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Sinusoidal Obstruction Syndrome

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Abstract

Sinusoidal obstructive syndrome (SOS) is a fibrous occlusive disease of hepatic sinusoids or hepatic venules. Small hepatic blood vessel damage, especially hepatic sinusoidal endothelial cell damage, is its main feature. Based on etiology, SOS is mainly classified into pyrrolidine alkaloids-related SOS, hematopoietic stem cell transplantation-related SOS, and SOS of unknown etiology. In recent years, the incidence of SOS has been increasing. However, due to the complexity of the etiology, the lack of specificity in clinical manifestations, the difficulty of early diagnosis, and the limited treatment options, it often leads to poor treatment effects and even death. This chapter aims to analyze and organize the pathogenesis, pathological characteristics, diagnosis, treatment, and prognosis of different types of SOS, to provide certain references for the prevention and treatment of the disease.

Keywords: sinusoidal obstructions syndrome, hepatic vascular endothelial injury, hepatic venous pressure gradient, nonportal cirrhosis, pyrrolidine alkaloids-related SOS, hematopoietic stem cell transplantation-related SOS

1. Introduction

Hepatic sinusoidal obstruction syndrome (SOS), formerly known as a hepatic veno-occlusive disease (HVOD), is an intrahepatic hepatic sinusoidal portal hypertension caused by obstruction of the hepatic sinusoidal outflow tract due to endothelial cell injury. The main features of SOS are luminal narrowing or occlusion due to endothelial cell injury of the hepatic blood sinusoids, small hepatic veins, and interlobular veins. This causes intrahepatic stasis, hepatic injury and intrahepatic sinusoidal portal hypertension as a characteristic hepatic vasculogenic disease. Its clinical manifestations are mainly pain in the liver area, jaundice, ascites and hepatomegaly. The first cases were documented in South Africa in 1920 when cirrhosis was thought to be caused by groundsel poisoning [1]. In 1953, Hill et al. reported that more than 100 Jamaican children developed “Serous Hepatosis” from the consumption of Senecio (also known as groundsel) [2]. In 1954, Bras and Jelliffe et al. used the term hepatic veno-occlusive disease (HVOD) in their report [3]. Since then, with the recognition of HVOD, in 2002, Deleve et al. suggested that it would be more appropriately named SOS [4, 5], which is now generally accepted and adopted by scholars. The etiology of SOS is diverse, with different etiologies in China and Western countries. Depending on the etiology, it is mainly divided into hematopoietic stem cell transplantation-induced SOS (HSCT-SOS) and pyrrolidine alkaloids-induced SOS (PA-SOS). In the West, SOS is usually associated with myeloablative pretreatment before HSCT, and the incidence of HSCT-SOS

ranges from 5.3% to 13.7% [6], even up to 60% in pediatric high-risk populations [7–9], and is an important complication and major obstacle of HSCT. In China, on the other hand, SOS is usually associated with oral intake of plants containing PA, with 50.0% to 88.6% of SOS caused by the consumption of sedum Tusanqi [10]. In recent years, the incidence of SOS has been increasing, but the complex etiology, lack of specificity of clinical manifestations, difficulties in early diagnosis and limited therapeutic means often lead to poor treatment outcomes and even death. The mortality rate of patients with multiple organ failure is greater than 80% [11]. However, the pathogenesis of the disease is not known. The existing guidelines are limited to “the SOS associated with hematopoietic stem cell transplantation in Western countries” and the “Nanjing criteria” developed by the Hepatobiliary Diseases Committee of the Chinese Society of Gastroenterology to diagnose and treatment of PA–HSOS [12, 13]. To this end, this section focuses on the research progress in the pathogenesis, clinical manifestations, diagnosis, treatment, prognosis, and preventive measures of SOS.

2. Etiology

2.1 Hematopoietic stem cell transplantation

HSCT is considered a major etiology of SOS in the West and is associated with high-dose chemotherapeutic drug pretreatment. Also, age, type of transplantation, secondary transplantation, cytokines produced by damaged tissues, endogenous microorganisms translocated by damaged mucosal barriers, immune factors, previous history of liver disease, systemic irradiation, local procoagulant status, and platelet adhesion are also risk factors for the development of HSCT-SOS [14–16].

2.2 Consumption of plants containing pyrrolidine alkaloids (PA)

In developing countries, such as China, Southeast Asian countries, and African countries, SOS is mainly caused by the consumption of plants containing PA. Plants containing PA are widely distributed around the world, and more than 300 of the more than 6000 species of plants are known to contain PA. For example, senecio, Tusanqi, lily, retrorsine, comfrey, etc. [17]. Since Chinese herbal medicine is widely used in China, SOS is mainly caused by poisoning with Tusanqi [18, 19]. In 1980, Hou et al. [20] reported for the first time two clinical cases of SOS caused by the administration of Tusanqi in China, which attracted widespread attention of clinicians, and since then, cases of SOS caused by Tusanqi have been reported throughout the country. PA and its hydrolysis products are not toxic, but when they reach the liver, they are deoxygenated by cytochrome P450 enzyme (CYP) 3A to form pyrrole-like derivatives. This metabolite binds to DNA/RNA in hepatocytes, thus affecting protein synthesis and inhibiting cell division, which in turn causes severe damage to the liver [21].

2.3 After radiation and chemotherapy

In addition to the above two common types, it has also been reported that SOS is associated with chemotherapy and radiotherapy for solid tumors, such as chemotherapy with cyclophosphamide. Common SOS-related drugs are cyclophosphamide, busulfan, dacarbazine, 6-mercaptopurine, 6-thioguanine, dacarbazine, actinomycin D, gemtuzumab, melphalan, oxaliplatin, cytarabine, and uratan [21].

2.4 After immune drug treatment

Recent reports say that SOS is associated with the use of immunosuppressive drugs [22]. As in the case of treatment with immunosuppressive agents after orthotopic liver transplantation, immune dysregulation is a direct cause of induction of SOS. Thus the indications for immunosuppressive agents, including azathioprine, also seem to be risk factors for SOS. This makes it difficult for researchers to establish the relationship between SOS and immunosuppression. Researchers believe that immune-related injury-induced damage is related to the pathogenesis of these rare lesions.

3. Pathological mechanism

The hepatic sinusoids are small vessels that constitute the hepatic microcirculation and are composed of hepatic sinusoidal endothelial cells (SEC) while being restricted by hepatic stellate cells. Therefore, the permeability of hepatic sinusoids is large, which facilitates the exchange of substances between hepatocytes and blood flow. When SOS occurs sinusoidal endothelial cells are damaged and shed, then migrate to the central veins of the hepatic lobules, leading to the formation of centripetal non-thrombotic obstruction of the hepatic sinusoids and central veins. Subsequently, coupled with the accumulation of erythrocytes and non-cellular debris, the formation of thrombus is another important factor that disrupts hepatic microcirculation and increases hepatic vascular resistance. A cascade of actions and interactions, as well as activation of exo-clotting factors, oxidative stress, and altered vascular permeability, all contributes to varying degrees to the obstruction of normal blood flow and increased venous resistance. This ultimately leads to portal hypertension, hepatic dysfunction and ascites retention [23] (**Figure 1**). Damage to SEC is manifested by intracellular glutathione depletion, decreased nitric oxide, and increased expression of matrix metalloproteinase (MMP) and vascular endothelial growth factor (VEGF). In addition to this, cytokines secreted by

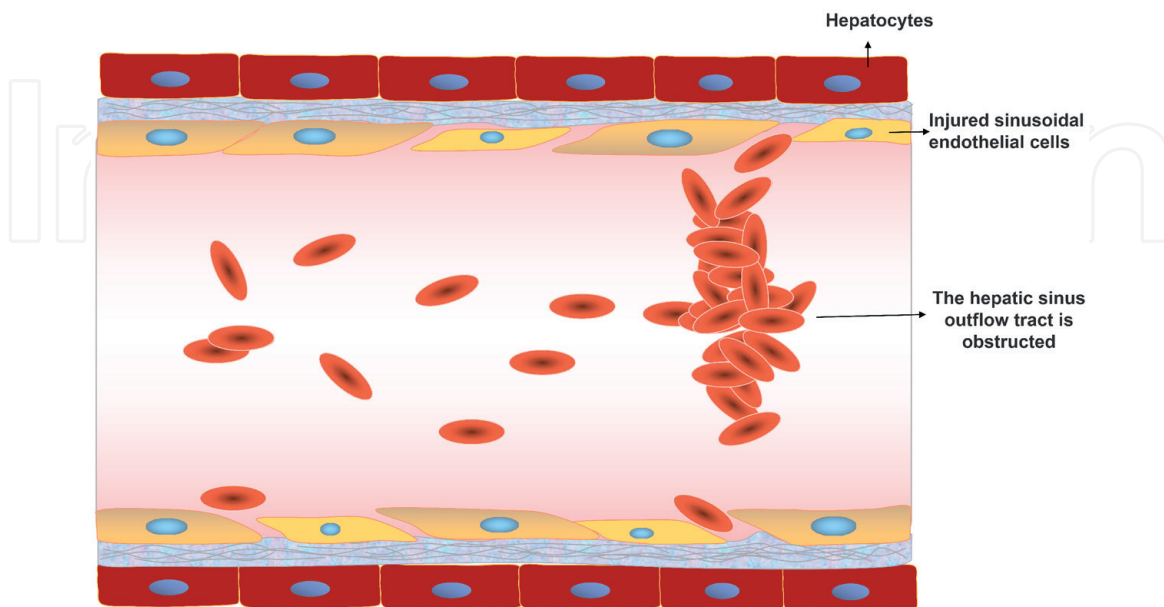


Figure 1. Sinusoidal obstruction syndrome (SOS) pathogenesis. Damage to the endothelial cells of the hepatic sinusoids due to HSCT or PA, etc. → blockage of the hepatic sinusoidal outflow tract → damage to the endothelial cells of the small and central hepatic veins → portal hypertension.

the damaged SEC lead to a weakened mucosal barrier between cells. This promotes the escape of erythrocytes, leukocytes, and platelets between hepatocytes and hepatic sinusoidal SEC, contributing to the initiation of inflammatory processes and thrombus formation [24, 25].

In HSCT-SOS, patients receiving high doses of toxic drugs (e.g., cyclophosphamide and leucovorin) during treatment are the cause of initial endothelial cell injury, which can lead to SOS, graft-versus-host disease (GVHD), capillary leak syndrome, implantation syndrome, and diffuse alveolar hemorrhage [26, 27]. In PA-SOS, the typical pathological changes are swelling, injury, and detachment of SEC in zone III of the hepatic acinus. The predominance of lesions in zone III of the hepatic acinus in PA-SOS is due to the abundance of CYP3A and the relative lack of glutathione (GSH) in this region. By constructing an animal model, Deleve et al. found that early damage to the endothelium of the hepatic sinusoids and central veins occurred before the development of veno-occlusive lesions, and that coagulative necrosis of hepatocytes occurred later than endothelial damage [3]. Besides, Harb et al. found that bone marrow progenitor cells were able to replace endothelial cells and thus repair the injury, while monocrotaline was able to inhibit endothelial progenitor cells in the bone marrow and circulation [28]. Therefore, PA damage to bone marrow progenitor cells and thus inhibition of endothelial cell repair may be another important pathogenetic mechanism. When SOS occurs, the hepatic sinusoidal stasis and dilatation; hepatic cord compression and atrophy; hepatocyte degeneration and necrosis; and central small vein occlusion and fibrosis are seen under light microscopy [29].

4. Clinical presentation

The main symptoms of SOS are non-specific: with or without ascites, pain, hepatomegaly, and jaundice. Clinical manifestations range from very few symptoms to multi-organ failure leading to patient death. The clinical manifestations of HSCT-SOS and PA-SOS differ in several aspects.

HSCT-SOS usually presents with abdominal distention, hepatomegaly, pain in the liver area, ascites, jaundice, loss of appetite, and weakness [30]. HSCT-SOS has a rapid onset, usually occurring within 21 d after bone marrow transplantation. And the proportion of seriously ill patients and mortality is high, most of them die from multi-organ dysfunction syndrome and sepsis [11]. A European multicenter study [6] graded SOS according to the severity of the disease: mild (about 8%) is self-limiting and recovers without special treatment; moderate (about 64%) recovers with aggressive treatment, and severe (about 28%) often leads to death because of progression, or no improvement after 100 d of treatment. In 2016, the European Society for Blood and Marrow Transplantation updated the HSCT-SOS scale, as shown in **Table 1** [26]. Due to the marked differences in incidence, genetic susceptibility, clinical presentation, prevention, treatment, and outcome between age groups, the European Society for Blood and Marrow Transplantation proposed new criteria specifically for SOS/VOD in children in 2018, as shown in **Table 2** [31].

PA-SOS mainly presents with abdominal distention and ascites [32], only about half of the patients present with hepatomegaly or jaundice, and a few patients have hepatoceles [33]. Most patients with PA-SOS have insignificant elevations in serum alanine aminotransferase, serum aspartate aminotransferase, alkaline phosphatase, γ -glutamyl transferase, and total bilirubin levels. PA-SOS occurs after a variable incubation period, which is usually about 30 d after drug administration and maybe up to several years. It can develop in both children and adults. In addition, PA-SOS

| | <i>Mild</i> | <i>Moderate</i> | <i>Sever</i> | <i>Very sever</i> <i>-MOD/MOF</i> |
|-----------------------------------------------|--------------|--------------------|----------------------|--------------------------------------|
| Time since first clinical symptoms of SOS/VOD | >7 Days | 5–7 Days | ≤4 Days | Any time |
| Bilirubin (mg/dL) | ≥2 and < 3 | ≥3 and < 5 | ≥5 and < 8 | ≥8 |
| Bilirubin (μmol/L) | ≥34 and < 51 | ≥51 and < 85 | ≥85 and < 136 | ≥136 |
| Bilirubin kinetics | | | Doubling within 48 h | |
| Transaminases | ≤2 × normal | >2 and ≤5 × normal | 45 and ≤8 × normal | 48 × Normal |
| Weight increase | < 5% | ≥5% and < 10% | ≥5% and < 10% | ≥10% |
| Renal function (baseline at transplant) | <1.2 | ≥ 1.2 and < 1.5 | ≥1.5 and < 2 | ≥2 or others signs of MOD/MOF |

EBMT, European society for Blood and Marrow Transplantation; MDO, multi-organ dysfunction; MOF, multi-organ failure; SOS, sinusoidal obstruction syndrome; VOD, veno-occlusive disease.

Table 1.
 New EBMT criteria for severity grading of a suspected SOS/VOD in adults.

| | <i>Mild</i> | <i>Moderate</i> | <i>Sever</i> | <i>Very sever</i> <i>-MOD/MOF</i> |
|-----------------------------------------|-------------|--------------------|-------------------------------------------------|-----------------------------------------------------------------------|
| LFT (ALT, AST, GLDH) | ≤2 × normal | >2 and ≤5 × normal | | >5 |
| Persistent RT | < 3 days | 3–7 days | | > 7 days |
| Bilirubin (mg/dL) | < 2 | | | ≥ 2 |
| Bilirubin (μmol/L) | < 34 | | | ≥ 34 |
| Ascites | Minimal | Moderate | Necessity for paracentesis (external drainage) | |
| Bilirubin kinetics | | | | Doubling within 48 h |
| Coagulation | Normal | Normal | Impaired coagulation | Impaired coagulation with need for replacement of coagulation factors |
| Renal function GFR (mL/min) | 89–60 | 59–30 | 29–15 | <15(renal failure) |
| Pulmonary function (oxygen requirement) | < 2 L/min | < 2 L/min | Invasive pulmonary ventilation (including CPAP) | |
| CNS | Normal | Normal | Normal | New onset cognitive impairment |

EBMT, European society for Blood and Marrow Transplantation; ALT, alanine transaminase; AST, aspartate transaminase; CNS, central nervous system; CPAP, continuous positive airway pressure; CTCAE, Common Terminology Criteria for Adverse Events; GFR, glomerular filtration rate; GLDH, glutamate dehydrogenase; LFT, liver function test; MOD/MOF, multi-organ dysfunction/multi-organ failure; RT, refractory thrombocytopenia; SOS/VOD, sinusoidal obstruction syndrome/veno-occlusive disease.

Table 2.
 EBMT criteria for grading the severity of suspected hepatic SOS/VOD in children.

has a lower rate of severe disease than HSCT-SOS [34, 35], and mortality is generally around 40%, with most deaths due to progressive liver failure and infection [36, 37]. Since PA-SOS is associated with extensive fibrosis in the central region of the lobules and histological examination shows venous-centered cirrhosis, it is difficult to distinguish from other causes of chronic lesions of cirrhosis.

5. Diagnosis

5.1 Symptoms and signs

Pain in the liver area, hepatomegaly, jaundice, ascites, and significant weight gain in a short period are more common.

5.2 Pathology

The biopsy is the gold standard for confirming the diagnosis of SOS. Liver histology is characterized by bruising of the liver tissue, dilatation of the hepatic sinusoids, swelling and damage to the endothelial cells of the hepatic sinusoids, and shedding. In particular, the thickening, fibrosis, luminal narrowing, and even occlusion of small hepatic veins are typical of the disease. However, hepatic stasis and swelling are associated with a high risk of puncture and can be falsely negative due to heterogeneous intrahepatic lesions.

5.3 Laboratory tests

Serum total bilirubin (TBil) or other liver functions (alanine aminotransferase, aspartate aminotransferase, total bile acids, and albumin).

5.4 Radiographic examinations

Ultrasonography shows a thin inner diameter of the hepatic vein (< 5 mm) with a smooth lining and luminal patency and a slowed flow velocity in the hepatic vein (< 20 cm/s). This is different from hepatic vein stenosis (Bard-Chiari syndrome). Also, the hepatic sinusoids and small venous lesions are not uniformly distributed within the liver in patients with SOS. As a result, areas of tissue bruising and necrosis may be distributed in a map-like fashion and appear on ultrasound images as heterogeneous intrahepatic echogenicity. Enhanced CT or MRI of the abdomen has diagnostic value, shows that the contrast in the portal and delayed phases is obstructed at the end of the portal branches and fails to enter the hepatic lobe segmental veins, resulting in unrepresented hepatic veins.

5.5 Hepatic venous pressure gradient measurement

The difference between free hepatic venous pressure and wedge pressure is the “hepatic venous pressure gradient (HVPG), measured by puncture of the internal jugular or femoral vein. When HVPG > 5 mmHg, it indicates the presence of portal hypertension in cirrhosis. When HVPG > 10 mmHg, the diagnostic specificity of SOS is 91%, and the chance of esophagogastric variceal bleeding and seroperitoneum will be greatly increased. The internationally recognized diagnostic criteria for HSCT-SOS are Seattle criteria, Baltimore criteria [38], and pediatric criteria [31], and PA-SOS diagnosis is mainly based on Nanjing criteria [13]. Several accepted diagnostic criteria are listed in **Table 3**.

| HSCT—SOS | | PA—SOS | |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Seattle criteria | Baltimore criteria | criteria for children | Nanjing criteria |
| <p>2 of the following 3 items within 20 d after bone marrow HSCT:</p> <ul style="list-style-type: none"> • Serum TBil \geq34.2 μmol/L; • Hepatomegaly or pain in the liver area; • Ascites or weight gain exceeding 2% of the original. | <p>Serum TBil \geq34.2 μmol/L and within 21 d after bone marrow HSCT, 2 of the following 3 items were present simultaneously:</p> <ul style="list-style-type: none"> • Hepatomegaly with hepatic pain; • Weight gain more than 5% of the original; • Ascites. | <p>The presence of two or more of the followinga:</p> <ul style="list-style-type: none"> • Onexplained consumptive and transfusion-refractory thrombocytopenia; • Otherwise unexplained weight gain on three consecutive days despite the use of diuretics or a weight gain 45% above baseline value; • Hepatomegaly (best if confirmed by imaging) above baseline value; • Ascites (best if confirmed by imaging) above baseline value; • Rising bilirubin from a baseline value on 3 consecutive days or bilirubin \geq2 mg/dL within 72 h. | <p>Have a clear history of PA-containing plant consumption, while excluding other known causes of liver injury, and present with 3 of the following or confirmed by pathology:</p> <ul style="list-style-type: none"> • Abdominal distention and/or pain in the liver region, hepatomegaly and ascites; • Elevated serum TBil or other liver function abnormalities; • Typical enhanced CT or MRI presentation. <p>The diagnosis was confirmed by pathology with the following typical pathological findings: swelling, damage, and loss of endothelial cells in the hepatic sinusoids of zone III of the hepatic acinus, and significant dilatation and congestion of the hepatic sinusoids.</p> |

SOS, sinusoidal obstruction syndrome; HSCT-SOS, hematopoietic stem cell transplantation-induced SOS; PA-SOS, pyrrolidine alkaloids-induced SOS; CT, computed tomography; MIR, magnetic resonance imaging.

Table 3.
Diagnostic criteria for hepatic SOS.

6. Treatment

The principles of treatment for SOS include discontinuing the use of plants containing PA in suspected patients and starting symptomatic and supportive treatment as soon as possible.

6.1 symptomatic and supportive treatment

Symptomatic and supportive treatment is particularly important for patients in the acute or subacute phase, including hepatoprotection, diuresis, nutritional support, protein and vitamin supplementation, and improvement of microcirculation. Oral furosemide and spironolactone are preferred as diuretics. If ascites are severe and not responding to pharmacological therapy, peritoneal drainage may be considered. For patients with fluid retention and severe renal failure, hemodialysis or hemofiltration should be performed. Patients with multiple organ failures should be admitted to the intensive care unit. In most patients, symptomatic and supportive treatment can reduce water-sodium retention, repair damaged hepatocytes, and promote recovery of liver function, but it cannot significantly reverse pathophysiological changes and needs to be combined with other treatments together [39].

6.2 Anticoagulant therapy

For patients in the acute or subacute phase, anticoagulation should be started as early as possible unless there are contraindications (including severe bleeding or bleeding tendency). The preferred choice is low-molecular-weight heparin at the recommended dose of 100 IU/kg, administered subcutaneously every 12 hours. In China, the cure rate of patients with PA-SOS treated with low-molecular heparin in the past was up to 70.7–88.9% [40–43]. Monitoring is not required in most patients because of the low side effects of low molecular heparin, but it should be used with caution in patients with renal failure. Oral warfarin, the oral anticoagulant of choice for long-term treatment, can also be administered. Its efficacy is evaluated by monitoring the international standardized ratio of prothrombin time (recommended 2.0 to 3.0). However, warfarin therapy has a narrow dose range, a wide variation in individual response, and a vulnerability to various food and drug interactions for efficacy. An imageological should be performed after 2 weeks of anticoagulation therapy, and clinical manifestations and liver function should be evaluated. If treatment is effective, anticoagulation therapy can be continued for up to 3 months. Conversely, if it is ineffective, treatment should be discontinued and alternative therapies may be considered.

6.3 Glucocorticoid

High-dose hormone therapy may be efficacious for HSCT-SOS, but the risk of infection is a concern and the level of evidence is low. The efficacy of glucocorticoid therapy for PA-SOS is also controversial [12, 44–46].

6.4 Defibrotide

Defibrotide (DF) is an effective drug for the prevention and treatment of HSCT-SOS and can be used to treat severe HSCT-HSOS [12]. DF has anti-ischemic, anti-inflammatory, anti-thrombotic, and thrombolytic activities as well as protecting the small vessel endothelium and inhibiting fibrin deposition. The mechanism may be the protection of endothelial cells and the maintenance of thrombus-fibrinolytic balance. However, the effectiveness of DF has not been tested in PA-SOS because its use for the treatment of SOS has not yet been approved in China.

6.5 Interventional therapy

Transjugular intrahepatic portosystemic shunt (TIPS) can be performed when medical treatment is ineffective. TIPS is effective in reducing portal pressure, improving clinical symptoms (ascites, hepatic distension, etc.), and preventing esophagogastric variceal hemorrhage [47]. TIPS is effective in patients with PA-SOS who have failed symptomatic treatment and require management of ascites and portal hypertension [48]. However, TIPS for acute HSCT-SOS has had variable results in one case report, with 5 of 10 patients dying after 10 days of TIPS placement, but the other 5 patients recovering significantly [49]. We need a longer follow-up to determine whether TIPS improves patient prognosis.

6.6 Liver transplantation

Liver transplantation is an effective treatment for various end-stage liver diseases, and it can be considered in patients with liver failure who have failed after the above treatments. Liver transplantation has been reported to improve the prognosis of patients with HSCT-SOS, but there are fewer reports on PA-SOS [38].

6.7 Other

Antithrombin III [50], recombinant human soluble thrombomodulin [51], N-acetyl-L-cysteine [52], and recombinant human tissue-plasminogen activator (t-PA) [53] have also been studied and reported for the treatment of HSCT-SOS. However, the efficacy of these drugs is unknown, and they lack evidence in the treatment of PA-SOS.

Prognosis: The overall morbidity and mortality rate is 20% to 50%. Mild patients heal better; most moderate patients can improve after symptomatic management and other treatments, and the morbidity and mortality rate is about 25%; severe patients are often complicated by multi-organ failure and have a morbidity and mortality rate of more than 90% despite active treatment [54].

7. Conclusion

In conclusion, there is no specific treatment for SOS and the prognosis of patients is poor, and only liver transplantation can prolong the survival time of patients with advanced disease. Therefore, the emphasis is on prevention, including pretreatment of transplantation and early treatment of underlying blood disorders to decrease the incidence and severity of HSCT-SOS, and increasing awareness of Chinese herbs such as Tusanqi to avoid accidental ingestion to reduce the incidence of PA-SOS. Besides, early diagnosis and assessment of patient risk through biomarkers is an effective tool for disease prevention and management [55].

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Conflict of interest

The authors declare no conflict of interest.

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