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The outcome and predictive model of allogeneic hematopoietic stem cell transplantation among elderly patients with severe aplastic anemia from the Chinese Blood and Marrow Transplant Registry Group

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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.

Allogeneic haematopoietic stem cell transplantation (allo-HSCT) remains a first-line therapeutic option for younger patients with severe aplastic anaemia (SAA)(1). The elderly age has been proven to be associated with relatively higher mortality of allo-HSCT treating SAA, partly due to poorer organ function(2). Data from the European Society for Blood and Marrow Transplant (EBMT) and the Center for International Blood and Marrow Transplant Research (CIBMTR) have demonstrated that allo-HSCT led to a 3-year overall survival (OS) of 56% among 499 SAA patients older than 50 years(3). In this large-size sample study, all transplants were from matched sibling (MSD) or matched unrelated donors (MUD) but lacked haploidentical donors(3). In recent decades, haploidentical donor (HID) HSCT has made great advances for SAA, and the upper limit of age among SAA recipients has been continuously broken (4, 5). A retrospective study indicated comparable survival outcomes between transplantation from HID and MSD or unrelated donors (URD) for SAA patients aged 40 years and older, with a median age of 43-48.5 years and 3-year OS of 86.7-100% among the three groups(6). However, the outcomes of allo-HSCT for SAA patients older than 50 years, especially including HID-HSCT, have rarely been reported.

We analysed the outcomes of SAA patients older than 50 years based on the data of the Chinese Blood and Marrow Transplant Registry Group (CBMTR), with the majority receiving HID HSCT. A total of 76 patients who underwent a first allo-HSCT between January 2014 and December 2022 were

enrolled from 25 transplant centres. The study protocol was approved by the institutional review board. All of the patients gave their written informed consent for the procedure. The details of conditioning regimen from different donor type have been summarized in Supplemental Table 1. The details of GvHD prophylaxis have been previously described(6, 7).

As shown in Table 1, 16 (21.1%) patients received HSCT from MSD, 55 (72.4%) from HID, and 5 (6.5%) from URD groups. The median time from diagnosis to allo-HSCT was 4.2 (range, 0.2-279.8) months in the entire cohort. For HSCT timing, forty-one patients underwent salvage transplantation after the failure of IST, and 22 received ATG including IST. The last follow-up for all living patients was September 30, 2023. The median follow-up for surviving patients following HSCT was 821 days (range, 278-3434). The comparisons of basic characteristics among different donor groups were provided in Supplemental Table 1.

Seventy-one patients survived for more than 28 days. A total of 70 (98.6%) patients achieved myeloid engraftment, and all of them were complete donor chimerism at 1 month post transplantation. The cumulative incidence of myeloid engraftment was 92.0±0.1% in the entire cohort, with the median time of 14 (range, 8–28) days. Fifty-nine patients achieved platelet engraftment within a median time of 15 (range 8–100) days. The cumulative incidence of platelet recovery was 77.6±0.2%. The cumulative incidences of myeloid

engraftment and platelet recovery among three groups were indicated in Supplementary Figure 1A and 1B.

With regard to acute GVHD, none of the patients in the MSD cohort experienced grade II-IV aGVHD. The cumulative incidences of grade II-IV aGvHD and III-IV aGvHD at 100 days were 10.9±0.2% vs. 20.0±4.0% (*P* = 0.295), 5.5 ± 0.1% vs. 20.0 ± 4.0% (*P* = 0.222) after HID and URD transplants (Supplementary Figure 1C and 1D). Patients who survival longer than 100 days were evaluable for the incidence of chronic GvHD based on 2014 NIH criteria. None of the patients in the URD group suffered cGvHD. HID patients had a seemingly higher three-year cumulative incidence of cGvHD than MSD patients, but the difference was not significant (24.8 ± 0.7% vs. 6.3 ± 0.4%, *P* = 0.230, Supplementary Figure 1E). The MSD and HID groups had similar three-year incidences of moderate cGvHD (6.3 ± 0.4% vs. 6.2 ± 0.2%, *P* = 0.896, Supplementary Figure 1F), and no severe cGvHD occurred.

In terms of virus reactivation within 100 days, the cumulative incidences of CMV and EBV were 43.4±0.3% and 17.1±0.2%, respectively, in the entire cohort. The MSD, HID and URD groups had similar CMV occurrences of 43.8 ±1.7%, 43.6±0.5%, and 40.0±6.8% (*P* = 0.896, Supplementary Figure 1G) and EBV of 18.8±1.0%, 18.2±0.3%, and 0% (*P* = 0.584, Supplementary Figure 1H), respectively. One patient in HID group suffered EBV related posttransplant lymphoproliferative disorders (PTLD).

A total of 17 patients suffered transplantation-related mortality (TRM), with a median of 51 (range, 4-384) days (Supplementary Table 1). The overall survival at 3 years was 77.2±4.9% in the whole cohort. In univariate analysis (Supplementary Table 2), the 3-year OS of patients in the MSD, HID, and URD groups was 100%, 71.8±6.2%, and 60.0±21.9%, respectively (P = 0.053, Figure 1). We also observed that older age of patients, female sex, and higher HCI-CI were associated with worse survival. In addition, a trend was observed for ABO blood type incompatibility, with incompatible pairs decreasing the OS probability. The above potentially significant factors for survival were included in the multivariate analysis. The multivariate analysis showed that the hazard ratio was increased for those with older age (≥ 55 years, relative risk (RR) 4.539, 95% CI 1.590–12.963, P = 0.005), higher HCT-CI (≥ 2, RR 7.726, 95% CI 2.761-21.620, P < 0.001), and ABO blood type incompatibility (RR 5.629, 95% CI 1.808-17.532, P = 0.003) when predicting OS. Combining these three parameters, a predictive risk model of allo-HSCT for elderly SAA patients was established: low risk (0 factor, n = 19), intermediate risk (1 factor, n = 41), and high risk (2-3 factors, n = 16). The probabilities of OS at three years after allo-HSCT were 100%, 82.9 ± 5.9%, and 31.3 ± 13.2% for the low-, intermediate-, and high-risk groups, respectively (P < 0.001; Figure 2).

The survival outcomes from CBMTR indicated that allo-HSCT led to a three-year survival of 77.2% among SAA patients older than 50 years. Currently, patients had estimated 3-year OS of 100% and 60% after

transplantation from MSD and MUD, and the corresponding 3-year OS rates of MSD and MUD HSCT were 57% and 48% from EBMT or CIBMTR(3). First, patients from CBMTR were younger than those from EBMT or CIBMTR, with a median age of 54 years versus 57.8 years at transplantation. Second, the transplants from EBMT or CIBMTR were performed between 2005 and 2016, while those from CBMTR were performed between 2014 and 2022. The improvement of transplantation techniques and supportive care was also a factor that cannot be ignored when transplantation was performed at different periods.

Herein, fifty-five patients with allo-HSCT were from haploidentical donors, resulting in a three-year OS of 71.8%. Previously, the efficacy of haploidentical transplantation has been proven among younger recipients (4, 5, 8). With the exception of early mortality, forty-nine of 50 patients (98%) achieved myeloid engraftment. The GvHD incidences were reported similarly to a previous study. The incidences of II-IV aGvHD and 3-year cGvHD were 10.9% and 24.8%, respectively, in our cohort. DeZern et al. observed II-IV aGvHD and 1-year cGvHD of 16% and 26% in haploidentical transplantation treating SAA(8). When the causes of mortality were analysed, severe infection and regimen-related toxicities were the most common causes, which might be attributable to weak immune function and fragile organ function among elderly SAA patients.

We observed that older age, higher HCT-CI scores and ABO blood type incompatibility were obviously adverse factors. Consistently, Giammarco *et al.* found that the 5-year survival of patients aged 50 to 59 years and aged over 60 years was 58% and 45% for SAA patients receiving MSD or URD transplantation (9). Besides, two previous studies have proven that higher HCT-CI scores were associated with inferior survival among SAA patients after haploidentical transplantation, meaning that higher comorbidity burdens resulted in poorer survival(10, 11). There are conflicting data on the impact of ABO incompatibility on survival in different disease categories(12, 13). Previously, minor ABO incompatibility was found to increase the rate of grade III-IV aGVHD but not affect survival in a haploidentical cohort for SAA(13).

Recently, the addition of eltrombopag to standard immunosuppressive therapy has been proven to improve the rate of hematologic response(14), thus the comparison of HSCT vs triple IST would be essential among the elderly. This retrospective study had small number of patients, especially in unrelated donor group, which may have weakened the statistical power of this study. The predictive model had limitations, due to lacking the validation set and limited sample size. Therefore, large-scale prospective studies are needed to validate these results.

In summary, allo-HSCT deserves consideration as an option among elderly SAA patients, especially for those younger than 55 years. For those older than 55 years, patients with lower comorbidity burdens might benefit from

allo-HSCT, and an ABO-compatible donor should also be recommended. In the future, prospective data are essential to forward the position of allo-HSCT among elderly SAA patients as a potentially curative disease approach.

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Table 1 Patient characters

Variables	Values
Age, median (range)	53 (50-74)
Gender	
Male	37 (48.7%)
Female	39 (51.3%)
Disease type	
SAA	60 (78.9%)
vSAA	16 (21.1%)
HSCT timing	
Upfront	35 (46.1%)
Salvage	41 (53.9%)
Disease course (months)	4.2 (0.2-279.8)
Previous treatment	
ATG not included	54 (71.1%)
ATG included	22 (28.9%)
Previous transfusion	
RBC (unit), median (range)	15 (2-396)
PLT (unit), median (range)	15 (1-550)
HCT-CI	
0	37 (48.7%)
1	24 (31.6%)
2	12 (15.8%)
3	3 (3.9%)
Donor type	
Matched sibling donor	16 (21.0%)
Haploidentical donor	55 (72.4%)
Matched unrelated donor	4 (5.3%)
Mismatched unrelated donor	1 (1.3%)
Donor recipient blood type	
Matched	41 (53.9%)
Minor mismatched	14 (18.4%)
Major mismatched	17 (22.4%)
Major and minor mismatched	4 (5.3%)
Graft type	
BM plus PB	45 (59.2%)
PB	31 (40.8%)
MNC, median (range)	10.5 (4.1-35.2)
CD34, median (range)	4.7 (0.6-15.3)

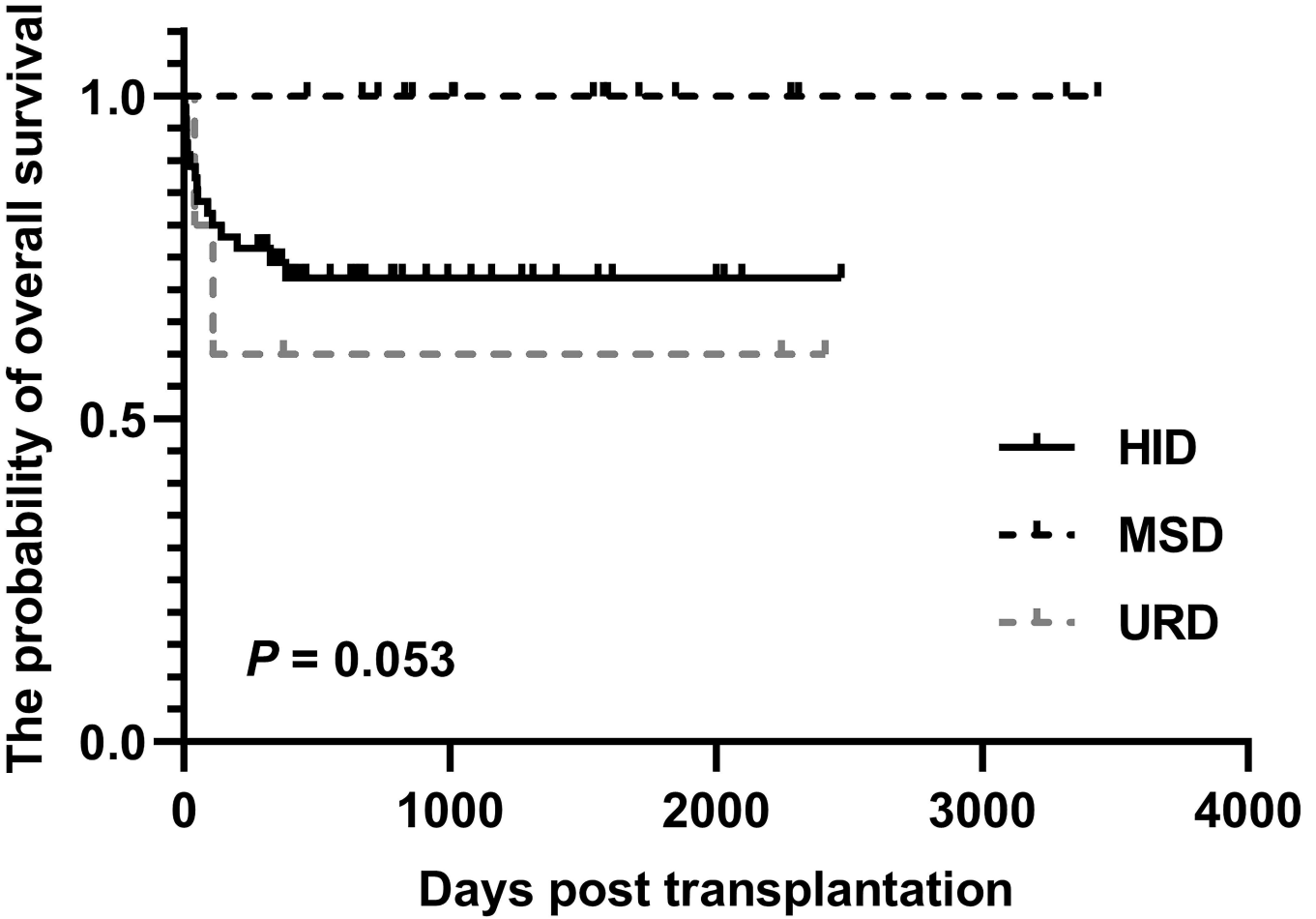
Abbreviations: SAA, severe aplastic anemia; vSAA, very severe aplastic anemia; ATG, antithymocyte globulin; RBC, red blood cell; PLT, platelet; HCT-CI, hematopoietic cell transplantation comorbidity index; BM, bone marrow; PB, peripheral blood; MNC,

mononuclear cell; Single unit means blood components extracted from single unit of once whole blood donation (approximately 200ml).

Figure legends.

Figure 1. The overall survival of allogeneic hematopoietic stem cell transplantation from different donors among severe aplastic anemia patients older than 50 years.

Figure 2. The probabilities of overall survival for the low risk, intermediate risk (inter- risk), and high risk groups among severe aplastic anemia patients older than 50 years. Older age (≥ 55 years), higher HCT-CI (≥ 2), and ABO blood type incompatibility were predictive factors of poorer survival. Based on these three parameters, a predictive risk model was established: low risk (0 factor), intermediate risk (1 factor), and high risk (2-3 factors).


The probability of overall survival
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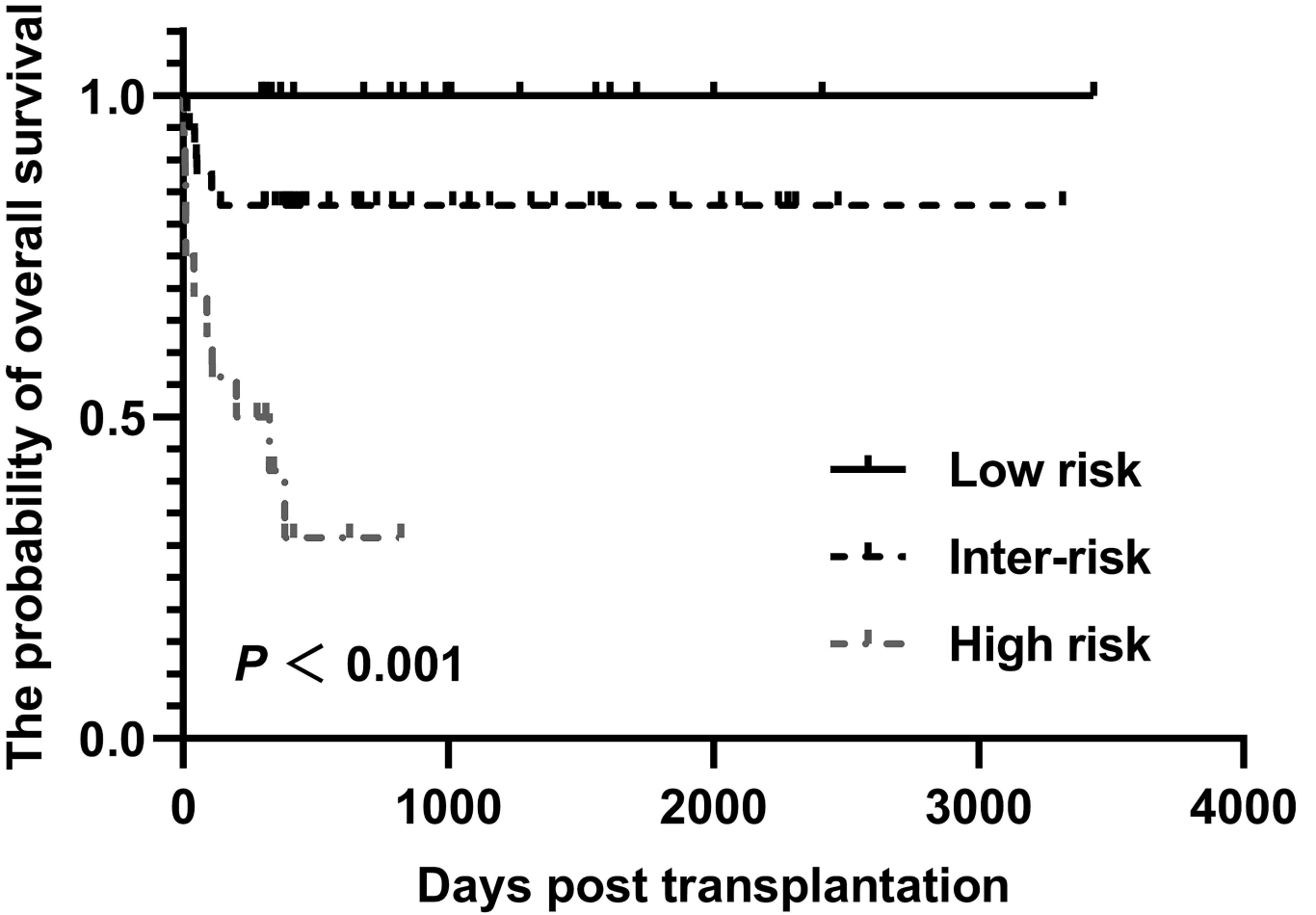
0.5
0.0
0
1000
2000
3000
4000
Days post transplantation
HID
MSD
URD
P = 0.053


The probability of overall survival
1.0
0.5
0.0
0
1000
2000
3000
4000
Days post transplantation
Low risk
Inter-risk
High risk
P < 0.001

Supplemental Table 1. The basic characteristics, conditioning regimen and transplantation related mortality among different donor groups.

	MSD	**HID**		**URD**	***P***
Age, median (range), years	52 (50-58)	54 (50-74)		52 (50-55)	0.200
Age ≥ 55 years, No. (%)	4 (25.0%)	20 (36.4%)		2 (40.0%)	0.673
Age ≥ 60 years, No. (%)	0	6 (10.9%)		0	0.288
Interval between the diagnosis to transplant, median (range), months	3.6 (0.2-260.5)	4.0 (0.4-279.8)		56.0 (3.6-245.3)	0.276
RBC infusions, median (range)	10 (4-50)	15 (2-396)		34 (10-50)	0.445
PLT infusions, median (range)	7.5 (2-550)	15 (1-234)		20 (20-28)	0.132
Conditioning regimen	Cy 200mg/kg r-ATG 10mg/kg (n=2)	**G-CSF/ATG based**	**PT-Cy based**	Cy 200mg/kg r-ATG 10mg/kg (n=1)	NA
	Flu 150mg/m^2 Cy 100 mg/kg r-ATG 10 mg/kg (n=6)	Bu 6.4mg/kg Flu 150mg/m^2 Cy 100mg/kg ATG 10mg/kg (n=41)	Bu 3.2mg/kg Flu 150mg/m^2 Cy 29mg/kg r-ATG 10mg/kg PT-Cy 100mg/kg (n=8)	Flu 150mg/m^2 Cy 100 mg/kg r-ATG 10 mg/kg (n=3)	
	Bu 3.2mg/kg Flu 150mg/m^2 Cy 100mg/kg r-ATG 10mg/kg (n=8)	TBI 3cGy Bu 6mg/kg Flu 120mg/m^2 Cy 50mg/kg ATG 10mg/kg (n=6)		Bu 3.2mg/kg Flu 150mg/m^2 Cy 29mg/kg r-ATG 10mg/kg PT-Cy 100mg/kg (n=1)	
Reasons of transplantation related	None	severe infection (n=8)		regimen-related toxicity (n=1)	

mortality		regimen-related toxicity (n=4) thrombotic microangiopathy, TMA (n=1) haemorrhagic events (n=1) primary graft failure leading to miscellaneous causes (n=1)	severe infection (n=1)	

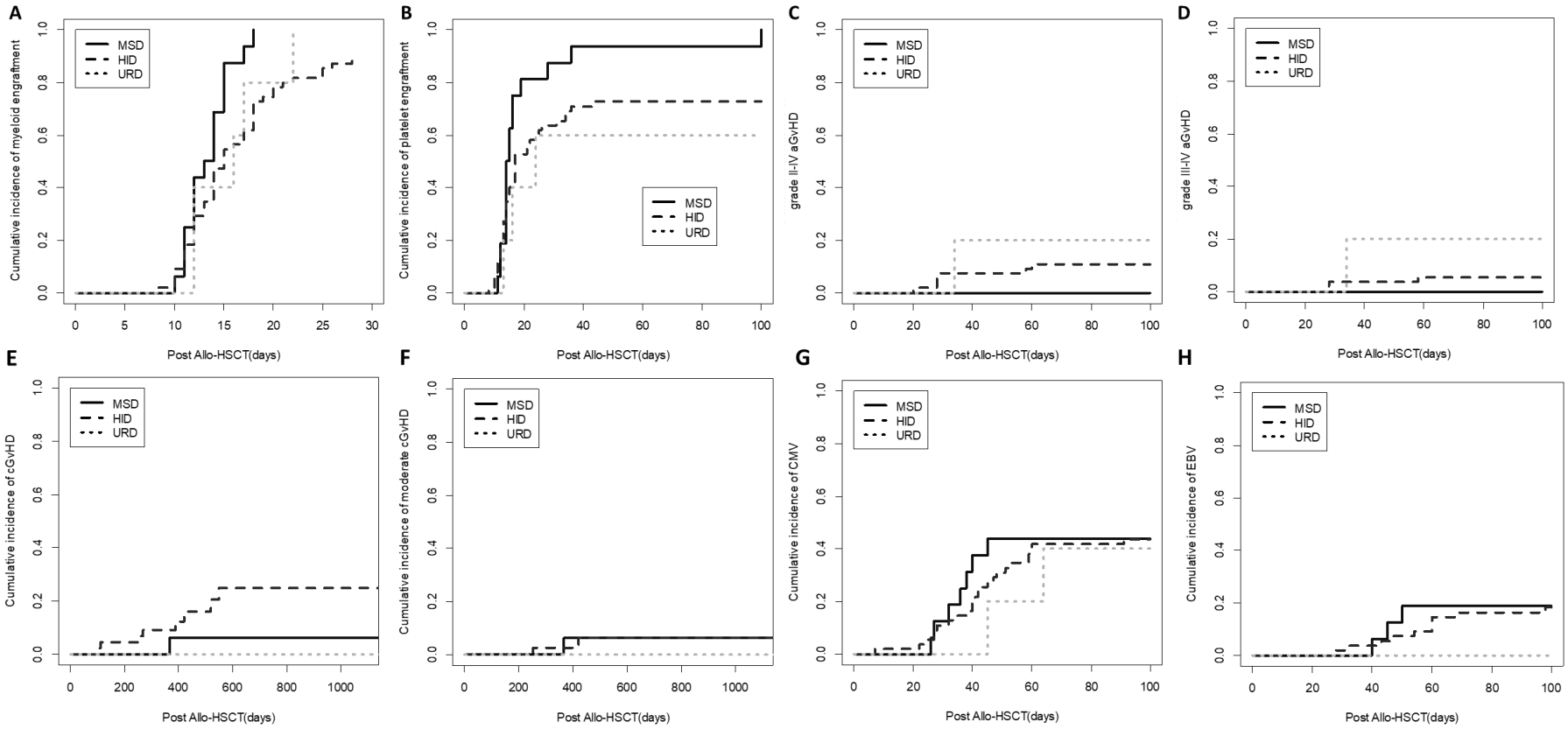
Abbreviations:
granulocyte colony-stimulating factor, G-CSF
busulfan Bu, fludarabine Flu, cyclophosphamide Cy
rabbit antithymocyte globulin r-ATG

Supplemental Table 2. The univariate analysis of overall survival outcomes.

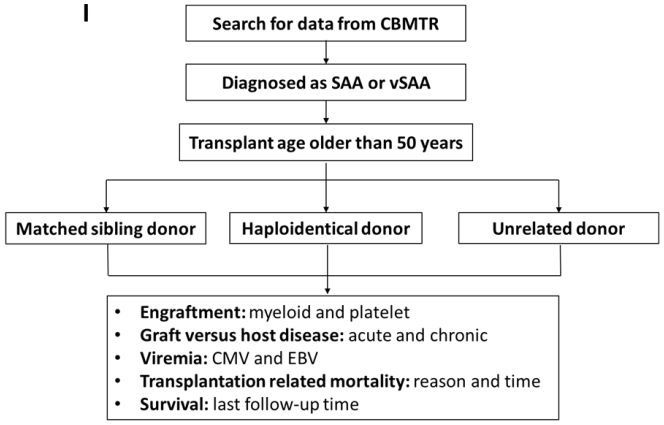
Variables	5-year OS	*P*
The total cohort (N=76)	**77.2±4.9%**	
Patient Age		**0.014***
Aged 50-54 (N=50)	86.0±4.9%	
Aged 55-74 (N=26)	60.8±9.7%	
Patient Gender		**0.028***
Male (N=37)	89.2±5.1%	
Female (N=39)	66.3±7.6%	
Disease type		0.332
SAA (N=60)	79.4±5.3%	
vSAA (N=16)	68.8±11.6%	
Timing of HSCT		0.587
Upfront (N=35)	79.5±6.9%	
Salvage (N=41)	75.3±6.8%	
Disease course		0.940
＜6 months (N=41)	77.4±6.7%	
⩾6 months (N=35)	76.9±7.2%	
Previous ATG		0.157
No (N=54)	81.0±5.4%	
Yes (N=22)	68.2±9.9%	
HCT-CI		**＜0.001***
0-1 (N=61)	86.9±4.3%	
2-3 (N=15)	38.1±12.9%	
Donor type		0.053
Matched sibling donor (N=16)	100%	

Haploidentical donor (N=55)	71.8±6.2%	
Unrelated donor (N=5)	60.0±21.9%	
HLA locus		0.119
Matched (N=20)	90.0±6.7%	
Mismatched (N=56)	72.3±6.1%	
ABO blood type incompatibility		0.054
Compatible (N=41)	84.9±5.7%	
Incompatible (N=35)	68.6±7.8%	
Graft type		0.267
BM plus PB (N=45)	82.0±5.8%	
PB (N=31)	70.3±8.4%	
MNC		0.848
＜10 (N=31)	77.4±7.5%	
⩾10 (N=43)	78.3±6.4%	
CD34		0.892
＜5 (N=39)	76.9±6.7%	
⩾5 (N=36)	76.6±7.3%	

Supplemental Figure 1. The cumulative incidence of myeloid engraftment (A) and platelet engraftment (B), grade II-IV aGvHD (C), III-IV aGvHD (D), cGvHD (E), moderate cGvHD (F), CMV (G) and EBV reactivation (H). The cumulative incidences of myeloid engraftment were 100%, 89.1±0.2%, and 100% in the MSD, HID and URD groups, respectively (P = 0.005). The retrospective incidences of platelet engraftment were 100%, 72.7±0.4%, and 60.0±6.8% in the MSD, HID and URD groups, respectively (P = 0.037). The description of data collection in the study (I).


A
Cumulative incidence of myeloid engraftment
MSD
HID
URD
Post Allo-HSCT(days)
B
Cumulative incidence of platelet engraftment
MSD
HID
URD
Post Allo-HSCT(days)
C
grade II-IV aGvHD
MSD
HID
URD
Post Allo-HSCT(days)
D
grade III-IV aGvHD
MSD
HID
URD
Post Allo-HSCT(days)
E
Cumulative incidence of cGvHD
MSD
HID
URD
Post Allo-HSCT(days)
F
Cumulative incidence of moderate cGvHD
MSD
HID
URD
Post Allo-HSCT(days)
G
Cumulative incidence of CMV
MSD
HID
URD
Post Allo-HSCT(days)
H
Cumulative incidence of EBV
MSD
HID
URD
Post Allo-HSCT(days)

I


Search for data from CBMTR
Diagnosed as SAA or vSAA
Transplant age older than 50 years
Matched sibling donor
Haploidentical donor
Unrelated donor
Engraftment: myeloid and platelet
Graft versus host disease: acute and chronic
Viremia: CMV and EBV
Transplantation related mortality: reason and time
Survival: last follow-up time