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ORIGINAL ARTICLE

Incidence, risk factors and outcomes of sinusoidal obstruction syndrome after haploidentical allogeneic stem cell transplantation

Xuan Cai[1,2,3] · Jin Wu[1,2,3] · Ruo-Yun Gui[1,2,3] · Qiu-Sha Huang[1,2,3] · Xiao Liu[1,2,3] · Ya-Zhen Qin[1,2,3] · Jing-Zhi Wang[1,2,3] · Qiao-Zhu Zeng[1,2,3] · Qian Jiang[1,2,3] · Hao Jiang[1,2,3] · Jin Lu[1,2,3] · Jing-Bo Wang[4] · Li Gao[5] · Xi Zhang[5] · Hong-Yu Zhang[6] · Jia Feng[6] · Xiang-Yu Zhao[1,2,3] · Ying-Jun Chang[1,2,3] · Yan-Rong Liu[1,2,3] · Lan-Ping Xu[1,2,3] · Kai-Yan Liu[1,2,3] · Xiao-Jun Huang[1,2,3] · Xiao-Hui Zhang[1,2,3]

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Abstract

Hepatic sinusoidal obstruction syndrome (SOS) has been rarely studied after haploidentical donor (HID) allogeneic hematopoietic stem cell transplantation (allo-HSCT). We performed a retrospective multicentre study on patients with SOS after allo-HSCT in China. The incidence, risk factors, and outcomes were compared between HID HSCT and matched related donor (MRD) HSCT. SOS developed in 0.4% of patients (HIDs: 0.4%, MRDs: 0.5%, $p = 0.952$) at a median time of 21.50 days (range, 1–55) after allo-HSCT (HIDs: 24 days, MRDs: 20 days, $p = 0.316$). For patients diagnosed with SOS, the 2-year cumulative incidence of relapse was 22.7% and 22.4% in patients receiving HID and MRD transplantation, respectively ($p = 0.584$). Overall survival (OS) at 2 year was 10.4% and 38.5% in the two groups ($p = 0.113$). The transplant-related mortality (TRM) at 100 days was 60.9% in the HID group and 38.5% in the MRD group ($p = 0.178$). According to the multivariate analyses, significant independent risk factors for the occurrence of SOS were delayed platelet engraftment ($p = 0.007$) and advanced disease status at the time of HSCT ($p = 0.009$). The outcomes of SOS after HID HSCT are similar to those after MRD HSCT.

Keywords Sinusoidal obstruction syndrome · Haploidentical hematopoietic stem cell transplantation · Matched related donors · Incidences · Risk factors · Outcomes

Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) has been regarded as a potential strategy for both hematological malignancies and nonmalignant conditions. The best outcomes of allo-HSCT have been obtained when the donor is an HLA-matched sibling. Unfortunately, patients have only about a 30% chance of having an HLA-matched sibling donor [1]. For those lacking a suitable matched donor, haploidentical donors are an alternative option [2]. Recently, a number of studies have been undertaken to improve the outcomes of haplo-HSCT. Haplo-HSCT has become the largest donor source compared with an identical sibling donor since 2013 and is now used in almost 48% of allo-HSCT in China [1].

Hepatic sinusoidal obstruction syndrome (SOS), also known as veno-occlusive disease (VOD), is a rare but lethal complication after allo-HSCT, with reported incidences of 8–14% and a mortality rate higher than 80% in the severe type [3–5]. SOS usually occurs within 30 days after allo-HSCT and is characterized clinically by jaundice, rapid weight gain, painful hepatomegaly, and ascites; it is characterized histologically by diffuse damage in the centrilobular zone of the liver [6]. The diagnosis and classification of SOS are based on clinical criteria and does not require histologic or hemodynamic

Corresponding author: Xiao-Hui Zhang

✉ Xiao-Hui Zhang
zhangxh100@sina.com

1 Peking University People's Hospital, Peking University Institute of Hematology, No. 11 Xizhimen South Street, Xicheng District, Beijing, China

2 Beijing Key Laboratory of Hematopoietic Stem Cell Transplantation, Beijing, China

3 Collaborative Innovation Centre of Hematology, Peking University, Beijing, China

4 Beijing Aerospace General Hospital, Beijing, China

5 Xinqiao Hospital, The Third Military Medical University, Chongqing, China

6 Shenzhen Hospital, Peking University, Shenzhen, China

confirmation [7]. It is sometimes difficult to distinguish SOS from other complications following allo-HSCT. Therefore, proper therapy may be delayed in some situations and these patients may progress rapidly to multi-organ failure. Recent reports show a decrease in the incidence of SOS, which may be attributed to the use of a reduced-intensity conditioning regimen [3, 5]. Although outcomes are gradually improving, they are still unsatisfactory. To date, SOS remains a major obstacle for transplant success, and effective strategies for prevention and early intervention need to be established to improve OS, especially after HID HSCT.

Although sufficient information is available on SOS after MRD HSCT, few studies have systematically investigated SOS after HID HSCT. With this aim, we conducted a retrospective study to assess the incidence, clinical characteristics, risk factors, and transplant outcomes of SOS following HID HSCT.

Patients and methods

Patients

This is a multicenter retrospective study. Between January 2003 and July 2018, 8037 patients received HID (5173 patients) or MRD (2864 patients) allo-HSCT according to donor availability at four large HSCT centers in China, including the Peking University Institute of Hematology. Among them, 36 patients diagnosed with SOS (HID: 23 patients, MRD: 13 patients) were included in the case group. For each case, controls were randomly selected at a ratio of 1:3–1:4 from the same cohort according to allo-HSCT time (± 30 days) and the length of follow-up (± 3 months). The Institutional Review Board of Peking University, Beijing, China, approved this study, and all of the patients included in this study provided written informed general consent for us to collect their clinical information before transplantation for research purposes according to the local ethics policy guidelines and the Declaration of Helsinki.

Conditioning regimens and GVHD prophylaxis

Patients with partially HLA-matched HSCT were treated with a regimen consisting of cytarabine (4 g/m^2/day on days − 10 and − 9, i.v.), busulfan (BU) (3.2 mg/kg/day on days − 8 to − 6, i.v.), cyclophosphamide (Cy) (1.8 g/m^2/day on days − 5 and − 4, i.v.), semustine (250 mg/m^2, day − 3, p.o.), and ATG (2.5 mg/kg/day on days − 5 to − 2, i.v.). Patients with HLA-identical HSCT received a regimen identical to that of haploidentical HSCT recipients without ATG [8, 9]. All patients received a cyclosporine A, mycophenolate mofetil, and short-term methotrexate regimen for GVHD prophylaxis [10].

SOS prophylaxis and treatment

Preventive therapies combine two approaches: reversal of SOS risk factors and pharmacological prevention. In those with a reversible condition (acute hepatitis, active disease), the HSCT would be delayed until its resolution. Effort would be made to avoid the use of hepatotoxins during the conditioning. Patients received intravenous prostaglandin E1 (PGE1) 0.3 μg/kg/h infusion continuously from the day before the start of conditioning to 21 days after HSCT.

Treatments for SOS were supportive in nature and included restriction of fluid and sodium supply, diuretic therapy, and use of albumin and transfusional support to minimize ischemic hepatic and renal injury. Heparin can inhibit platelet aggregation, protect endothelial cells, and prevent thrombosis. Ursodeoxycholic acid (UDCA) can provide the therapeutic benefit for SOS by reducing hepatic oxidative stress injury and increasing endogenous antioxidants in the liver [11, 12].

Diagnosis and classification of SOS

The diagnosis of SOS was based on clinical criteria [13–15] that required the occurrence of two of the following events within 20 days of HSCT: hyperbilirubinemia (≥ 2 mg/dL), hepatomegaly or right upper quadrant pain of hepatic origin, or unexplained weight gain (> 2% of baseline bodyweight) due to fluid accumulation. No other explanation for these symptoms and signs could be present at the time of diagnosis of SOS. The severity of SOS was defined as mild, moderate, severe, or very severe [13–16].

Definitions and evaluation

The day of stem cell transfusion was counted as day 0, and all intervals were calculated based on this date. Engraftment of neutrophils was defined as the first of three consecutive days when the absolute neutrophil count achieved 0.5×10^9 L^{-1} without granulocyte colony-stimulating factor stimulation (G-CSF) [17, 18]. Engraftment of platelets was defined as the first of seven consecutive days when the platelet count was $\geq 20 \times 10^9$ L^{-1}, independent from platelet substitution [17, 18]. Relapse was defined as the recurrence of BM blasts > 5%, reappearance of blasts in the blood, or development of extramedullary disease infiltrates at any site [17, 19]. The patients who died without relapse were classified as having transplant-related mortality (TRM) [17, 19, 20]. Overall survival (OS) was defined as the time from allo-HSCT to death from any cause or last follow-up [19, 20]. Both acute GVHD (aGVHD) and chronic GVHD (cGVHD) were diagnosed and graded according to the traditional criteria [21, 22]. Advanced status was defined as status with a high minimal residual disease load (> 10^{-4} leukemic cells) [13, 21, 23].

Statistical analysis

Baseline characteristics of allogeneic HSCT recipients among the case and control groups and clinical features of SOS among HID and MRD groups were compared using Student's *t* test for continuous variables, and data are reported as medians. Pearson's chi-squared test ($T \geq 5$ and $n \geq 40$), chi-squared test with continuity correction ($1 \leq T < 5$ and $n \geq 40$), and Fisher's exacts were used for categorical variables. The potential risk factors affecting the occurrence of SOS were identified using univariate Cox analyses, and $p < 0.2$ was chosen for multivariate Cox analyses. The cumulative incidence of relapse, OS, and TRM was estimated using the Kaplan-Meier method and compared using the log-rank test. Unless otherwise specified, all reported *p* values were based on two-sided hypothesis tests. Alpha was set at 0.05. Analysis was performed using SPSS 22.0 (International Business Machines Corporation. http://www.ibm.com/cn/) and R 3.4.1.

Results

Patient characteristics and incidence of SOS

MRD and HID HSCT patients with SOS

SOS was found in 36/8037 (0.4%) of patients (HIDs: 23 patients, MRDs: 13 patients). The median age was 31 years, and 52.8% of the patients were male. The median follow-up time was 2.5 months. The MRD and HID HSCT groups were similar with respect to the incidence of SOS. There was no statistically significant difference between the two groups in terms of gender, distribution of disease, interval from diagnosis to HSCT, disease status at the time of HSCT, donor-patient sex match, donor-patient ABO match, stem cell source, follow-up time, engraftment time, and the cumulative incidence of aGVHD or cGVHD. HID patients were younger than patients in the MRD cohort (Table 1).

Patients with SOS and controls

The main clinical characteristics of the patients diagnosed with SOS and the controls are shown in Table 1. The two cohorts were similar with regard to gender, HLA mismatch, donor-patient sex match, ABO compatibility, stem cell sources, follow-up time, engraftment time, and the cumulative incidence of aGVHD or cGVHD. Patients with SOS were younger than controls. Indications for transplantation were significantly different between the two cohorts. The interval between diagnosis and transplant was longer in SOS than that in controls. More patients with SOS were transplanted at an advanced period than patients without SOS.

Clinical outcomes of patients with SOS

The median day of diagnosis of SOS was 21.50 days after allo-HSCT (range, 1–55). Among the diagnostic criteria for SOS, hyperbilirubinemia was observed in 24 (66.7%), right upper quadrant pain in 21 (58.3%), hepatomegaly in 28 (77.8%), ascites in 32 (88.9%), and weight gain in 32 (88.9%) patients. The severity of SOS was mild in 1 (2.8%), moderate in 5 (13.9%), severe in 6 (16.7%), and very severe in 24 (66.7%) patients (Table 2). The HID and MRD groups were comparable in terms of median time to diagnosis, presentation, and severity.

Relapse incidence, OS, and TRM

The 2-year cumulative incidence of relapse post-transplantation did not significantly differ between the HID and MRD patients with SOS (22.7% vs. 22.4%, respectively, $p = 0.584$, Fig. 1). Furthermore, no significant difference in the 2-year cumulative probabilities of OS was identified among the two groups (10.4% vs. 38.5%, respectively, $p = 0.113$, Fig. 2). Moreover, HID HSCT provides a 100-day cumulative TRM rate comparable to MRD HSCT for patients with SOS (60.9% vs. 38.5%, $p = 0.178$).

Similarly, there was no significant difference in the 2-year cumulative incidence of relapse post-transplantation between the SOS and control groups (4.8% vs. 28%, respectively, $p = 0.166$, Fig. 3). However, the case group had significantly lower OS than the control group (21.2% vs. 33.2%, $p = 0.016$, Fig. 4). The 100-day cumulative incidence of TRM in the SOS group was similar to that in the control group (52.8% vs. 43.6%, $p = 0.237$).

Risk factors for the occurrence of SOS

According to the univariate analysis (Table 3), the frequency of SOS did not differ significantly in terms of donor type ($p = 0.222$), prior use of vancomycin ($p = 0.711$), presence of acute GVHD ($p = 0.750$), patients older than 31 years ($p = 0.324$), female to male donor–recipient matching ($p = 0.651$), ABO incompatibility ($p = 0.489$), hypoalbuminemia ($p = 0.295$), or hepatitis ($p = 0.464$). However, months from diagnosis to allo-HSCT > 12 months ($p = 0.050$), delayed platelet engraftment ($p = 0.004$), and advanced disease status at the time of HSCT ($p = 0.013$) were significant risk factors for the development of SOS in the univariate analyses. AST > 2 ULN ($p = 0.132$) and ALT > 2 ULN ($p = 0.065$) showed marginal significance.

Multivariate analysis demonstrated that factors associated with a higher incidence of SOS post allo-HSCT included delayed platelet engraftment ($p = 0.007$) and advanced disease status at the time of HSCT ($p = 0.009$). According to the multivariate analysis, the risks of SOS did not differ significantly by interval between diagnosis and transplantation > 12 months ($p = 0.187$), AST > 2 ULN ($p = 0.944$), and ALT > 2 ULN ($p = 0.633$).

Table 1 Characteristics of patients following allo-HSCT

Characteristics	SOS				No SOS	*p* value
	Total	Haploidentical	HLA-identical	*p* value		
No. of patients	36	23	13	–	120	–
Incidence of SOS (%)	0.4	0.4	0.5	0.952	–	–
Age(years, range)	31(8–54)	28(8–54)	33(15–47)	0.018	36(3–62)	0.015
Gender (%)				0.549		0.389
Male	52.8	56.5	46.2		60.8	
Female	47.2	43.5	53.8		39.2	
Underlying diseases (%)				0.651		0.012
ALL	22.2	26.1	15.4		35.8	
AML	16.7	13.0	23.1		35.8	
CML	16.7	21.7	7.7		8.3	
MDS	25.0	21.7	30.8		10	
AA	2.8	0	7.7		1.7	
Other	16.7	17.4	15.4		8.3	
Interval between the diagnosis of underlying diseases and transplantation (months, range)	8.5(1–112)	9(1–112)	6(2–48)	0.091	7(2–71)	0.001
Disease status (%)				1.000		0.034
Advanced	36.1	34.8	38.5		19.2	
CR	63.9	65.2	61.5		80.8	
HLA mismatch (%)				–		0.293
0 Locus mismatch	36.1	–	–		26.7	
1 Locus mismatch	0	–	–		5.0	
2 Locus mismatch	19.4	–	–		13.3	
3 Locus mismatch	44.4	–	–		55.0	
Donor-patient sex match (%)				0.170		0.383
Female-female	16.7	8.7	30.8		10.0	
Female-male	22.2	21.7	23.1		20.8	
Male-male	30.6	34.8	23.1		39.2	
Male-female	30.6	34.8	23.1		30.0	
ABO match (%)				0.549		0.059
Match	30.6	30.4	30.8		54.2	
Major mismatch	33.3	30.4	38.5		21.7	
Minor mismatch	25.0	21.7	30.8		19.2	
Major and minor mismatch	11.1	17.4	0		5.0	
Stem cell source (%)				0.124		0.253
BM + PB	88.9	95.7	76.9		94.2	
BM	0	0	0		1.7	
PB	11.1	4.3	23.1		4.2	
Median follow-up time (months, range)	2.5(0–60)	2(0–60)	4(0–27)	0.573	3(0–62)	0.608
Engraftment						
Neutrophil engraftment, days, median (range)	15.5(10–31)	15(10–24)	16(12–31)	0.660	14(8–39)	0.435
Platelet engraftment, days, median (range)	16(8–30)	15(10–23)	17(8–30)	0.990	14(5–52)	0.703
Acute GVHD (%)				0.418		0.414
None	38.9	30.4	53.8		50	
Grades I–II	36.1	39.1	30.8		25.8	
Grades III–IV	25	30.4	15.4		24.2	
Chronic GVHD (%)				0.645		0.106
None	83.3	87.0	76.9		90.0	
Limited	0	0	0		3.3	
Extensive	16.7	13.0	23.1		6.7	

Abbreviations: *SOS* sinusoidal obstruction syndrome, *HLA* human leucocyte antigen, *ALL* acute lymphoblastic leukemia, *AML* acute myeloid leukemia, *CML* chronic myelogenous leukemia, *MDS* myelodysplastic syndrome, *AA* aplastic anemia, *CR* complete remission, *BM* bone marrow, *PB* peripheral blood, *GVHD* graft versus host disease

Discussion

HID HSCT is an alternative treatment for patients lacking identical donors or who are refractory to immunosuppressive therapy [10, 24, 25]. Moreover, the use of HLA-mismatched related donors is a priority for urgent transplantation and the donor is available for additional stem cells or lymphocytes in the event of graft failure or relapse. Recent studies reported that the outcomes after HID HSCT are comparable to those after MRD HSCT in hematological diseases [20, 26, 27].

Hepatic SOS is a significant complication after HSCT as a result of endothelial and hepatic damage caused by the

Table 2 Clinical features of patients with SOS

Parameter	Total	Haploidentical	HLA-identical	*p* value
Median time to Dx after transplantation (days, range)	21.50(1–55)	24(1–55)	20(8–52)	0.316
Criteria present, *n* (%)				
Hyperbilirubinemia	24(66.7)	13(56.5)	11(84.6)	0.143
Right upper quadrant pain	21(58.3)	15(65.2)	6(46.2)	0.310
Hepatomegaly	28(77.8)	19(82.6)	9(69.2)	0.422
Ascites	32(88.9)	21(91.3)	11(84.6)	0.609
Weight gain	32(88.9)	21(91.3)	11(84.6)	0.609
Severity, *n* (%)				0.678
Mild	1(2.8)	1(4.3)	0(0)	
Moderate	5(13.9)	2(8.7)	3(23.1)	
Severe	6(16.7)	4(17.4)	2(15.4)	
Very severe	24(66.7)	16(69.6)	8(61.5)	

Abbreviations: *SOS* sinusoidal obstruction syndrome, *HLA* human leucocyte antigen, *Dx* diagnosis

conditioning regimen [28]. The clinical manifestations are thought to be caused by hepatic sinusoidal obstruction and the occlusion of intrahepatic central venules, resulting from the dysfunction of hepatic sinusoidal endothelial cells [7]. The causes of SOS remain unclear but many risk factors have been reported, including previous hepatotoxic treatment [29], hepatic dysfunction [30], iron overload [31], thalassemia major [32], and a conditioning regimen with Bu and Cy. In our study, delayed platelet engraftment [32] and advanced disease status at the time of HSCT [31] were risk factors for SOS, as previously reported. Our data indicated that the risks of SOS did not differ significantly by the type of transplant [33, 34], which is in line with previous publications. Identifying the risk factors associated with SOS can lead to more effective early treatment strategies for this fatal complication. As allo-HSCT has undergone substantial changes in terms of conditioning regimens, donor type, and supportive care, a more comprehensive understanding of emerging risk factors is indispensable for better management of this disease.

The diagnosis and assessment of SOS severity are often made based on clinical criteria [13–15]. Here, the incidence of SOS in our study was 0.4%, which is much lower than that reported in other countries [3, 5, 33, 35]. The low incidence of SOS in our population may be explained by differences in previous chemotherapy, race, and the presence of other risk factors. Moreover, our conditioning regimen was less

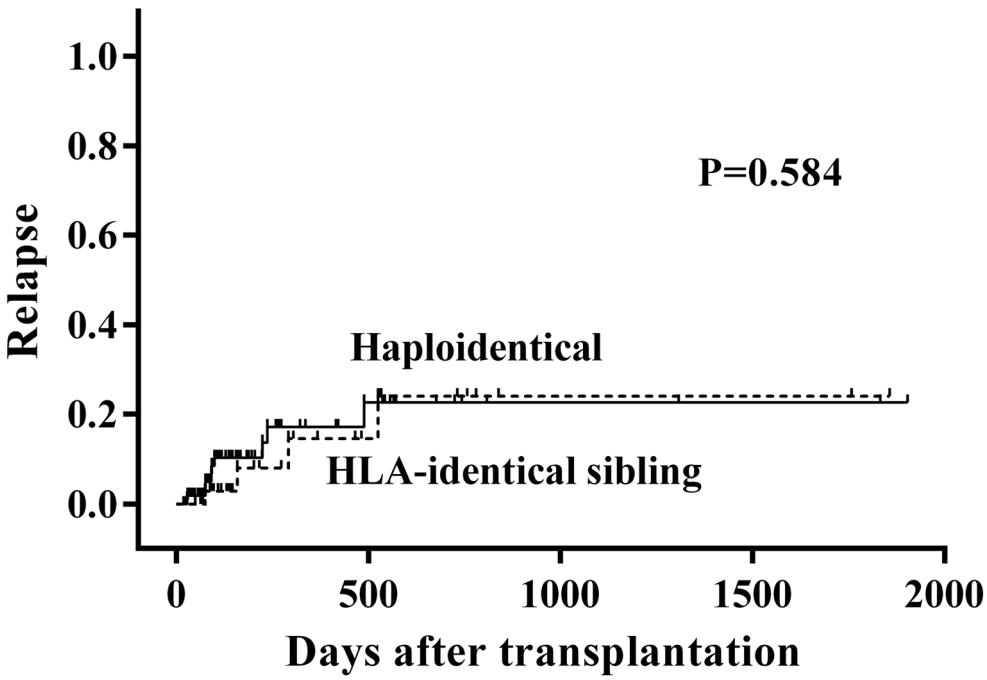

Fig. 1 Comparison of the cumulative incidence of relapse post-transplant between haploidentical HSCT and HLA-identical sibling HSCT patients

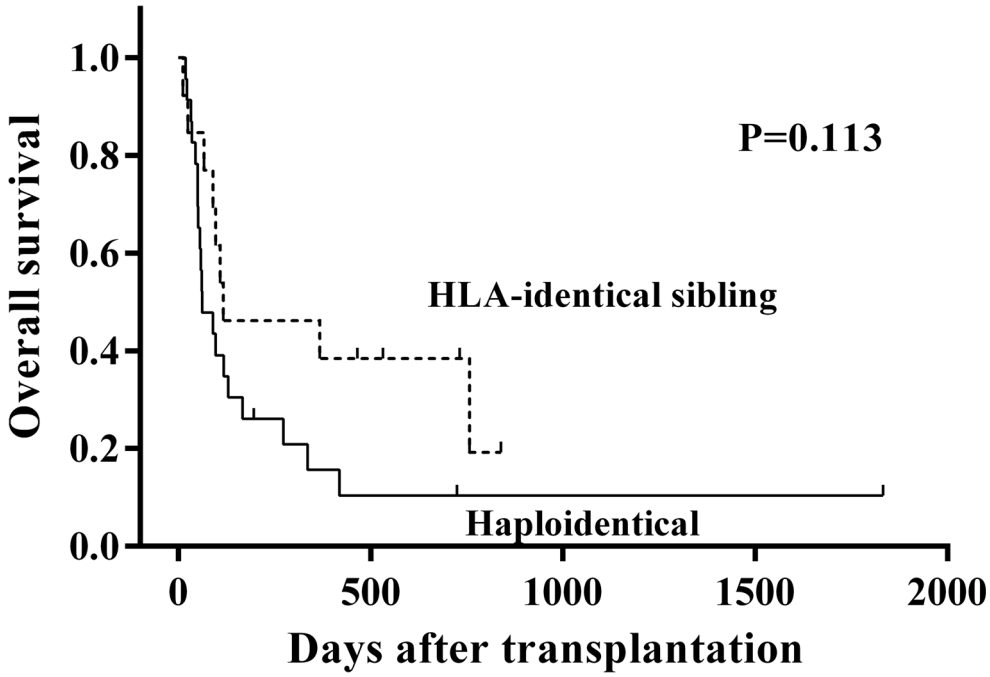

Fig. 2 Comparison of the rate of overall survival post-transplant between haploidentical HSCT and HLA-identical sibling HSCT patients

intensive than other regimens due to the low dose of intravenous BU and a short duration, which may cause less damage to endothelial cells. Using PGE1 for the prophylaxis of SOS in our practice was effective. We did not detect any significant difference in the incidence and the 2-year overall survival of SOS between the period 2003 to 2010 and 2011 to 2018. This finding may be the result of a combination of several factors. During the past decades, we have not changed our transplant protocols, including the conditioning regimen, GVHD prophylaxis and treatment, SOS prophylaxis and treatment, and anti-infection treatment. Better supportive care and training of the clinical staff could have contributed to a better outcome. However, the widespread use of reduced-intensity conditioning allowed us to perform allo-HSCT in patients with risk factors who would otherwise be ineligible for this procedure. The extension of the age limit for transplantation, the inclusion of patients with relapsed or resistant disease, and second HSCT had a fundamental influence on the transplantation outcomes. The gold standard to confirm the diagnosis of SOS are measurement of the hepatic venous

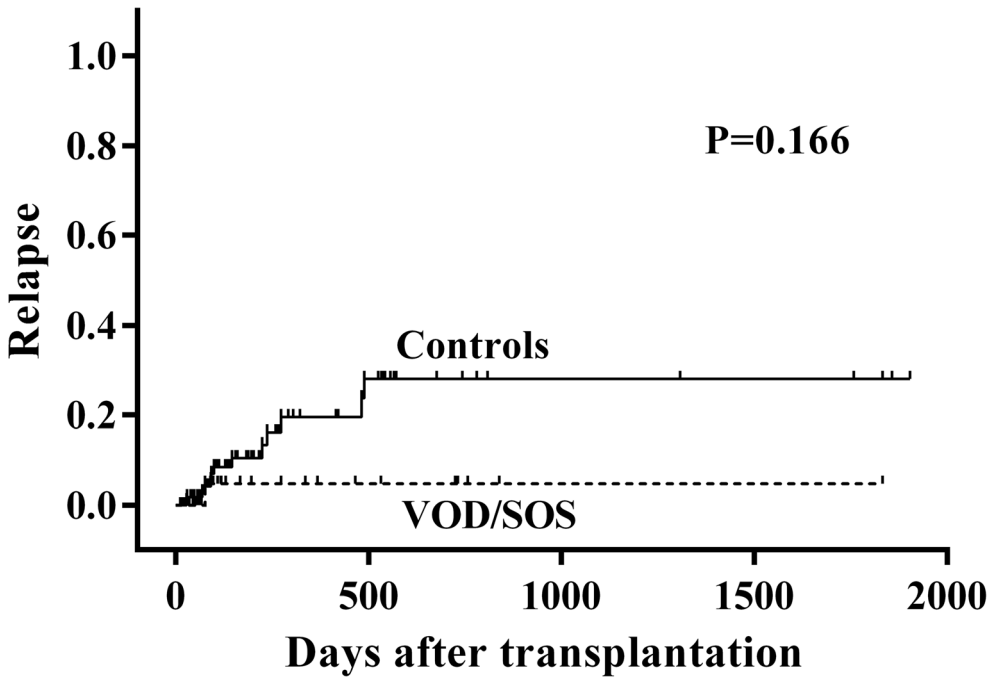

Fig. 3 The incidence of relapse after transplantation between the SOS group and control group

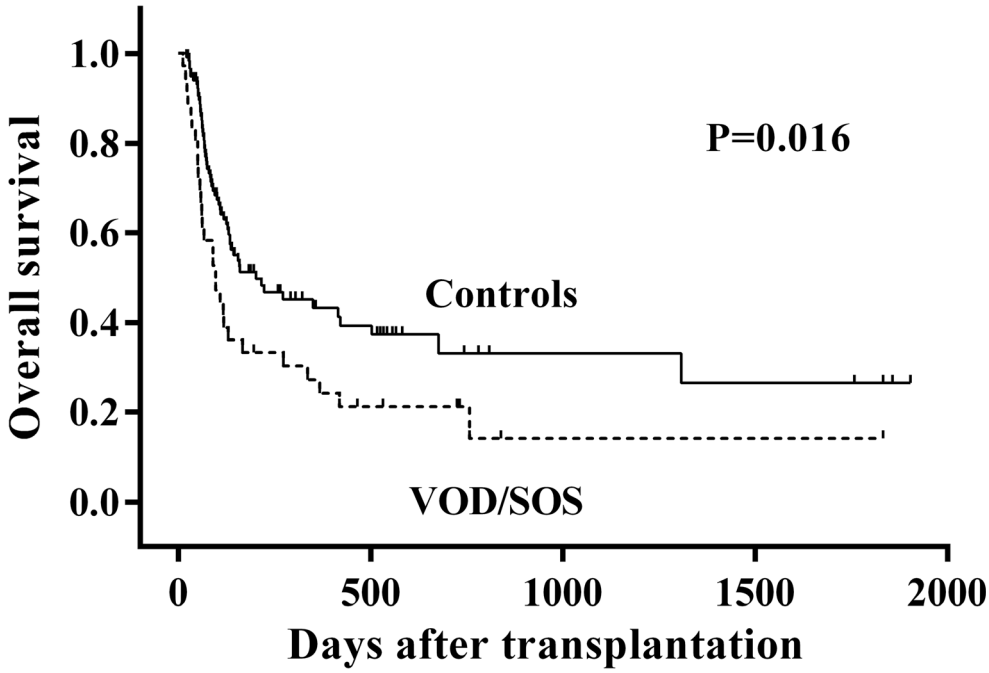

Fig. 4 The rate of overall survival after transplantation between the SOS group and control group

gradient pressure through the jugular vein and liver biopsy, which are invasive and difficult to perform in routine practice [36]. Under such circumstances, establishing more sensitive and specific diagnostic criteria seems indispensable. An attractive way to aid diagnosis would be identifying potential biomarkers for predicting the occurrence of SOS, which is currently being studied. Our data revealed no significant difference in the incidence of SOS between patients receiving HID and MRD HSCT.

Although patients with mild forms of SOS can recover in a few weeks without intervention, the severe type is associated with multi-organ failure and a high mortality rate [3]. In our study, the OS of patients with SOS was remarkably lower than

Table 3 Risk factors for the occurrence of SOS

Risk factors	No. of patients		Univariate			Multivariate		
	SOS	No SOS	HR	95%CI	*p* value	HR	95%CI	*p* value
Interval between diagnosis and transplantation more than 12 months	15	24	1.576	1.000–2.483	0.050*	1.372	0.858–2.195	0.187
HLA-mismatched donor	23	88	1.288	0.858–1.936	0.222			
Vancomycin	3	2	0.767	0.188–3.120	0.711			
Delayed platelet engraftment (> 30 days post-HSCT)	24	44	1.771	1.196–2.621	0.004*	1.751	1.164–2.635	0.007**
Presence of acute GVHD	22	60	0.942	0.654–1.358	0.750			
Age > 31	19	74	0.828	0.570–1.204	0.324			
Female to male allo-HSCT	8	25	0.903	0.579–1.407	0.651			
Incompatible ABO typing	25	55	1.138	0.789–1.643	0.489			
Hypoalbuminemia	7	11	1.399	0.746–2.624	0.295			
Advanced disease status	13	23	1.806	1.134–2.874	0.013*	1.895	1.170-3.069	0.009**
AST > 2 ULN	4	4	2.178	0.791–5.992	0.132*	1.084	0.115–10.256	0.944
ALT > 2 ULN	5	5	2.364	0.948–5.895	0.065*	1.643	0.213–12.651	0.633
Hepatitis	19	48	1.148	0.793–1.663	0.464			

Abbreviations: *SOS* sinusoidal obstruction syndrome, *HLA* human leucocyte antigen, *HR* hazard ratio, *95% CI* 95% confidence interval, *allo-HSCT* allogeneic hematopoietic stem cell transplantation, *GVHD* graft versus host disease, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *ULN* the upper limit of normal value

*$p < 0.2$ in univariate analysis

**$p < 0.05$ in multivariate analysis

that described in the literature [34, 35]. We applied the classification criteria to grade the severity of SOS within our cohort, and most of our patients (66.7%) were classified as very severe, which may explain the high mortality rate. There was no significant difference in the cumulative incidence of relapse and TRM post-transplantation between the SOS and non-SOS groups. However, patients who developed SOS had poorer survival than those who did not. Therefore, we need to further investigate the factors that influence the prognosis of SOS. A better knowledge of the disease, strict monitoring, and a more timely initiation of treatment may be required to reduce the overall mortality observed in our study population.

Given that patients can progress rapidly from mild forms of SOS to severe type and that the treatment of severe SOS remains inadequate with a very high fatality rate, an accurate and prompt diagnosis is essential for early therapy [37]. However, no consensus regarding standard treatment is currently available. While significant progress has been made in understanding the pathogenesis of SOS, pharmacologic options for SOS treatment are very limited and consist primarily of supportive care, which focuses on fluid and sodium management, oxygen therapy, the avoidance of hepatotoxins, and the prevention of infections [38, 39]. Specific therapy usually aims at preventing thrombotic obstruction of hepatic sinusoids and venules or restoring the function of sinusoidal endothelial cells. Many studies have shown promising results of defibrotide (DF) for treatment in clinical trials [37, 40]. However, this investigational drug has not been approved for application in our country. There is no DF in clinical use in China, and therefore, we could not analyze the efficacy of DF for prophylaxis and treatment. Finally, more attentions should be paid to other promising therapies, such as UDCA, low-molecular-weight heparin, and other antithrombotics, to determine whether they may offer real benefit [12, 41].

Because we currently do not have therapies with satisfactory efficacy, prevention remains the primary strategy for managing SOS after allo-HSCT, which combines two approaches: reversal of risk factors and pharmacological prevention [7]. Prophylactic medications currently used or under investigation include PGE1 [4, 42], heparin [41, 42], UDCA [43, 44], DF [45, 46], and fresh frozen plasma [47, 48]. While the use of pharmacological measures to prevent SOS remains very controversial, the foremost preventive measure is to avoid any additional risk factors in allo-HSCT patients [11]. The incidence of relapse, OS, and TRM in patients with SOS did not significantly differ between HID and MRD HSCT. While MRD HSCT remains the best choice, HID HSCT is available for patients without an HLA-identical donor.

There are several limitations of our retrospective cohort study. The principle limitation is the diversity of the patient populations, particularly when attempting to compare the mortality post-transplant between HID HSCT and MRD HSCT. In addition, there is the possibility of selection bias due to the limited number of cases. Despite these limitations, our data offer compelling comparative evidence of the value of HID HSCT as a front-line treatment.

So far, there are still no randomized clinical trials comparing the incidence and prognosis of SOS after haplo-HSCT with other alternative donors. Future challenges lie in determining the expedient tools to minimize the incidence and improve the outcomes of SOS after haplo-HSCT.

In conclusion, our study suggests that haploidentical transplantation may achieve similar results compared with a matched related donor in the incidence and outcomes of SOS. The occurrence of SOS did not differ by donor type, and the OS of patients with SOS was lower than that of controls. Further large and multicenter prospective studies may be warranted to confirm our findings.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendment or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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