Haploidentical Related Donor versus Matched Sibling Donor Allogeneic Hematopoietic Stem Cell Transplantation for Acute Myeloid Leukemia and Myelodysplastic Syndrome Aged Over 50 Years: A Single-Center Retrospective Study.

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Abstract

BACKGROUND Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a potentially curative therapeutic option for patients with acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS). Increasing data supports the utility of haploidentical related donor (HID) HSCT in fit older patients and resulting in improvement of outcomes. This study compared the outcomes of acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) patients age ≥50 years underwent haploidentical related donor (HID) or matched sibling donor (MSD) allogeneic hematopoietic stem cell transplantation (allo-HSCT).METHODS We retrospectively studied 38 patients with AML/MDS aged ≥50 years who underwent HID transplantation and compared their outcomes with 55 similarly aged patients who underwent MSD transplantation.RESULTS The 100-day cumulative incidence of II-IV° acute graft-versus-host disease (GVHD) were 34.2 ± 7.7% and 23.6 ± 5.7%, respectively, in HID and MSD groups (P = 0.189), and III-IV° acute GVHD were similar between two groups (5.3% and 7.3%, respectively, P=0.700). The 2-year cumulative incidence of limited and extensive chronic GVHD was not statistically different in HID and MSD groups(22.8 ± 10.8% vs. 18.2 ± 6.0% and 18.3 ± 10.4% vs. 22.1 ± 6.8%, P = 0.890 and P=0.424, respectively). The 2-year cumulative incidences of relapse (29.5±10.3% and 20.7 ±6.1%, P=0.458), 2-year overall survival (58.5±9.7% and 67.9±6.8%, P=0.373), 2-year transplant-related mortality (17.3±6.4% and 15.0±5.3%, P=0.717), 2-year progression free survival (56.8±9.7% and 64.6±7.4%, P=0.312) were similar in the two groups.CONCLUSION The present data showed similar outcomes in patients aged 50 years and older underwent HID compared to MSD at our institution.

Background

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a curative therapy for patients with acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS). However, most of these patients are older adults aged ≥60 years(1). Historically, older adults were not considered for allo-HSCT given their frequent comorbidities and increased transplant-related mortality. With technical advances in allo-HSCT, its use in the older population has broadened, and its upper age limit has risen from 40 to 45 to 70 and to 75 years over the past 4 decades(2, 3). A growing number of studies have demonstrated that allo-HSCT results in improved outcomes and is not contraindicated in older patients with AML or MDS(4-8).

Although the HLA-identical sibling donor (matched sibling donor (MSD)) is the best choice for allo-HSCT, it is a difficult option for older patients since siblings would be expected to be similar in age and are thus often unavailable or ineligible(9). In comparison, a haploidentical donor (HID) is available to nearly all patients requiring allo-HSCT. Over the last decade, the efficacy and safety of HID transplants in hematologic malignancies have been confirmed. Some studies have shown that an HID might achieve comparable outcomes to an HLA-matched sibling donor (MSD) in hematologic malignancies(10-13). In this report, we compared the transplant outcomes between HID and MSD transplants for AML and MSD patients aged ≥50 years. The results show that HID transplantation is feasible and safe for elderly AML/MDS patients.

Methods

Study Design and Data Collection

This is a retrospective study based on data from the transplantation database in our center. The inclusion criteria of this study were patients aged ≥50 years diagnosed with de novo AML or MDS who underwent HID transplant or MSD transplant between January 2013 and June 2018. This study was performed in accordance with the principles of the Declaration of Helsinki. Data were obtained from the patient medical records. Variables collected for all patients included demographic features, pretransplant-related parameters, transplant-related parameters and graft-versus-host disease (GVHD) status, relapse-related parameters, treatments-related parameters, survival, infections, and so on. Written informed consent for submitting data to our database was routinely obtained when a patient was admitted to our center.

HLA typing

High-resolution DNA typing for HLA-A, HLA-B, HLA-C, HLA-DRB1, and HLA-DQB1 was performed for all patients and donors. MSDs were related sibling donors matching ≥9/10 HLA molecules, and HIDs were related donors matching 5–8/10 HLA molecules.

Conditioning and Transplants

All patients received myeloablation conditioning regimens including BuCy (busulfan 3.2 mg/kg/day, days -7 to -4, cyclophosphamide 60 mg/kg/day, days -3 and -2, and simustine 250 mg/m2, day -3), BF (busulfan 3.2 mg/kg/day, days -6 to -3, fludarabine 30 mg/m2/day, days -7 and -3, and simustine 250 mg/m2, day -3) or TBI+Cy (total body irradiation with 4.5 Gy/day, days -5 and -4, and cyclophosphamide 60 mg/kg/day, days -3 and -2). In the HID group, 21 patients received BuCy, 11 patients received BF, and 6 patients received TBI+Cy. In the MSD group, 31 patients received BuCy, 19 patients received BF, and 5 patients received TBI+Cy. All HID patients were transplanted with a combination of bone marrow (BM) and peripheral blood stem cell (PBSC) grafts, whereas all MSD patients received PBSC grafts. Ciclosporin A (CsA), methotrexate (MTX) (on days +1, +3, and +6) and mycophenolate (MMF) were administered to patients undergoing MSD transplant for GVHD prophylaxis. CsA + MTX + MMF+ ATG was administered to patients undergoing HID transplant for GVHD prophylaxis(14, 15).

Evaluation points and definitions

This study mainly focused on engraftment, GVHD, relapse, transplant-related mortality (TRM), overall survival (OS), and progression-free survival (PFS). TRM was estimated as death without evidence of leukemia recurrence. PFS was defined as survival in continuous complete remission without hematological relapse. aGVHD and cGVHD were graded according to the guidelines in the literature(16).

Statistical analysis

Our study data were analyzed on June 30, 2019. Comparisons of categorical variables were made by means of chi-squared and Fisher exact tests for small numbers. Differences between numerical variables were calculated by means of a 2-sample t test. The incidence of time-dependent variables was estimated by the Kaplan-Meier method. A Cox regression model was used to analyze prognostic factors for relapse, PFS, TRM and OS. Numerical variables were analyzed as categories based on their values being below or above the median of the entire cohort. All statistical tests were two-sided, and a P-value less than 0.05 was considered significant. A multivariate analysis was performed using the Cox proportional hazards model. Variables were included in the multivariate model if they were conceptually important or if they approached or attained statistical significance by univariate analysis. All data analysis was performed with SPSS 24.0 (SPSS, IBM, USA).

Results

Patient Clinical and Transplant Characteristics

A total of 93 AML or MDS patients aged ≥50 years after allo-HSCT were enrolled in this retrospective study, including 38 patients who underwent HID allo-HSCT and 55 patients who underwent MSD allo-HSCT. The median age of the patients was 58 (range, 50.4 to 69) years in the HID group and 57.5 (range, 50.5 to 68) in the MSD group (P=0.762). The median follow-up was 13.1 m (range, 0.4-67.8 m) in the HID group and 17.2 m (range, 2.1–68.8 m) in the MSD group (P=0.350). Thirty-four patients in the HID group were diagnosed with AML (29 CR and 5 no-CR), and 4 were diagnosed with MDS. In the MSD group, 46 patients had AML (38 CR and 8 no-CR), and 9 had MDS. The proportion of patients with refractory AML in the two groups was similar (P=0.999). The characteristics of the patients, donors and transplants are summarized in *Table 1.* Significant differences were noted in the donor age, the stem cell source and the family relationship between recipients and donors between both groups. There were no significant differences in patient age, sex, sex match, disease status, conditioning regimen, hematopoietic cell transplantation comorbidity index (HCT-CI) score, time of follow-up, or dose of nucleated cells between the two groups. The patients' clinical and transplant characteristics are shown in *Table 1.*

Engraftment

All patients achieved hematopoietic reconstitution except one patient in the HID group who died of graft failure. Neutrophil reconstruction occurred in the HID group at a median of 12 d (range, 9–18) and in the MSD group at a median of 12 d (range, 8–22) (P=0.458). Platelet reconstruction in the HID and MSD groups occurred at a median of 13 d (range, 10–53) and 13 d (range, 8–91), respectively (P=0.333).

GVHD

The 100-day cumulative incidences of grade II-IV aGVHD were 34.2 ± 7.7% and 23.6 ± 5.7% in the HID and MSD groups, respectively (P = 0.189). The incidences of grade III-IV aGVHD were 5.3 ± 3.6% and 7.3 ± 3.5% in the HID and MSD groups, respectively (P = 0.700). One patient died of grade IV gut aGVHD in the MSD group, while no patients died of aGVHD in the HID group. The 2-year cumulative incidences of

limited and extensive cGVHD were 7.3 ± 5.0% and 9.2 ± 6.4% and 14.8 ± 5.2% and 18.0 ± 5.8% in the HID and MSD groups, respectively (P = 0.890 and P=0.424, respectively). One patient died of cGVHD in the HID group, and three died of cGVHD in the MSD group (2.63% vs. 5.45%, P=0.642). The incidences of aGVHD and cGVHD are shown in Figure 1 and Figure 2. Sex mismatches were significantly associated with a higher risk of grade II-IV aGVHD and cGVHD (HR 2.400, CI 1.013-5.402, P=0.032 and HR 2.275, CI 1.022-5.011, P=0.042, respectively) in the multivariate analysis (*Table 3*).

TRM

The causes of death included relapse (n = 15) and TRM (n = 16). Of the 16 patients who died of TRM, infections (56.3%, n = 9) were the main cause, including 4 (25.0%) infectious diseases for HID transplant recipients and 5 (31.3%) for MSD transplant recipients. Other causes included aGVHD (6.3%, n = 1), cGVHD (18.9%, n = 3), thrombotic microangiopathy (6.3%, n = 1), cerebral infarction (6.3%, n = 1), and graft rejection (6.3%, n = 1). The 2-year cumulative incidences of TRM in the HID and MSD groups were 17.3 ± 6.4% and 15.0 ± 5.3%, respectively (P = 0.717, Figure 3A). Patient age and sex mismatch were significantly associated with a higher risk of TRM (HR 3.703, CI 1.332-11.013, P=0.018 and HR 4.901, CI 1.310-14.011, P=0.003, respectively) in the multivariate analysis (*Table 3*).

Infections

Patients in the HID group had significantly higher rates of CMV DNAemia than patients in the MSD group (p = 0.0005). The incidence of other major infectious complications, including sepsis, CMV disease, EBV DNAemia and invasive fungal infection, were similar between the 2 groups (*Table 2*).

Relapse and Survival

The median follow-up was 13.1 m (range, 0.4-67.8 m) in the HID group and 17.2 m (range, 2.1–68.8 m) in the MSD group (P=0.350). No difference was observed in the cumulative incidence of relapse, PFS and OS according to donor type. Leukemia relapse occurred in 7 and 9 patients in the HID and MSD groups, respectively (P = 0.559). The 2-year cumulative incidence of relapse (29.5 ± 10.3% and 20.7 ± 6.1%, respectively, P = 0.458), 2-year PFS (56.8±9.7% and 64.6±7.4%, respectively, P=0.312) and 2-year OS (58.5±9.7% and 67.9±6.8%, respectively, P=0.373) were similar in the HID and MSD groups (Figure 3B, Figure 4). Disease status at transplant was significantly associated with an increased risk of relapse (HR 6.756, CI 2.345-19.455, P<0.001) in the multivariate analysis (*Table 3*). Patient age (older than 60), disease status at transplant and sex mismatch were independent risk factors for OS (HR 2.135, CI 1.008-5.620, P=0.044; HR 3.353, CI 1.633-7.908, P=0.003; and HR 3.450, CI 1.543-7.211, P=0.001, respectively) and PFS (HR 2.324, CI 1.112-5.405, P=0.048; HR 3.659, CI 1.629-8.714, P=0.001; and HR 3.357, CI 1.631-6.976, P=0.001, respectively).

Discussion

Here, we report the outcomes of HID versus MSD allo-HSCT for patients with AML/MDS aged ≥50 years. The results showed that the two cohorts had comparable outcomes, including incidences of TRM and GVHD as well as relapse and survival.

Traditionally, allo-HSCT in the elderly has had a higher risk of TRM because of the patients' frequent comorbidities and poor performance status. Reports from main transplant centers for older patients have shown 2-year TRM rates ranging from 7% to 35%(2, 7, 17-19). Some studies have reported that a myeloablative conditioning regimen (MAC) is associated with higher TRM rates than a nonmyeloablative conditioning (NMAC) or a reduced-intensity (RIC) conditioning regimen(20-23). In the present study, the 2-year cumulative incidences of TRM in the HID and MSD groups ranged from 15% to 17.3%. A report from Seattle of 1,055 patients undergoing allo-HSCT showed that the 2-year rate of TRM was 14%, 21%, and 41% for patients with HCT-CI scores of 0, 1 to 2 and 3 or more, respectively(24). A reasonable interpretation of the relatively lower rate of TRM is that our patients had relatively lower HCT-CT scores than the patients in other studies. In this report, only 18.4% of the patients in the HID group and 16.3% of the patients in the MSD group had HCT-CI scores ≥3. Additionally, 11 patients (28.9%) in the HID group and 19 patients (34.5%) in the MSD group received a BuF MAC. This may also be one of the reasons for the lower TRM. We and other researchers have shown that patients who receive a BuF MAC have a lower TRM incidence than those who receive BuCy(25, 26). Whether HID transplants have a higher rate of TRM than MSD transplants is currently under study. A growing number of studies show that there is no difference between HID and MSD transplants in terms of TRM, including in elderly patients(17-19, 27, 28). Similar results were obtained in this study.

Relapse is a major cause of failure in patients undergoing allo-HSCT. Many factors influence relapse, such as donor resources, disease status at transplants, patient age, conditioning regimen, and so on(29-31). In terms of donor resources, some studies showed that HID transplantation had a stronger GVL effect than MSD transplantation, decreasing the rate of relapse(14, 32, 33). Other studies suggested that there was no difference in the relapse rate between two donor resources(13, 17, 18, 34, 35). In the present study, there was no difference in relapse between the two groups. In multivariate analysis, we found that disease status at transplant was an independent risk factor for relapse, similar to other reposts(36, 37).

GVHD is the most common transplant-related complication that affects the outcomes of transplant patients(38, 39). Traditionally, HID transplantation was associated with a higher incidence of GVHD than MSD transplantation. Over the last decade, great improvements have been made in prophylaxis for GVHD in HID transplantation, especially the use of T-cell depletion in vivo by means of Cy or ATG(17, 32, 40). A growing amount of evidence has shown that the incidences of GVHD in HID transplantation are not different from those in MSD transplantation, especially in terms of cGVHD(14, 17, 27, 40-42). In the ATG protocol, our previous results showed that the incidences of grade II-IV aGVHD were higher for HID transplantation than for MSD transplantation, but the incidences of severe aGVHD and cGVHD were comparable between the two groups(14, 32, 42). In this study, HID transplantation was associated with a trend of higher incidences of grade II–IV aGVHD than those seen in MSD transplantation. In multivariate analysis, we found that a sex-mismatched donor (female donor/male recipient) was significantly

associated with a higher risk of aGVHD and cGVHD than a sex-matched donor. Several other studies have also reported the same results(43-47).

As we know, ATG as GVHD prophylaxis are associated with an increased incidence of infections, especially fatal viral infections(48-50). In the present study, although HID transplantation was associated with much higher incidences of CMV DNAemia than MSD transplantation, the number of deaths caused by viral diseases and other infectious diseases did not differ between the two groups. A possible explanation for these results might be the extensive experience at the study centers in effectively managing infectious diseases, resulting in many patients with CMV or other infections avoiding TRM.

The limitations of this study are the relatively small number of patients and the retrospective nature of this single-center study. We were not able to perform subgroup analyses, which would have been informative in some specific settings, such as in terms of advanced cytogenetics and/or older age. The sample size limitations in the oldest age group may have masked smaller differences in outcomes. Selection bias may also have influenced inferences from the data. It is possible that the older patients included in this study were a highly selected group with lower HCT-CI scores.

Conclusion

The present data showed similar outcomes in patients aged 50 years and older who underwent HID transplantation compared to MSD transplantation at our institution. We conclude that HID transplantation is feasible and safe for elderly AML/MDS patients. The lack of an HLA-identical donor in elderly patients with AML/MDS should not preclude allo-HSCT.

Abbreviations

Allo-HSCT: allogeneic hematopoietic stem cell transplantation

AML: acute myeloid leukemia

ATG: anti-thymocyte globulin

BM: bone marrow

Bu: busulfan

CI: confidence interval

CMV: cytomegalovirus

CsA: ciclosporin A

Cy: cyclophosphamide

CR: complete remission

EBV: Epstein-Barr Virus

GVHD: graft-versus-host disease

GVL: graft-versus leukemia

HCT-CI: hematopoietic cell transplantation comorbidity index

HID: haploidentical related donor

HLA: human leukocyte antigen

HR: hazard ratio

MAC: myeloablative conditioning

MDS: myelodysplastic syndrome

MMF: mycophenolate

MSD: matched sibling donor

MTX: methotrexate

NMAC: nonmyeloablative conditioning

OS: overall survival

PBSC: peripheral blood stem cell

PFS: progression-free survival

RIC: reduced-intensity

TBI: total body irradiation

TRM: transplant-related mortality

Declarations

Ethics approval and consent to participate: The study’s protocol was approved by Southern Medical University Nanfang Hospital’s Research Ethics Committee, and all the study’s procedures were undertaken in accordance with the principles of the 1983 revision of the Declaration of Helsinki.

Consent for publication: Not applicable.

Availability of data and material: The datasets are available from the corresponding authors on reasonable request.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: QL generated the study idea. FH, ZF, NX, LX, HL, PS, LJ, YZ and JS collected data, and JH carried out statistical analysis and drafted the manuscript. QL revised the manuscript. All authors read and approved the manuscript.

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Tables

Table 1. Patient clinical and Transplants Characteristics.

Characteristics	HID group(N=38)	MSD group(N=55)	P value
Age, median (range)	58(50.4-69)	57.5(50.5-68)	0.762
Sex			0.823
Male	26(68.4%)	39(70.1%)	
Female	12(31.6%)	16(29.1%)	
Follow-up in months, median (range)	13.1(0.4-67.8)	17.2(2.1-68.8)	0.350
Disease, N (%)			0.264
AML	34(89.5%)	44(80.0%)	
MDS	4(10.5%)	11(20.0%)	
Stem cell source N (%)			<0.0001
BM+PBSC	38(100%)		
PBSC		55(100%)	
AML in CR, N (%)			0.999
CR	29(85.29%)	38(82.61%)	
No CR	5(14.71%)	8(17.39%)	
Donor age, median (range)	26(14-48)	49(39-62)	<0.0001
Sex mismatch, N (%)			0.167
Female donor/Male recipient	8(21.1%)	20(36.4%)	
Others(M/M,F/F,M/F)	30(78.9%)	35(63.6%)	
Relationship between donor and recipient, N (%)			<0.0001
sibling	10(26.3%)	55 (100%)	
child	28(73.4%)	0	
HCT-CI score			
0-2	31(81.6%)	46(83.7%)	0.788
≥ 3	7(18.4%)	9(16.3%)	
Mononucleated cell count (range, 108/kg)	9.9(3.5-12.5)	10.0(6.05-38)	0.432

HID, haploidentical related donor;MSD, matched sibling donor; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; BM, bone marrow; PBSC, peripheral blood stem cell; CR, complete remission; HCT-CI, hematopoietic cell transplantation comorbidity index.

Table 2. Characteristics of infectious complications post-SCT

	HID group(N=38)	MSD group(N=55)	P
Sepsis	7(18.42%)	7(12.73%)	0.558
CMV DNAemia	23(60.53%)	13(23.64%)	0.001
CMV disease	1(2.63%)	1(1.82%)	0.999
EBV DNAemia	2(5.26%)	4(7.27%)	0.999
Invasive fungal infection	12(31.58%)	19(34.55%)	0.826
Urinary tract infection	3(7.89%)	1(1.82%)	0.301

HID, haploidentical related donor; MSD, matched sibling donor; CMV, cytomegalovirus; EBV, epstein-barr virus.

Table 3. Multivariate analysis of outcomes.

Outcome/variable	HR(95% CI)	P
OS		
Patients age		
≥60	2.135(1.008-5.620)	**0.044**
<60	1	
Disease status at SCT		
No CR	3.353(1.633-7.908)	**0.003**
CR	1	
Sex mismatch		
Female donor/male recipient	3.450(1.543-7.211)	**0.001**
Others(M/M,F/F,M/F)	1	
Type of transplant		
HID	1.038(0.728-1.882)	0.243
MSD	1	
PFS		
Patients age		
≥60	2.324(1.112-5.405)	**0.048**
<60	1	
Disease status at SCT		
No CR	3.659(1.629-8.714)	**0.001**
CR	1	
Sex mismatch		
Female donor/male recipient	3.357(1.631-6.976)	**0.001**
Others(M/M,F/F,M/F)	1	
Type of transplant		
HID	1.004(0.732-1.741)	0.303
MSD	1	
TRM		
Patients age		
≥60	3.703(1.332-11.013)	**0.018**
<60	1	
Disease status at SCT		
No CR	1.554(0.355-7.328)	0.588
CR	1	
Sex mismatch		
Female donor/male recipient	4.901(1.310-14.011)	**0.003**
Others(M/M,F/F,M/F)	1	
Type of transplant		
HID	1.114(0.539-1.591)	0.389
MSD	1	

Relapse		
Patients age		
≥60	1.211(0.273-5.325)	0.813
<60	1	
Disease status at SCT		
No CR	6.756(2.345-19.455)	**<0.001**
CR	1	
Sex mismatch		
Female donor/male recipient	2.335(0.786-6.803)	0.124
Others(M/M,F/F,M/F)	1	
Type of transplant		
HID	0.945(0.539-1.843)	0.314
MSD	1	
II-IV°aGVHD		
Patients age		
≥60	1.221(0.412-3.531)	0.695
<60	1	
Sex mismatch		
Female donor/male recipient	2.400(1.013-5.402)	0.032
Others(M/M,F/F,M/F)	1	
Type of transplant		
HID	1.390(0.529-2.602)	0.194
MSD	1	
cGVHD		
Patients age		
≥60	1.283(0.413-3.509)	0.741
<60	1	
Sex mismatch		
Female donor/male recipient	2.275(1.022-5.011)	0.042
Others(M/M,F/F,M/F)	1	
Type of transplant		
HID	1.193(0.408-3.489)	0.402
MSD	1	

OS, overall survival; PFS, progression free survival; TRM, transplant related mortality; aGVHD, acute graft-versus-host disease; cGVHD, chronic graft-versus-host disease; CR, complete remission; HID, haploidentical related donor; MSD, matched sibling donor.

Figures

Fig 1

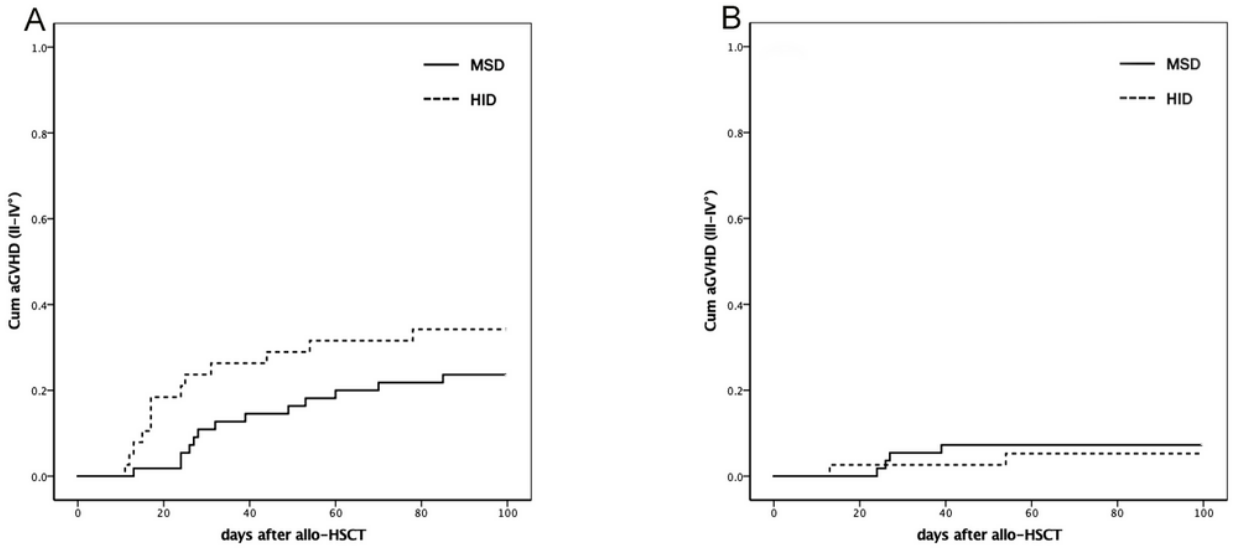

Figure 1

(A)Cumulative incidence of II-IV°aGVHD after HID or MSD transplants (P = 0.189); (B) cumulative incidence of III-IV° aGVHD (P = 0.700).

Fig 2

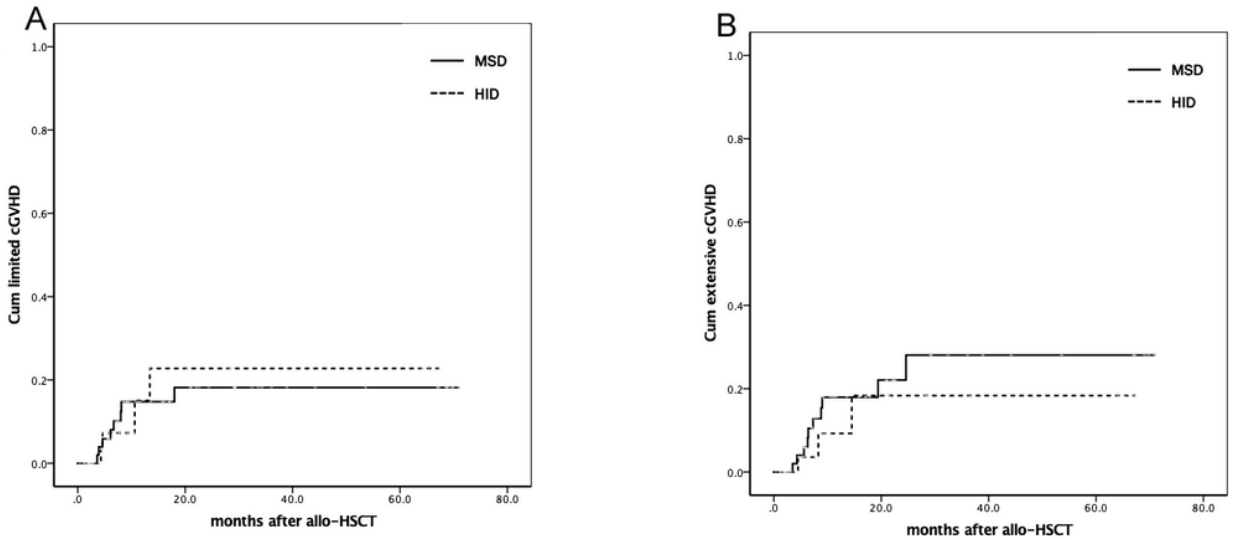

Figure 2

(A) cumulative incidence of limited cGVHD(P=0.890) ;(B) cumulative incidence of extensive cGVHD(P=0.424).

Fig 3

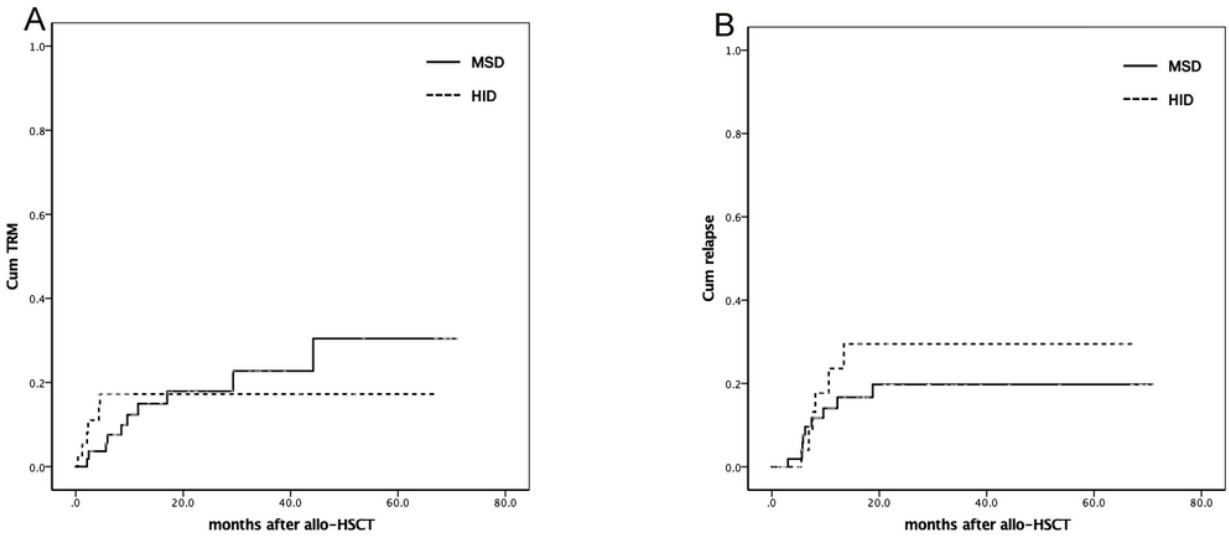

Figure 3

(A) cumulative incidence of TRM (P = 0.717); (B) cumulative incidence of relapse (P = 0.458).

Fig 4

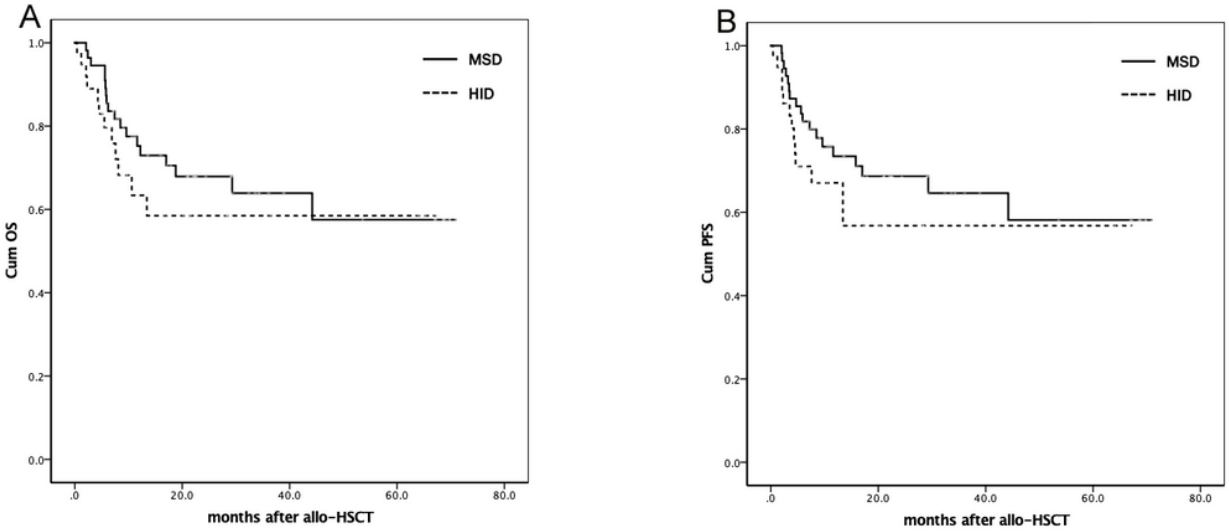

Figure 4

(A) probability of survival (P=0.373); (B) probability of PFS (P=0.312).