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

Allogeneic hematopoietic stem cell transplantation (HSCT) remains a first-line therapeutic option for younger patients with severe aplastic anemia (SAA).[1] Elderly age has been proven to be associated with a relatively higher mortality following allogeneic HSCT for the treatment of 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) demonstrated that allogeneic HSCT led to a 3-year overall survival of 56% among 499 SAA patients older than 50 years.[3] In this large study, all transplants were from matched sibling donors (MSD) or matched unrelated donors (MUD) but did not include haploidentical donors (HID).[3] In recent decades, HID HSCT for SAA has made great advances, and the upper limit of age for such transplants 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: the 3-year overall survival ranged from 86.7-100% in the three groups.[6] However, the outcomes of allogeneic HSCT in SAA patients older than 50 years, especially including HID HSCT, have rarely been reported.

Based on data from the Chinese Blood and Marrow Transplant Registry (CBMTR), we analyzed the outcomes of SAA patients older than 50 years, most of whom had undergone HID HSCT. A total of 76 patients who underwent a first allogeneic HSCT between January 2014 and December 2022 were enrolled from 25 transplant centers. The study protocol was approved by the institutional review board. All patients gave their written informed consent to the procedure. The details of conditioning regimens for transplants from different types of donors are summarized in *Online Supplementary Table S1*. The details of graft-*versus*-host disease (GvHD) prophylaxis have been described previously.[6,7] As shown in Table 1, 16 (21.1%) patients received HSCT from MSD, 55 (72.4%) from HID, and five (6.5%) from URD. The median time from diagnosis to HSCT was 4.2 months (range, 0.2-279.8) in the entire cohort. With regard to HSCT timing, 41 patients underwent salvage transplantation after the failure of immunosuppressive therapy, and 22 received immunosuppressive therapy including anti-thymocyte globulin. 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, 278-3,434). The comparisons

Table 1. Patients' characteristics.

Variables	Values
Age in years, median (range)	53 (50-74)
Gender, N (%)	
Male	37 (48.7)
Female	39 (51.3)
Disease type, N (%)	
Severe aplastic anemia	60 (78.9)
Very severe aplastic anemia	16 (21.1)
HSCT timing, N (%)	
Upfront	35 (46.1)
Salvage	41 (53.9)
Disease course in months, median (range)	4.2 (0.2-279.8)
Previous treatment, N (%)	
Anti-thymocyte globulin not included	54 (71.1)
Anti-thymocyte globulin included	22 (28.9)
Previous transfusion	
RBC units, median (range)	15 (2-396)
Platelet units, median (range)	15 (1-550)
HCT-CI score, N (%)	
0	37 (48.7)
1	24 (31.6)
2	12 (15.8)
3	3 (3.9)
Donor type, N (%)	
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, N (%)	
Matched	41 (53.9)
Minor mismatched	14 (18.4)
Major mismatched	17 (22.4)
Major and minor mismatched	4 (5.3)
Graft type, N (%)	
Peripheral blood plus bone marrow	45 (59.2)
Peripheral blood	31 (40.8)
Mononuclear cells, $x10^9$/kg, median (range)	10.5 (4.1-35.2)
CD34 cells, 10^6/kg, median (range)	4.7 (0.6-15.3)

HSCT: hematopoietic stem cell transplantation; RBC: red blood cell; HCT-CI: Hematopoietic Cell Transplantation Comorbidity Index. A unit of a blood component means the component extracted from one unit of a whole blood donation (approximately 200 mL).

of basic characteristics among different donor groups are provided in *Online Supplementary Table S1*.

Seventy-one patients survived for more than 28 days. A total of 70 (98.6%) patients achieved myeloid engraftment, and all of them showed complete donor chimerism at 1 month after transplantation. The cumulative incidence of myeloid engraftment was 92.0±0.1% in the entire cohort, with engraftment occurring at the median time of 14 days (range, 8-28). Fifty-nine patients achieved platelet engraftment within a median time of 15 days (range, 8-100). The cumulative incidence of platelet recovery was 77.6±0.2%. The cumulative incidences of myeloid engraftment and platelet recovery in the three groups are indicated in *Online Supplementary Figure S1A, B*.

With regard to acute GvHD, none of the patients in the cohort of MSD recipients experienced grade II-IV acute GvHD. The cumulative incidences of grade II-IV and grade III-IV acute GvHD 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, respectively (*Online Supplementary Figure S1C, D*). Patients who survived longer than 100 days were evaluable for chronic GvHD based on 2014 National Institutes of Health criteria. None of the patients in the groups transplanted from URD suffered chronic GvHD. HID transplant recipients had a seemingly higher 3-year cumulative incidence of chronic GvHD compared to MSD transplant recipients, but the difference was not statistically significant (24.8±0.7% *vs*. 6.3±0.4%; *P*=0.230) (*Online Supplementary Figure S1E*). The MSD and HID groups had similar 3-year incidences of moderate chronic GvHD (6.3±0.4% *vs*. 6.2±0.2%; *P*=0.896) (*Online Supplementary Figure S1F*), and no severe chronic GvHD occurred.

In terms of virus reactivation within 100 days, the cumulative incidences for cytomegalovirus and Epstein-Barr virus were 43.4±0.3% and 17.1±0.2%, respectively, in the entire cohort. The MSD, HID and URD groups had similar incidences of cytomegalovirus (43.8±1.7%, 43.6±0.5%, and 40.0±6.8%, respectively; *P*=0.896) (*Online Supplementary Figure S1G*) and of Epstein-Barr virus (18.8±1.0%, 18.2±0.3%, and 0%, respectively; *P*=0.584) (*Online Supplementary Figure S1H*). One patient in the HID group suffered an Epstein-Barr virus-related post-transplant lymphoproliferative disorder.

A total of 17 patients died of transplant-related causes, at a median of 51 days (range, 4-384) after transplantation (*Online Supplementary Table S1*). The overall survival at 3 years was 77.2±4.9% in the whole cohort. In univariate analysis (*Online Supplementary Table S2*), the 3-year overall survival 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 Hematopoietic Cell Transplantation-specific Comorbidity Index (HCT-CI) score were associated with worse survival. In addition, a trend was observed for ABO blood type incompatibility, with overall survival probability being worse for incompatible donor-recipient pairs. The above potentially significant factors for survival were included in the multivariate analysis. The multivariate analysis showed that the hazard ratio was increased for older patients (≥55 years, relative risk [RR]=4.539, 95% confidence interval [95% CI]: 1.590-12.963; *P*=0.005), those with a higher HCT-CI score (≥2, RR=7.726, 95% CI: 2.761-21.620; *P*<0.001), and recipients with ABO blood type incompatible donors (RR=5.629, 95% CI: 1.808-17.532; *P*=0.003) when predicting overall survival. Combining these three parameters, a predictive risk model for the outcome of allogeneic HSCT in elderly SAA patients was established: low risk (0 factors, n=19), intermediate risk (1 factor, n=41), and high risk (2-3 factors, n=16). The probabilities of overall survival at 3 years after allogeneic 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).

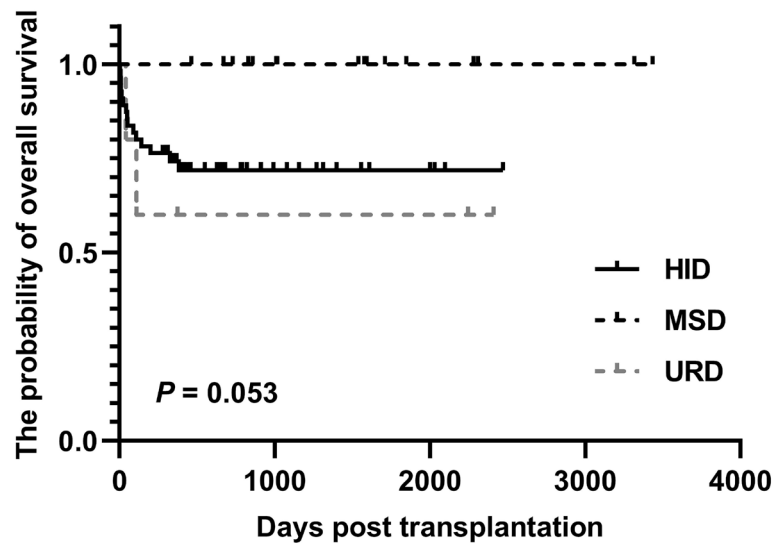

Figure 1. The overall survival of patients with severe aplastic anemia older than 50 years who underwent allogeneic hematopoietic stem cell transplantation from different donors. HID: haploidentical donor; MSD: matched sibling donor; URD: unrelated donor.

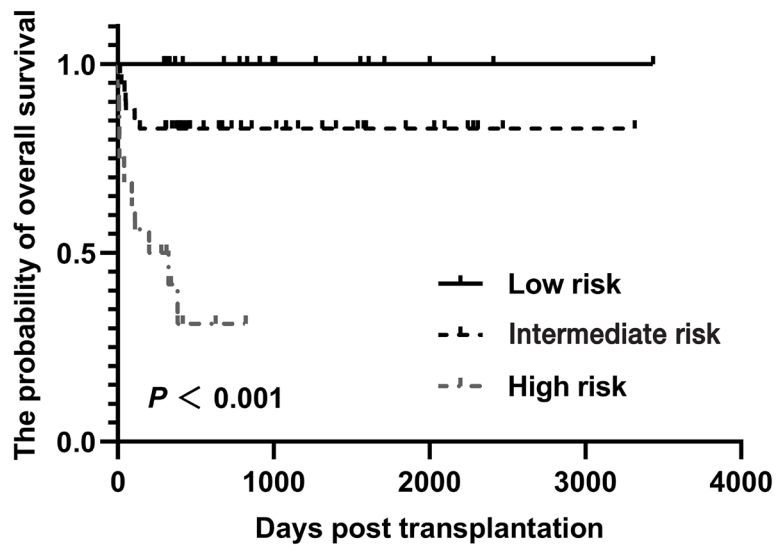

Figure 2. The probabilities of overall survival for low-risk, intermediate-risk, and high-risk groups among patients with severe aplastic anemia older than 50 years of age. Older age (≥55 years), higher Hematopoietic Cell Transplantation Comorbidity Index score (≥2), and ABO blood type incompatibility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

The data from the CBMTR indicated that allogeneic HSCT led to a 3-year survival of 77.2% among SAA patients older than 50 years. Currently, patients have estimated 3-year overall survival rates of 100% and 60% after transplantation from MSD and MUD, respectively; the corresponding 3-year overall survival rates of MSD and MUD HSCT recipients from the EBMT and CIBMTR were 57% and 48%, respectively.[3] It should be noted, first, that patients in the CBMTR were younger than those from the EBMT or CIBMTR, with a median age of 54 years *versus* 57.8 years, respectively, at transplantation. Second, the transplants by the EBMT and CIBMTR were performed between 2005 and 2016, while those from the CBMTR were performed between 2014 and 2022. Improvements in transplantation techniques and supportive care are factors that cannot be ignored when comparing transplants performed in different periods.

In this study, 55 patients undergoing allogeneic HSCT had HID, and their transplants resulted in a 3-year overall survival of 71.8%. Previously, the efficacy of haploidentical transplantation had been proven among younger recipients.[4,5,8] Excluding the early deaths, 49 of 50 patients (98%) achieved myeloid engraftment. The GvHD incidences were similar to those in a previous study. The incidences of grade II-IV acute GvHD and 3-year chronic GvHD were 10.9% and 24.8%, respectively, in our cohort. DeZern *et al*. observed grade II-IV acute GvHD and 1-year chronic GvHD incidences of 16% and 26% following haploidentical transplantation to treat SAA.[8] When the causes of mortality were analyzed, 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 obvious adverse factors. Consistently, Giammarco *et al*. found that the 5-year survival rates of patients aged 50 to 59 years and those aged over 60 years were 58% and 45% for SAA patients undergoing MSD or URD transplantation.[9] Besides, two previous studies showed 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 acute GvHD but not to affect survival in a cohort of SAA patients undergoing haploidentical transplantation.[13]

Recently, the addition of eltrombopag to standard immunosuppressive therapy was shown to improve the rate of hematologic response,[14] thus the comparison of HSCT *versus* triple immunosuppressive therapy would be essential among the elderly. This retrospective study had a small number of patients, especially in the group with unrelated donors, which may have weakened the statistical power of the study. The predictive model has limitations, due to the lack of a validation set and limited sample size. Large-scale prospective studies are, therefore, needed to validate these results.

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

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Contributions

X-JH designed the research. Z-LX, L-PX, and X-JH analyzed the data and wrote the manuscript. All authors provided data on patients and gave final approval of 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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