

Among the 308 patients (161 HID and 147 ISD) who were followed up for more than 3 years, 96.7% in the HID group

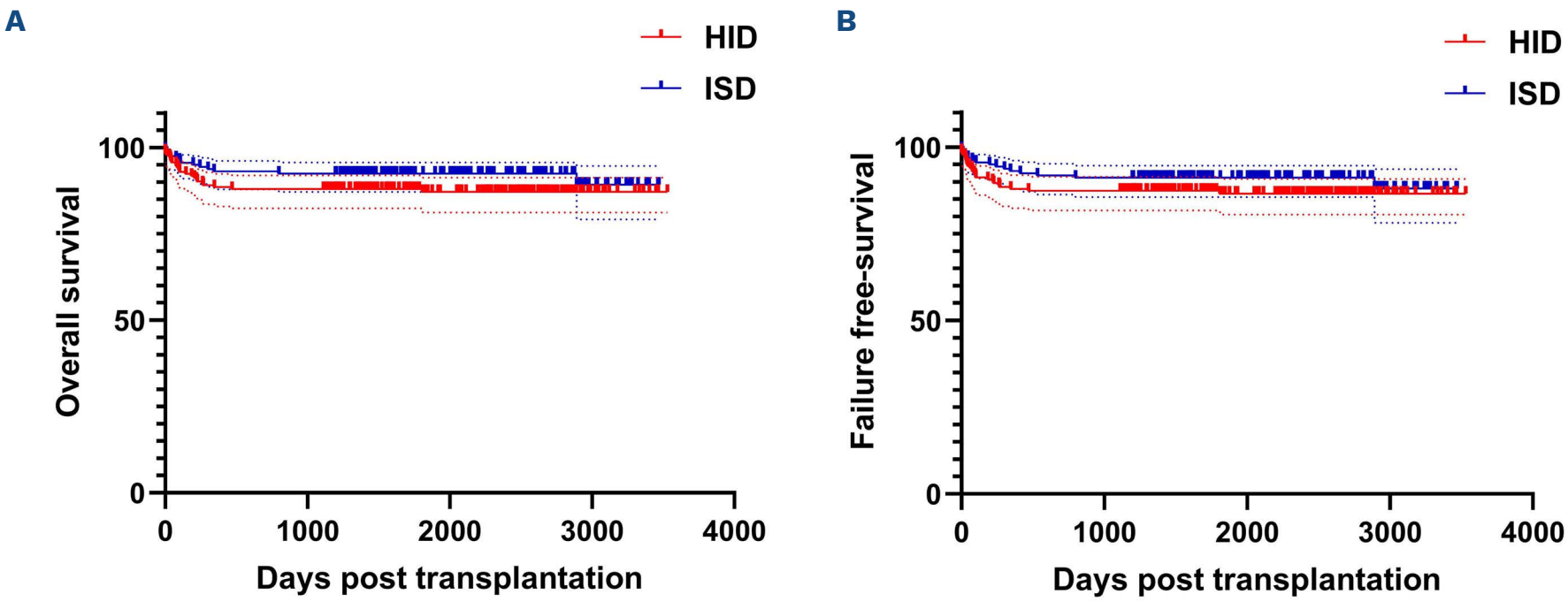

Figure 1. The survival outcomes stratified by donor source. (A) Overall survival in haploidentical donor (HID) or identical sibling donor (ISD) stem cell transplantation (SCT) cohort. (B) Failure-free survival in HID or ISD SCT cohort.

and 96.5% in the ISD group achieved normal complete blood counts (*P*=0.913). All of these patients achieved transfusion independence.

Late complications and fertility

Late complications in both cohorts were not common (Table 4), including cardiovascular, respiratory, kidney complications, second malignancy, and femoral head necrosis. During our follow-up, a total of 16 recipients (6 male in HID, 9 male and 1 female in ISD) successfully gave birth to children post allo-HSCT.

Quality of life evaluation

The estimated QoL trends are shown in Figures 2 and 3 for children and adults, respectively. Longitudinal trends were examined separately by donor sources. In children with HID HSCT, psychological, emotional, social, and role well-being improved from pre-HSCT to the 3-year time point and then further improved to the 5-year time point with significance (Figure 2). In children from the ISD HSCT group, four domain well-being improved significantly from pre-HSCT to the 3-year time point and then remained stable up to the 5-year time point (Figure 2). Among adults with HID or ISD, both physical component summary (PCS) and mental component summary (MCS) levels improved significantly at 3 years and further became more elevated through 5 years (Figure 3).

Table 2. Multivariate analysis of adverse factors associated with survival outcomes.

Outcome	Hazard ratio (95% confidence interval)	*P* value
Overall survival		
SAA course >2 in months (range)	2.138 (1.022-4.474)	**0.044**
ECOG >1 (range)	2.291 (1.161-4.517)	**0.017**
Failure-free survival		
SAA course >2 in months (range)	2.093 (1.033-4.239)	**0.040**
ECOG >1 (range)	2.370 (1.243-4.518)	**0.009**

SAA: severe aplastic anemia; ECOG: Eastern Cooperative Oncology Group scale.

Table 3. The detailed reasons of transplant-related mortality in the haploidentical and identical sibling donor cohorts.

Cohort (N)	Early TRM (within 1 year post SCT) (N)	Late TRM (1 year later post SCT) (N)
HID group (23)	Severe infection (14) GVHD (5) PTLD (1) TMA (1)	Severe infection (1) Intracerebral hemorrhage (1)
ISD group (13)	Severe infection (8) GVHD (2) SOS (1)	Severe infection (1) DAH (1)

TRM: transplant-related mortality; SCT: stem cell transplantation; HID: haploidentical donor; ISD: identical sibling donor; GVHD: graft-*versus*-host disease; PTLD: post transplant lymphoproliferative disorders; DAH: diffuse alveolar hemorrhage; TMA: thrombotic microangiopathy; SOS: sinus vein obstruction syndrome.

A comparison based on donor sources was also conducted. In the child cohort, physical, emotional, social, and role well-being did not differ by donor source at the time points of pre-HSCT, at 3 years and at 5 years (Figure 2). As shown in Figure 3A, the levels of PCS, including GH, RP, PF, and BP, were not significantly different for adults who received HID or ISD HSCT at different time points. For the assessment of MCS, patients treated with HID HSCT functioned worse than ISD HSCT at 3 years post-HSCT, mainly due to lower scores of VT, SF, and MH at 3 years. At 5 years, the levels of MCS were comparable between the HID and ISD HSCT cohorts.

Factors other than donor source affecting QoL scores at the 3-year point after transplantation were analyzed in the respective child and adult cohorts (*Online Supplementary Tables S2* and *S3*). The physical, social and role subscale scores were worse among children with a longer disease course before transplantation. In addition, the following factors affected at least one subscale among adults: age at transplant (GH, PF, SF, VT, MH) and marital status (BP and MH). The occurrence of cGVHD indicated a significant adverse impact on both eight subscales among adults and four subscales among children.

Table 4. Late complications and fertility in the haploidentical and identical sibling donor cohorts.

Long-term evaluation post HSCT	HID (N), time in years* (range)	ISD (N), time in years* (range)
Second malignancy	None	Hypophysoma (1), 8.1
Cardiovascular complication	None	Ventricular premature beats (1), 5.8
Respiratory complication	Bronchiolitis obliterans (1), 1.3	None
Kidney complication	Chronic renal failure (1), 6.6	IgA nephropathy (1), 7.9 Chronic renal failure (1), 8.1
Femoral head necrosis	(3), 1.4 (1.2-4.3)	(4), 1.2 (0.8-5.8)
Birth experience in female adults	None	(1), 5.5
Birth experience in male adults	(6), 6.9 (3.8-8.5)	(9), 4.5 (2.2-8.1)

*The time in the table refers to the interval between allogeneic stem cell transplantation to the incidence of events, median (range) years. HSCT: hematopoietic stem cell transplantation, HID: haploidentical donor; ISD: identical sibling donor.

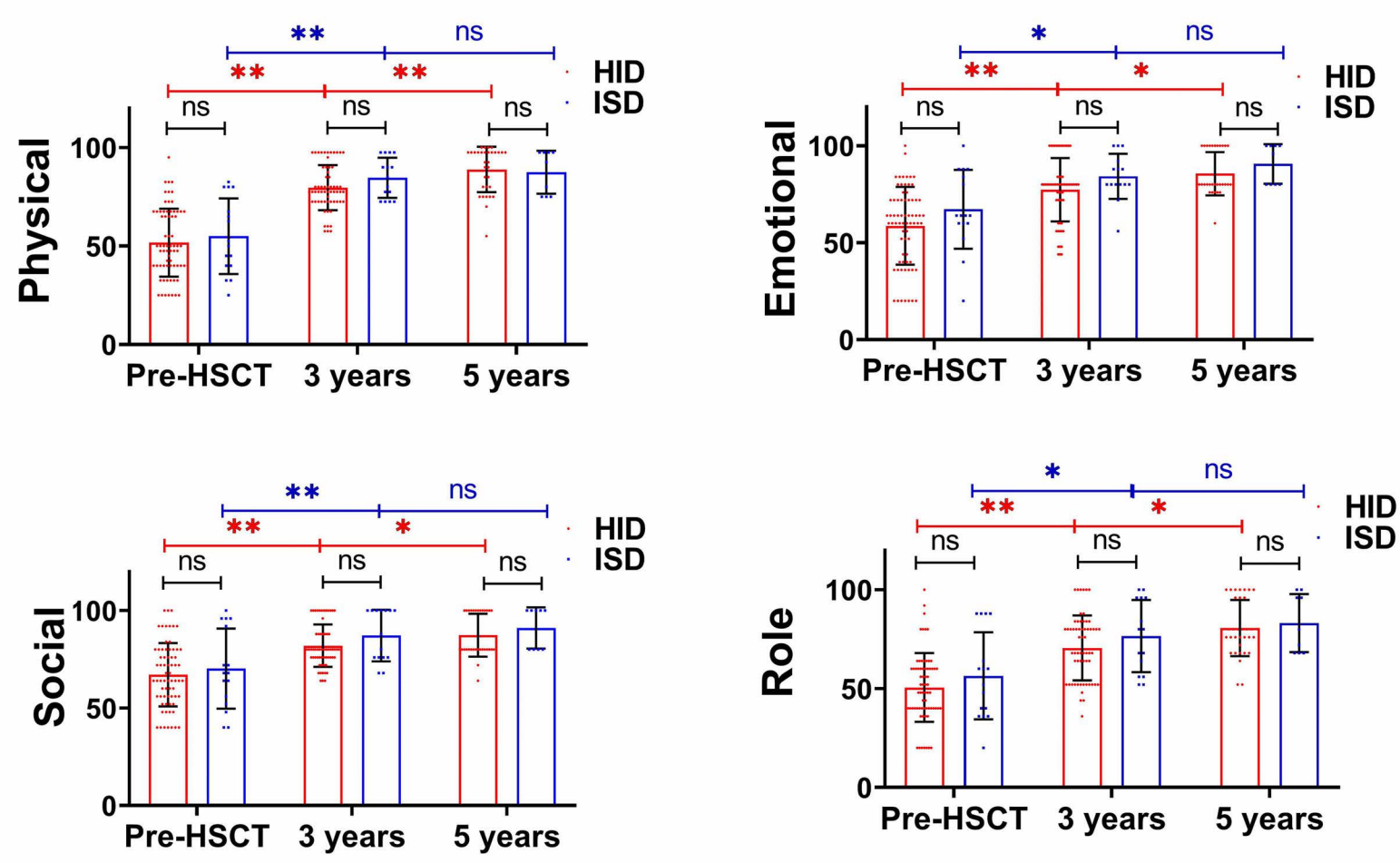

Figure 2. Comparison of longitudinal results for quality of life (PedsQL 4.0) in severe aplastic anemia children with haploidentical donor or identical sibling donor stem cell transplantation. HID: haploidentical donor (HID); ISD: identical sibling donor; SAA: severe aplastic anemia; QoL: quality of life; HSCT: hematopoietic stem cell transplantation.

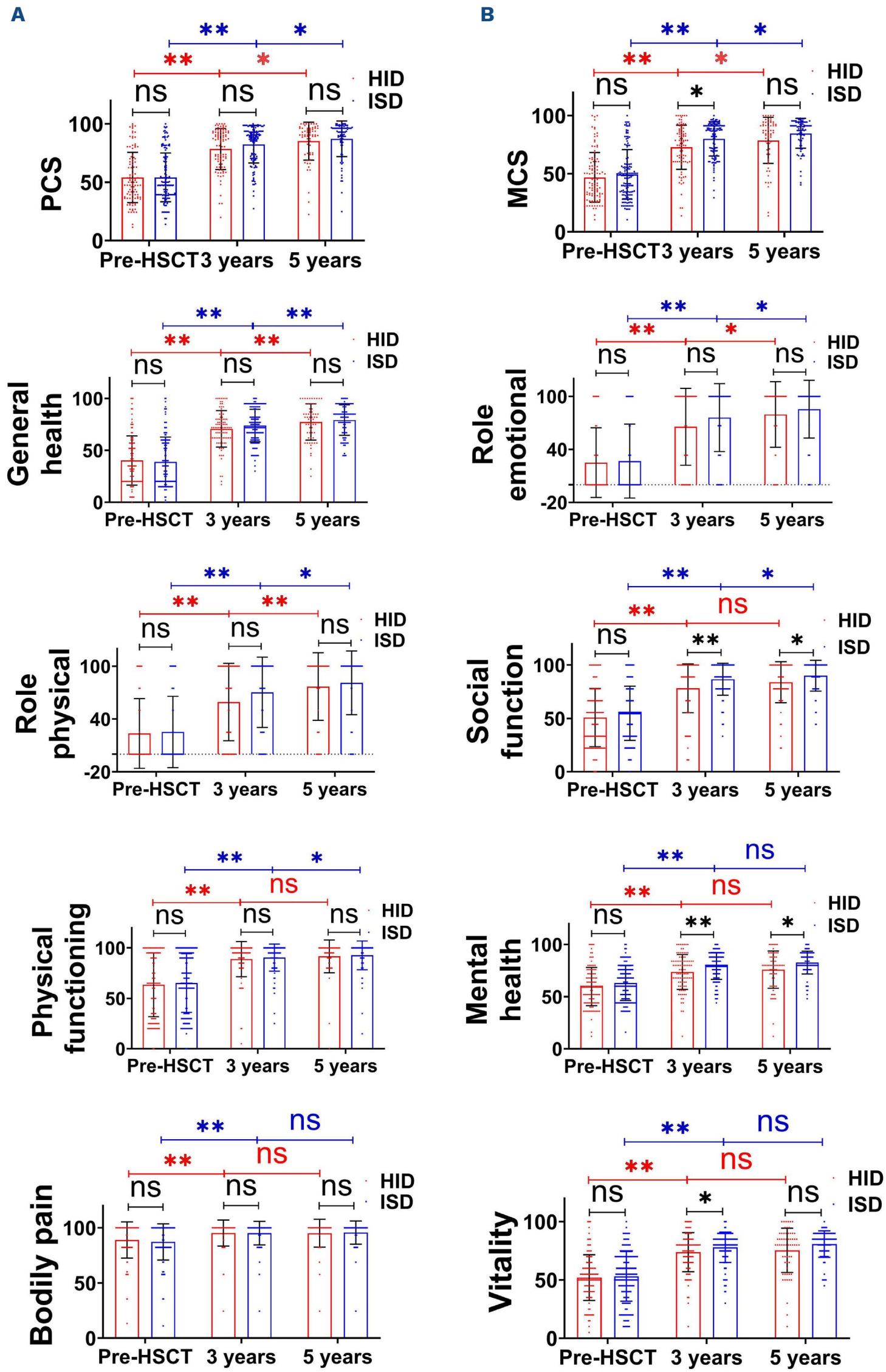

Figure 3. The comparison of longitudinal results for quality of life (SF-36) in severe aplastic anemia adults with haploidentical donor or identical sibling donor stem cell transplantation. (A) Physical component summary (PCS), including general health, role-physical, physical functioning and bodily pain. (B) Mental component summary (MCS), including role-emotional, social functioning, mental health and vitality. SF-36: social functioning questionaire.

Return to society

At the final follow-up, a total of 306 patients, including 79 children and 227 adults, were alive. In the database, the data on whether returning to society were missing were as follows: 13 children with HID-SCT, three children with ISD-SCT, 30 adults with HID-SCT, and 29 adults with ISD-SCT. In the child cohort, 39 of 50 (78.0%) in the HID group and 11 of 13 (84.6%) in the ISD group returned to school, with a median of 24.7 (range, 6.5-45.2) and 26.1 (range, 12.5-49.3) months post-transplantation (P=0.582). In the adult cohort, 50 of 67 (74.6%) and 82 of 101 (81.2%) returned to school or work, with medians of 24.1 (5.7-60.2) and 21.4 (5.8-86.5) months post-transplantation, respectively (P=0.147).

Discussion

This study compares long term outcomes between upfront HID and upfront ISD transplantation for SAA, with the largest number of SAA patients. Similar to the upfront ISD setting, upfront HID SCT had inspiring survival, complete hematologic recovery, excellent quality of life, rare late complications, and a high proportion of returning to society during the long-term follow-up.

Achieving long-term survival is a vital goal in SAA recipients. As reported previously, first-line ISD-SCT has resulted in a 10-year OS of 92% and FFS of 87% among SAA children.[5] The EBMT data for SAA patients grafted from upfront ISD demonstrated survival at 10 years of 86%, 76%, and 55% for patients aged 1-20, 21-40, and over 40 years, respectively.[2] For unrelated donor transplants, the 10-year OS were 85%, 77%, 66% and 49% for SAA patients aged 1-10, 11-30, 31-40 and over 40 years.[2] However, long-term survival from upfront HID SCT has rarely been reported. DeZern *et al.* reported favorable results in 37 patients (20 with refractory and 17 with treatment naïve SAA) receiving upfront HID SCT with the application of post-transplantation cyclophosphamide (PT-Cy), showing a 2-year OS of 86% among 17 patients in upfront cohort with a median follow-up of 32 months.[17] In our cohort, we showed comparable long-term survival outcomes in terms of 9-year OS (87.1% *vs*. 89.3%) and FFS (86.5% *vs*. 88.1%) with the use of upfront HID compared to ISD. Our group has previously compared haplo-SCT and IST in SAA as first-line treatment in the respective child and adult cohorts.[18,19] Although OS was comparable, FFS was superior in the first-line haplo-SCT setting, showing FFS rates of 89.3% *versus* 52.6% among children and 83.7% *versus* 38.5% among adults with upfront HID SCT or upfront IST. These data suggest that upfront HID SCT had similar long-term survival outcomes as ISD SCT but more favorable FFS than IST.

As for the prognostic factors affecting survival, our multivariate analysis proved that longer SAA course and higher ECOG score were associated with worse survival. However, we failed to indicate that age affected survival, which was inconsistent with previous studies.[2,20] Age was also an identified factor in our relapsed/refractory SAA cohort.[21] It is speculated that upfront transplants blunt the adverse effects of older age by protecting organ reserves mainly due to less transfusions and infections.

Stable hematologic recovery was another advantage of upfront allo-HSCT. Allo-HSCT has been indicated to restore hematopoiesis faster than IST in SAA.[4,18,19] Historically, the widespread use of haplo-SCT in SAA has been hampered due to the high incidence of graft failure, with the reporting rates of over 50% in the initial attempts.[22,23] Recently, the application of an intensive conditioning regimen has sovled this problem with the introduction of G-CSF/ATG-based or PT-Cy-based protocols.[11,24] The modified PT-Cy regimen by adding ATG has resulted in graft failure rates of 11%.[17] Our previous and current cohorts using G-CSF/ATG based protocol supported a similar incidence of engraftment with upfront HID and ISD.[11] With extended follow-up, long-term survivors showed stable donor-derived hematopoiesis, especially in the upfront HID cohort. Our findings underline that ISD SCT was associated with a higher incidence of mixed chimerism (18.7% *vs.* 2.8%), in line with results reported previously.[14,25] The results suggest that more intensive regimens might be attempted in ISD-SCT. For the recovery of routine blood tests in HID or ISD SCT, more than 95% of patients achieved normal complete blood counts at the final follow-up.

The recovery of health-related quality of life has been recognized as a major concern in allo-HSCT recipients, especially in non-malignant diseases.[15] A recent study has proven that SAA patients treated with upfront haplo-SCT scored significantly better in QoL than those treated with IST.[4] Regardless of the donor source, physical and mental well-being among SAA children and adults significantly improved at 3 years after HSCT in comparison with those before HSCT in our longitudinal analysis. Among children treated with HID SCT, the levels of QoL were further elevated to 5 years post-HSCT, which was not observed in children with ISD-SCT. Among adults treated with HID or ISD, QoL scores improved from pre-HSCT to 3 years post-HSCT and further improved to 5 years post-HSCT with regard to physical or mental evaluation. Due to the excellent QoL, the majority of children and adults returned to school or work without a significant difference between the upfront HID and ISD SCT groups.

GVHD was a major complication post allo-HSCT, especially in haploidentical cohort. Consistent with our previous report, the incidence of aGVHD was higher in HID-SCT than ISD-SCT.[11] The GFFS in recipients from HID-SCT was also inferior, however, it might be unsuitable as a long-term in-

dicator because the majority of aGVHD could be controlled in short term. Importantly, severe GVHD-related TRM was similar between the two cohorts. The occurrence of cGVHD was an identified risk factor for predicting poor QoL at 3 years, including eight subscales in adults and four subscales in children. Numerous studies have supported this finding.[26-28] Compared with the ISD group, children in the HID group had comparable scores in physical, emotional, social and role functioning at different time points. At 3 years, adults with HID SCT had a worse mental component summary than those with ISD SCT, which was probably due to a higher incidence of cGVHD history. At 5 years, the physical and mental scores were similar between the two cohorts. In the future, how to further reduce the incidence of GVHD in HID-SCT cohort is very meaningful to further improve outcomes.

We acknowledge important limitations of our study, mainly related to its retrospective nature. However, this is the largest reported series to date providing proof of long-term outcomes from upfront HID or ISD SCT, not only in survival results but also in terms of QoL and returning to society. Currently, the consensus from the Chinese Society of Hematology recommends haplo-SCT for newly diagnosed SAA patients without HLA-matched donors.[10]

In summary, the current national registry-based study presented comparable long-term transplantation outcomes with upfront haploidentical or identical sibling donors. Inspired survival, sustained donor-derived hematologic recovery, excellent QoL, and high rates of returning to society are advantages of upfront transplantation approaches. The comparable data suggest that haploidentical transplant can be considered a potential therapeutic option in the upfront setting for SAA patients in the absence of an HLA-identical related or unrelated donor.

Disclosures

No conflicts of interest to disclose

Contributions

X-JH designed the research. Z-LX, L-PX and X-JH. analyzed the data and wrote the manuscript. D-PW, S-QW, XZ, RX, S-JG, L-HX, J-MY, MJ, XW, Q-FL, JC and MZ provided patient data. All authors gave final approval for the manuscript.

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Data-sharing statement

The data that support the findings of this study are available upon reasonable request from the corresponding author.

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