BMC Pediatrics

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Hemorrhagic cystitis in pediatric severe aplastic anemia undergoing haploidentical hematopoietic stem cell transplantation: incidence, risk factors and outcomes

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Abstract

Background Hemorrhagic cystitis (HC) is a common complication of hematopoietic stem cell transplantation (HSCT) and may adversely affect the prognosis of patients. However, the risk factors associated with HC and its influence on prognosis remain unclear in pediatric Severe aplastic anemia (SAA) patients who underwent haploidentical HSCT (haplo-HSCT).

Methods Clinical data from 116 SAA patients who received haplo-HSCT based on the 'Beijing Protocol' at the Children's Hospital of Soochow University between 2018 and 2023 were examined retrospectively. Potential risk factors were identified by univariate and multivariate logistic regression, and the effect of HC on overall survival (OS) was analyzed by Kaplan–Meier curves and log-rank tests.

Results 32 out of 116 patients (27.6%) developed HC and the median time to onset of HC was 12 days (range: 1–157 days) after HSCT. In multivariate analysis, Very SAA (VSAA) (OR = 3.47, 95% CI: 1.15–10.44), II-IV acute graft versus host disease (aGVHD) (OR = 2.75, 95% CI: 1.05–7.18) and pre-transplant iron overload (OR = 3.90, 95% CI: 1.27–11.94) were regarded as risk factors. Compared to the non-HC group and mild HC group, the severe HC group had the worst 2-year OS rates (non-HC: 94.0% ± 2.6%; mild HC: 96.0% ± 3.9%; severe HC: 71.4% ± 1.7%, $P = 0.047$).

Conclusion For pediatric SAA patients, VSAA, II-IV aGVHD, and pre-transplant iron overload elevate the risk of HC following haplo-HSCT. The development of severe HC can affect the clinical outcomes of patients.

Keywords Hemorrhagic cystitis, Severe aplastic anemia, Haploidentical hematopoietic stem cell transplantation, Risk factors, Children

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Introduction

Severe aplastic anemia (SAA) is an uncommon and life-threatening disease, marked by bone marrow failure and pancytopenia [1]. Immunosuppressive therapy (IST) and matched sibling donor hematopoietic stem cell transplantation (MSD-HSCT) are the preferred recommended treatments [2]. However, IST is ineffective in about one-third of patients, and those responders still face a considerable risk of relapse [3]. In recent decades, there has been significant progress in haploidentical HSCT (haplo-HSCT) for SAA. Several studies have found that for patients lacking MSD-HSCT, haplo-HSCT offers an alternative option [4]. Nevertheless, some transplant-related complications are more common in haplo-HSCT, such as acute graft versus host disease (aGVHD), infection and hemorrhagic cystitis (HC) [4, 5].

HC is a diffuse inflammatory bladder disease with varying clinical manifestations. In mild cases, it may be present only as microscopic hematuria, while in severe cases, patients can experience urinary irritative symptoms, difficulty urinating, and even chronic renal failure due to hydronephrosis [6].The prevalence of HC in pediatric HSCT recipients was approximately 3.6%−14.6%, affecting their quality of life [7, 8]. In addition, severe HC has been shown to be associated with poorer survival outcomes [9].

The HC-related risk factors have been reported in many studies. Sex, busulfan (BU), and aGVHD were considered to be potential risk factors for HC [10, 11]. However, the risk factors for post-transplant HC remain elusive for pediatric patients with SAA undergoing haplo-HSCT. Thus, we retrospectively analyzed 116 pediatric SAA patients after haplo-HSCT to identify relevant elements for HC and its impact on prognosis.

Method

Patients

This study comprised 116 pediatric patients with SAA who underwent haplo-HSCT based on the 'Beijing Protocol' [12] at the Children's Hospital of Soochow University between 2018 and 2023. Peripheral blood stem cells, bone marrow stem cells, and both were used as the sources of graft. Patients should satisfy the subsequent criteria: (a) diagnosed with SAA and Diagnosed with SAA and excluding congenital bone marrow disorders (such as Fanconi anemia, GATA2 deficiency, and telomere diseases). (b) received first unmanipulated haplo-HSCT; (c) age at transplantation is 18 years or younger; (d) complete clinical information and laboratory test data.

Transplantation procedure

A reduced-intensity conditioning regimen, with or without BU (3.2 mg/kg, 2 days), was given to nearly all patients (98.3%). Only 2 patients were treated with a myeloablative conditioning regimen based on total body irradiation. All patients received pre-transplant cyclophosphamide (30 mg/kg/day) from days −5 to −2, along with rabbit anti-thymocyte globulin (ATG, 2.5 mg/kg/day) or ATG-Fresenius (ATG-F, 4 mg/kg/day). Additionally, fludarabine was administered at a dosage of 45 mg/m^2 daily from days −7 to −4. Granulocyte colony-stimulating factor was administered starting on day + 6 until the absolute neutrophil count exceeded 1×10^9/L.

GVHD prophylaxis was based on methotrexate (15 mg/m^2 on day + 1 and 10 mg/m^2 on days + 3, + 6, and + 11) and mycophenolate mofetil, combined with either cyclosporin A (target blood level: 200–250 ng/mL) or tacrolimus (target blood level: 10–15 ng/mL).

To mitigate the toxic effects of cyclophosphamide on the urinary epithelium, all patients were administered mesna and hydration from the start of treatment until 24 h after the completion of cyclophosphamide infusion. The treatment for HC follows standardized protocols based on the severity of the condition [10].

Definition

SAA was defined as meeting at least two of the following criteria: absolute neutrophil count (ANC) < 0.5×10^9/L, platelet count < 20×10^9/L, or reticulocyte count < 20×10^9/L, with bone marrow cellularity < 25%. Very SAA (VSAA) was further defined as SAA with ANC < 0.2×10^9/L [13]. HC refers to the presence of gross or microscopic hematuria and urinary frequency, diagnosed after excluding other bleeding disorders and obtaining negative bacterial cultures from urine. HC can be classified into four grades based on clinical manifestations: Grade 1: microscopic hematuria; Grade 2: gross hematuria; Grade 3: gross hematuria accompanied by blood clots; Grade 4: gross hematuria with blood clots, urinary obstruction, and renal injury [14]. HC is classified into early-onset and late-onset HC, with 1 week after HSCT as the cutoff. Iron overload is defined when serum ferritin levels are ≥ 1000 ng/mL [15]. Overall survival (OS) is the interval time between HSCT and death. Cytomegalovirus (CMV) and Epstein-Barr virus (EBV) seropositivity is considered when the CMV DNA level is ≥ 500 copies/mL in two consecutive tests. It was considered neutrophil engraftment when ANC ≥ 0.5×10^9/L sustained for 3 days straight. Consider platelet engraftment if the platelet count is ≥ 20×10^9/L and without transfused for 7 days straight. The diagnosis of aGVHD was in accordance with previous criteria [16].

Statistical analysis

Based on whether HC was present or not, the patients were separated into two groups. Logistic regression was used to estimate odds ratios and 95% confidence intervals. Utilize logistic regression to perform univariate analysis of correlated variables and incorporate variables with P-values ≤ 0.10 into multivariate analysis. The visualization of OS was performed employing Kaplan–Meier curves, and comparisons were assessed using the log-rank test. A p-value < 0.05 indicates statistical significance. All statistical analyses were performed using BM SPSS Statistics 25 and R 4.3.3.

Results

Patient characteristics

The median age of 116 included patients was 90.0 (4.0–194.0) months. Among them, there were 56 females and 60 males. 41 patients were SAA, and the remaining 75 patients were VSAA. The median time to neutrophil engraftment was 11 days (8-22 days), and platelet engraftment was 12 days (7-34 days). The median dose of infused CD34 + cells was 6.66 (0.69–12.30) $\times 10^6$ /kg, and mononuclear cells was 7.65 (0.83–20.6) $\times 10^8$/kg. The general characteristics of the included patients can be found in Table 1.

Incidence and risk factors

In our study, 32 out of 116 patients (27.6%) developed HC. HC onset occurred at a median time of 12 days (range: 1–157 days) after HSCT. There were 7 cases of early-onset HC and 25 cases of late-onset HC. Grade 1 HC was observed in 7 patients, Grade 2 HC in 18 patients, and Grade 3 HC in 7 patients, with no cases of Grade 4 HC reported.

In univariate analysis, we analyzed potential risk factors, including age, sex, underlying disease, disease cause, previous IST, conditioning regimen, graft source, ABO match, MNC, CD34, neutrophil engraftment time, platelet engraftment time, CMV seropositivity, EBV seropositivity, aGVHD, and iron overload, respectively. We found that there was no association between transplantation-related factors and the occurrence of HC. However, several significant risk factors were identified. Compared to SAA, HC was more prevalent in patients with VSAA ($P = 0.009$). The rates of HC in patients with II-IV aGVHD were 88.2% compared to 25.4% in patients without ($P = 0.005$). In addition, patients with iron overload before transplantation were more prone to developing HC ($P = 0.005$). Then, in the multivariate analysis, we included underlying disease, II-IV aGVHD, iron overload, and platelet

Table 1 Baseline characteristics of all patients included in this study

Variable	Cohort (n)
Age (month), median (range)	90.0 (4.0-194)
Gender	
Male	60 (51.7%)
Female	56 (48.3%)
Disease	
VSAA	75 (64.7%)
SAA	41 (35.3%)
Disease course (month), median (range)	4.40 (1.10-99.80)
Previous IST	
CSA+ATG	18 (15.5%)
ATG not included	98 (84.5%)
Graft source	
PB	15 (12.9%)
BM	3 (2.6%)
PB+BM	98 (84.5%)
Conditioning intensity	
RIC	114 (98.3%)
MAC	2 (1.7%)
ATG-F	16 (13.8%)
Yes	16 (13.8%)
No	100 (86.2%)
ABO match	
Match	66 (56.9%)
Major mismatch	14 (12.1%)
Minor mismatch	30 (25.9%)
Major-minor mismatch	6 (5.2%)
HLA compatibility	
5/10	60 (51.7%)
6/10–8/10	52 (44.8%)
9/10	4 (3.4%)
Donor type	
Parent	81 (69.8%)
Sibling	35 (30.2%)
CMV seropositive	77 (66.4%)
EBV seropositive	40 (34.5%)
II-IV aGVHD	32 (27.6%)
Iron overload	73 (62.9%)
MNC, $\times 10^8$/kg	7.7 (0.8-20.6)
CD34, $\times 10^6$/kg	6.7 (0.7-12.3)
Neutrophil engraftment time (d), median (range)	1.0 (8.0-22.0)
Platelet engraftment time (d), median (range)	12.0 (7.0-34.0)

Abbreviations: *SAA* severe aplastic anemia, *VSAA* very severe aplastic anemia, *IST* immunosuppressive therapy, *CSA* cyclosporin a, *ATG* anti-thymocyte globulin, *PB* Peripheral blood, *BM* bone marrow, *MAC* myeloablative conditioning, *RIC* reduced-intensity conditioning, *ATG-F* ATG- Fresenius, *HLA* human leukocyte antigen, *CMV* Cytomegalovirus, *EBV* Epstein-Barr virus, *aGVHD* acute graft versus host disease, *MNC* mononuclear cells

engraftment time ($P=0.096$). The subsequent elements were regarded as risk factors for HC: VSAA (OR = 3.47, 95%CI: 1.15–10.44), II-IV aGVHD (OR = 2.75, 95%CI: 1.05–7.18) and iron overload (OR = 3.90, 95%CI: 1.27–11.94). The results of the univariate and multivariate analyses can be found in Table 2.

Outcome

In our study cohort, no primary transplant failure cases were observed. 3 patients experienced secondary transplant failure. These patients did not undergo a second HSCT and died soon after due to infection or thrombotic microangiopathy (TMA). The post-transplant chimerism of all patients remained above 95%, except for those with secondary transplant failure. The follow-up period ended on October 1, 2024, and the median follow-up time was 21.3 (2.0–65.5) months. There were 8 deaths during the study period, with 5 deaths occurring in the non-HC group and 3 deaths in the HC group. The causes of death included TMA ($n=2$), aGVHD ($n=1$), infections ($n=4$), and bronchiolitis obliterans ($n=1$). The 2-year OS rates between the HC group and the non-HC group showed no difference (93.8% ± 4.3% versus 92.8% ± 2.8%, $P=0.498$). Then, we compared survival differences among the non-HC, mild HC (grades 1–2), and severe HC (grades 3–4) groups, finding that survival was significantly poorer in the severe HC group (non-HC: 94.0% ± 2.6%; mild HC: 96.0% ± 3.9%; severe HC: 71.4% ± 1.7%, $P=0.047$, Fig. 1).

Discussion

Although many patients with SAA undergoing HSCT achieve favorable clinical outcomes, they still face some fatal transplant-related complications. HC is a common complication following HSCT, especially in haplo-HSCT [5]. Currently, there are limited investigations into HC following haplo-HSCT in children with SAA. Therefore, we conducted this study to investigate the risk factors and prognosis for HC after haplo-HSCT in children with SAA.

A total of 32 patients developed HC, resulting in an incidence rate of 27.6%, which is slightly higher than previously reported rates [6]. This may be due to our focus on patients who underwent haploidentical transplantation, which is associated with inherent immunodeficiency from HLA mismatching [5, 17]. Older age has been identified as a risk factor for HC in pediatric cohorts, possibly due to the higher rate of viral infections in older children [18, 19]. In our study, the HC and non-HC groups showed no significant age difference ($P=0.326$). This may be because the study included only AA patients. There is no clear consensus on the relationship between sex and HC. Hale et al. revealed that males have a higher incidence of HC in children [20]. Whereas our results align with some previous studies, indicating that sex has no impact on the occurrence of HC [21, 22].

In our study, which included only children with AA, we unexpectedly found that VSAA is an independent risk factor (OR = 3.47, 95%CI: 1.15–10.44). The ANC served as a significant prognostic factor for patients with AA. A previous study involving 416 patients with aplastic anemia showed that the ANC was comparatively greater than the non-responder group, regardless of whether they received IST plus eltrombopag or IST alone [23]. In addition, for AA patients undergoing HSCT, Nakamura et al. categorized 883 patients into three groups: low ANC (0/ μL), medium ANC (1–199/ μL), and high ANC (≥ 200/ μL). The results indicated that the low ANC group had the highest risk of infections and pre-engraftment mortality [24]. However, further studies are needed to verify this result.

ATG and ATG-F are commonly used for GVHD prophylaxis in haploidentical transplantation. Due to differences in the source of immunizing antigen and the methods used for antibody development, this may result in variations in immunosuppressive effects and toxicity. A recent retrospective study compared the clinical outcomes of transplant patients with different ATG preparations, finding that ATG-F demonstrated a superior advantage in reducing the risk of HC [25]. However, this advantage was not observed in our study, maybe as a result of the limited number of patients who received ATG-F.

The association between aGVHD and HC remains unclear. A prospective study exploring HC-related risk factors in children and adolescents after transplantation indicates that aGVHD increases the risk of HC, particularly in cases of intestinal aGVHD [26]. However, several studies have indicated that aGVHD has no effect on the development of HC [22, 27]. In our study, children who developed II-IV aGVHD were more prone to experiencing HC. The mechanisms by which aGVHD leads to HC may be as follows: on one hand, bladder epithelial cells may serve as targets for GVHD [28]. On the other hand, the immunosuppressants required to treat GVHD can promote the activation of opportunistic infections, leading to the occurrence of HC [27].

SAA patients typically require blood transfusion support, making iron overload common before transplantation. Our results indicated that iron overload was an independent risk factor for HC. Lin et al. found that in children with aplastic anemia receiving haploidentical transplantation, pre-transplant iron overload increases the risk of aGVHD and its severity [15]. In addition, iron is a key substance required for the growth of microbial

Table 2 Univariate and multivariate analysis of hemorrhagic cystitis (HC)

	Non-HC ($n = 84$)	HC ($n = 32$)	Univariate analysis *p* value	Multivariate analysis *p* value	OR (95%CI)
Age (month)	88.0 (4.0-188.0)	91.5(29.0-194.0)	0.326		
Gender			0.142		
Male	47 (56.0%)	13 (40.6%)			
Female	37 (44.0%)	19 (59.4%)			
Disease			**0.009***	**0.027***	3.47 (1.15-10.44)
SAA	36 (42.9%)	5 (15.6%)			
VSAA	48 (57.1%)	27 (84.4%)			
Disease course	4.50 (1.10-99.80)	4.50 (1.10-99.80)	0.596		
Previous IST			0.984		
CSA+ATG	13 (15.5%)	5 (15.6%)			
ATG not included	71 (84.5%)	27 (84.4%)			
Graft source			0.255		
PB	8 (9.5%)	7 (21.9%)			
BM	3 (3.6%)	0 (0.0%)			
BM+PB	73 (86.9%)	25 (78.1%)			
Conditioning intensity			0.999		
RIC	82 (97.6%)	32 (100.0%)			
MAC	2 (2.4%)	0 (0.0%)			
ATG-F			0.724		
Yes	11 (13.1%)	5 (15.6%)			
No	73 (86.9%)	27 (84.4%)			
ABO match			0.707		
Match	47 (56.0%)	19 (59.4%)			
Major mismatch	21 (25.0%)	9 (28.1%)			
Minor mismatch	12 (14.3%)	2 (6.2%)			
Major-minor mismatch	4 (4.8%)	2 (6.2%)			
HLA compatibility			0.699		
5/10	41 (48.8%)	19 (59.4%)			
6/10–8/10	40 (47.6%)	12 (37.5%)			
9/10	3 (3.6%)	1 (3.1%)			
Donor type			0.289		
Parent	61 (72.6%)	20 (62.5%)			
Sibling	23 (27.4%)	12 (37.5%)			
MNC, $\times 10^8$/kg	7.6 (0.8-20.6)	8.1 (3.4-14.2)	0.676		
CD34, $\times 10^6$/kg	6.8 (0.7-11.5)	6.4 (1.8-12.3)	0.801		
Neutrophil engraftment time	11.0 (8.0-22.0)	12.0 (10.0-20.0)	0.262		
Platelet engraftment time	11.0 (7.0-34.0)	12.5 (8.0-31.0)	**0.096***	0.103	1.09 (0.98-1.20)
CMV seropositive			0.739		
Yes	55 (65.5%)	22 (68.8%)			
No	29 (34.5%)	10 (31.2%)			
EBV seropositive			0.673		
Yes	28 (33.3%)	12 (37.5%)			
No	56 (66.7%)	20 (62.5%)			
II-IV aGVHD			**0.005***	**0.039***	2.75 (1.05-7.18)
Yes	17 (20.2%)	15 (46.9%)			
No	67 (79.8%)	17 (53.1%)			
Iron overload			**0.005***	**0.017***	3.90 (1.27-11.94)
Yes	46 (54.8%)	27 (84.4%)			
No	38 (45.2%)	5 (15.6%)			

Abbreviations: *SAA* severe aplastic anemia, *VSAA* very severe aplastic anemia, *IST* immunosuppressive therapy, *CSA* cyclosporin a, *ATG* anti-thymocyte globulin, *PB* Peripheral blood, *BM* bone marrow, *MAC* myeloablative conditioning, *RIC* reduced-intensity conditioning, *ATG-F* ATG- Fresenius, *HLA* human leukocyte antigen, *CMV* Cytomegalovirus, *EBV* Epstein-Barr virus, *aGVHD* acute graft versus host disease, *MNC* mononuclear cells

*$P \leq 0.10$ in univariate analysis and $P < 0.05$ in multivariate analysis

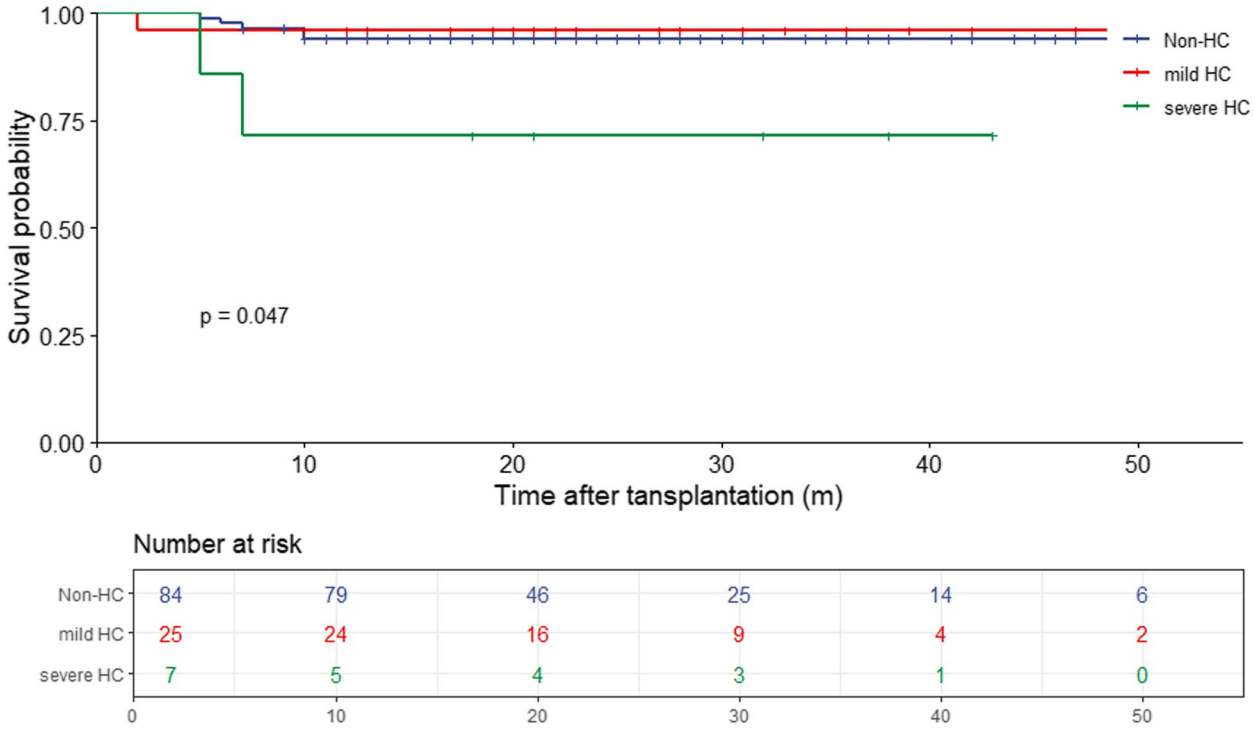

Fig. 1 Overall survival of patients based on hemorrhagic cystitis (HC) severity

pathogens and may impair immune barriers by inhibiting macrophage phagocytosis [29]. Thus, iron overload serves as an important risk factor for infections [29]. When transplant candidates have iron overload before transplantation, iron chelation therapy can be considered to reduce the risk of aGVHD and infections, thereby lowering the occurrence of HC.

BK virus (BKV) is a polyomavirus, with primary infection typically occurring during childhood and usually being asymptomatic [30]. After primary infection, BKV remains latent in the renal tubular epithelial cells of the renal-urinary tract and may reactivate during periods of immunosuppression [30]. BKV reactivation is more common after HSCT [22, 31]. BKV is associated with late-onset HC with an incidence of BKV-HC ranges from 2.7% to 14.4% [32–34]. The risk of late-onset HC significantly increases when the plasma BK virus load rises by at least 3 log units [35]. BKV infection also can predict severe HC in children [36]. Thus, early detection and management of BKV infection may reduce the development of HC. Regrettably, BKV is not regularly monitored at our institution.

In our study, the 2-year OS rate was comparable between the HC group and the non-HC group (93.8% ± 4.3% versus 92.8% ± 2.8%, $P = 0.498$). After stratifying by the severity of HC, the results showed that the 2-year OS rate was the lowest in the severe HC group (non-HC: 94.0% ± 2.6%; mild HC: 96.0% ± 3.9%; severe HC: 71.4% ± 1.7%, $P = 0.047$). In fact, the relationship between HC and prognosis remains unclear. Some studies have found that HC does not increase the risk of mortality [37, 38], while others suggest that severe HC is associated with poorer outcomes [39]. Few studies have reported cases where HC directly leads to patient death. In our study, 2 out of 7 patients in the severe HC group died and both due to TMA, suggesting that HC is a complication of the post-transplant immunosuppressive state and may not be directly related to prognosis.

The primary limitations of our study are small sample size and retrospective methodology, which may reduce statistical power. Additionally, we only included patients with SAA who received haplo-HSCT, so the results may not be applicable to other transplant patients. Finally, BK virus regular monitoring was not conducted at our institution.

In conclusion, we discovered that the risk variables for HC were VSAA, II-IV aGVHD, and pre-transplantation iron overload. Severe HC had an adverse effect on the 2-year OS rate. Our findings may help clinicians identify transplant patients at high risk for HC. In addition, further studies are needed to verify our results, particularly regarding the newly identified risk factors of VSAA and pre-transplantation iron overload.

Abbreviations

SAA	Severe aplastic anemia
VSAA	Very severe aplastic anemia
IST	Immunosuppressive therapy
HSCT	Hematopoietic stem cell transplantation
AGVHD	Acute graft versus host disease
TMA	Thrombotic microangiopathy
HC	Hemorrhagic cystitis
BU	Busulfan
ATG	Rabbit anti-thymocyte globulin
OS	Overall survival
CMV	Cytomegalovirus
EBV	Epstein-Barr virus
ANC	Absolute neutrophil count

Acknowledgements
Not applicable.

Clinical trial number
Not applicable.

Authors' contributions
K.C. and S. Z: study design and manuscript drafted. M. l. and C.H.: statical analysis. J. C. and Y.W.: data collection. J. L. and S. H.: result interpretation and manuscript revision.

Funding
This study was supported by the following grants: The National Key Research and Development Program of China (no.2022YFC2502700), the National Natural Science Foundation of China (NSFC, 82170218, 82470221), Suzhou Municipal Key Laboratory (SZS201615, SKY2022012, SZS2023014) to Shaoyan Hu.

Data availability
Relevant data from this study can be obtained from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
This study adhered to the Declaration of Helsinki and was approved by the institutional Review Board of the Children's Hospital of Soochow University. As the retrospective nature of this study, informed consent was waived by the institutional Review Board of the Children's Hospital of Soochow University.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 8 November 2024 Accepted: 11 February 2025
Published online: 26 March 2025

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