Review article

Burden of illness of non-hematopoietic stem cell transplant-related hepatic sinusoidal obstruction syndrome: A systematic review

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ARTICLE INFO

ABSTRACT

Background: Sinusoidal obstruction syndrome (SOS)/veno-occlusive disease (VOD) is generally associated with hematopoietic cell transplant (HCT), but little is known about this condition outside the HCT setting. This systematic review examines the burden of illness and current management approaches in non-HCT SOS/VOD.

Methods: We searched Embase, Medline, and grey literature sources for non-HCT SOS/VOD studies published 2002–2023. Inclusion criteria were studies of any design reporting incidence, diagnosis, underlying disease and any ongoing treatment at the time of SOS/VOD onset, management of non-HCT SOS/VOD, clinical burden, health-related quality of life, healthcare resource use, costs, and patients' unmet needs. Studies investigating pulmonary VOD or SOS/VOD related to the ingestion of pyrrolizidine alkaloids were excluded.

Two authors independently screened results, extracted data, and assessed the methodological quality of studies using the Motheral scale for retrospective studies, Newcastle-Ottawa scale for prospective studies and case control studies, the Cochrane risk of bias tool for randomized controlled trials, and the Joanna Briggs Institute critical appraisal tool for case series. Results were synthesized narratively.

Results: Ninety-two studies were included; 57 % were retrospective cohort studies and 70 % were conducted in the US or Europe. The study populations included hematological and solid tumor cancers, various indications for liver transplant, Wilms' tumor, and transfusion-dependent beta thalassemia. Non-HCT SOS/VOD occurs most frequently in people with colorectal liver metastases (CRLM), acute lymphoblastic leukemia (ALL), and acute myeloid leukemia (AML). Approximately 35 % of oxaliplatin-treated CRLM patients and 5 % of ALL and AML patients have non-HCT SOS/VOD. Diagnosis varies according to initial disease setting. Defibrotide is the most frequently reported treatment. Most studies did not clearly report their data sources or methods of outcome assessment.

Conclusion: Non-HCT SOS/VOD occurs in diverse disease conditions, therefore guidelines on diagnosis and treatment are needed to optimize management in clinical practice.

1. Introduction

Hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS), is a serious liver injury characterized by toxic damage to sinusoidal endothelial cells and hepatic vasculature. The consequent obstruction of hepatic venules and sinusoids can be life-threatening multi-organ failure. SOS/VOD has historically been associated with hematopoietic cell transplantation (HCT) and its preceding conditioning regimens but it has also been associated with solid organ transplants, ingestion of pyrrolizidine alkaloids, and radiotherapy and chemotherapy regimens, including antibody-drug conjugates, outside the HCT setting.

Incidence estimates of HCT-related SOS/VOD range from 5 % to 20 % in most populations and up to 60 % in very high-risk pediatric subgroups [1,2], while the mortality rate of severe, untreated post-HCT SOS/VOD has been reported to be as high as 80 % [3]. Agents that have been associated with an increased risk of SOS/VOD include inotuzumab ozogamicin (INO) [4,5], gemtuzumab ozogamicin (GO) [5], pegylated asparaginase [6], and vincristine with actinomycin D [7]. Other risk factors include having undergone HCT previously, receiving bone marrow from an unrelated donor, and older age [8]. Signs and symptoms of SOS/-VOD—hyperbilirubinemia, painful enlarged liver (hepatomegaly), fluid retention, weight gain, and ascites—typically occur during the first month after transplant [9]. Histological features include sinusoidal dilatation, sinusoidal fibrosis, and venule wall hemorrhage [10]. Diagnosis of HCT-related SOS/VOD has evolved since the Seattle [11] and Baltimore [12] criteria were first reported in 1984 and 1987, respectively. A revised set of diagnostic guidelines published by the European Society for Blood and Marrow Transplantation (EBMT) in 2016 [13] aimed to increase the sensitivity and specificity of SOS/VOD diagnostic criteria for adults, which were then further refined in a 2023 EBMT publication [14]. EBMT also published separate diagnosis criteria for children in 2018 [15]. In contrast to the Seattle and Baltimore criteria, the EBMT approach characterizes probable, clinical, and proven SOS/VOD, as well as distinguishing between early-onset SOS/VOD (within 21 days of HCT) and late-onset SOS/VOD (>21 days after HCT) [14]. Additionally, the EBMT recommendations include definitions of mild, moderate, severe, and very severe SOS/VOD [14].

The only treatment approved by the Food and Drug Administration (FDA) and the European Medicines Agency for hepatic SOS/VOD following HCT is defibrotide, which has anti-inflammatory and anti-thrombotic properties and protects the endothelial cells from further damage [16]. Defibrotide is also approved in Japan for both HCT-related and non-HCT SOS/VOD [17] but no other treatments are approved anywhere specifically for non-HCT SOS/VOD. Clinical guidelines and expert consensus statements recommend treating HCT-related SOS/VOD with defibrotide and supportive care [1,8,18]. Off-label use of corticosteroids is also recommended in certain cases [1], while tissue plasminogen activator and N-acetylcysteine are not recommended due to a high risk of hemorrhage and lack of efficacy, respectively [16,18].

Non-HCT related SOS/VOD may have different characteristics and prognosis from HCT-related SOS/VOD and may respond differently to treatment. Reports have been published describing SOS/VOD in various disease settings outside of HCT, including liver transplant [19] and non-transplant chemotherapy for Wilms' tumor [20], colorectal liver metastases [21], liver resection [22], and hematological cancers [23,24] but no systematic review investigating the epidemiology, patient characteristics, and outcomes of non-HCT SOS/VOD has yet been published. A comprehensive examination of the published literature is crucial to enhance the health care professionals' awareness and understanding of this condition to be able to recognize and manage it appropriately. The objective of this systematic review is to identify and synthesize the current evidence base relating to non-HCT SOS/VOD in terms of incidence, diagnosis, clinical burden and management, mortality, humanistic burden, and economic burden.

2. Methods

Embase and MEDLINE databases were searched via Ovid.com to identify articles published between 2002 and 2023 investigating non-HCT SOS/VOD. In the bibliographic databases, Medical Subject Heading (MeSH) and Embase thesaurus (Emtree) terms were used in conjunction with free-text words to identify studies relevant to the population, study design, and publication type of interest. The search strategies used are provided in supplementary materials (Additional Table 1). In addition, hand searches of conference proceedings from 2019 to 2023 of the European Society for Medical Oncology (ESMO), International Liver Congress (ILC), and the EBMT were undertaken and ClinicalTrials.gov was searched for ongoing studies. Two reviewers independently screened the titles and abstracts of the records identified by the literature searches. Studies were then retrieved in full-text form and screened independently by 2 reviewers, with any conflicts resolved by a third reviewer.

Inclusion criteria were studies of any design with 5 or more participants reporting 1 or more cases of non-HCT SOS/VOD and at least 1 of the following outcomes: incidence, diagnosis method, relevant medical history (ie, underlying disease and any ongoing treatment at the time of SOS/VOD onset), management of non-HCT SOS/VOD, clinical burden, health-related quality of life, healthcare resource use, direct and indirect costs, and patients' unmet needs. Studies investigating pulmonary VOD or SOS/VOD related to the ingestion of pyrrolizidine alkaloids were excluded.

All relevant data for the aforementioned outcomes were extracted by 1 reviewer into a Microsoft Excel file and fully validated independently by another reviewer. The nature of the outcomes of interest were not appropriate for meta-analysis. The data were synthesized narratively according to availability of data in each study for each of our outcomes of interest. Where data availability allowed, charts were used to present results of syntheses. Methodological quality assessment tools specific to different study designs were used for critical appraisal of the included studies that were published as full papers. The Motheral scale [25] was used for retrospective studies, the Newcastle-Ottawa scale [26] was used for prospective studies and case control studies, the Cochrane risk of bias tool [27] was for randomized controlled trials (RCTs), and the Joanna Briggs Institute critical appraisal tool [28] was used for case series.

Table 1

Methods of diagnosing non-HCT SOS/VOD.

Diagnostic criteria	Number of studies	Disease settings
No diagnostic criteria reported	35	–

EBMT [13]
    Adults: within 21 days[a]
    Bilirubin ≥2 mg/dL and ≥2 of the following: painful hepatomegaly; ascites; weight gain ≥5 %
    Adults: late onset, more than 21 days[a]
● As above
Or
● Histologically proven SOS/VOD
Or ≥2 of the following: bilirubin ≥2 mg/dL; painful hepatomegaly; ascites; weight gain ≥5 %
And
● Hemodynamic or/and ultrasound evidence of SOS/VOD
Children [15]
≥2 of the following: unexplained consumptive and transfusion-refractory thrombocytopenia; unexplained weight gain on 3 consecutive days, despite the use of diuretics, or weight gain >5 % above baseline value; hepatomegaly; ascites; rising bilirubin from a baseline value on 3 consecutive days or bilirubin ≥2 mg/dL within 72 h.
	6	Hematological cancers [36–39]
		Studies including >1 cancer (hematological and non-hematological) [40–42]

McDonald/Seattle [11] ≥2 of the following before day 30 post-transplant: jaundice; hepatomegaly and/or abdominal pain in the right upper quadrant; ascites and/or unexplained weight gain.	6	Hematological cancers [43–46] Wilms' tumor [47] Other solid tumors [20]
Modified Seattle [48] ≥2 of the following within 20 days[a]: weight gain >2 % of baseline due to fluid accumulation; hepatomegaly or right upper quadrant pain; hyperbilirubinemia (total serum bilirubin >2 mg/dL).	13	Hematological cancers [49–56] Wilms' tumor [7,47,57] Non-hematological cancers [58] Studies including >1 cancer (hematological and non-hematological) [59]
Baltimore [12] Bilirubin >2 mg/dL within 21 days[a] and at least 2 of the following: painful hepatomegaly, ascites or weight gain ≥5 %.	7	Hematological cancers [49,51–55] Non-hematological cancers [58]

Ponte di Legno
    Verified SOS/VOD: ≥3 of the following: hyperbilirubinemia; hepatomegaly; ascites; weight gain ≥5 %; thrombocytopenia (transfusion-resistant and/or otherwise unexplained by treatment).
    Normal findings on Doppler ultrasound of the liver should not exclude SOS/VOD.
    Probable SOS/VOD: 2/5 of the above criteria.
    Possible SOS/VOD: Unexplained hyperbilirubinemia, with no additional criteria met.
	3	Hematological cancers [38,54,60]

Rubbia-Brandt With reference to sinusoidal dilatation: ● 0: Absent ● 1: Mild (centrilobular involvement limited to one-third of the lobule) ● 2: Moderate (centrilobular involvement extending in two-thirds of the lobule) ● 3: Severe (complete lobule involvement or centrilobular involvement extending to adjacent lobules with bridging congestion)	18	CRLM [61–76] Liver transplant [29] Non-hematological cancers [30]
Unspecified criteria using biopsy Examination of biopsy for histological signs of SOS/VOD	19	Hematological cancers [31–34] CRLM [70,77–79] Other solid tumors [80–82] Liver transplant [29,35,83–87] Wilms' tumor [7] Studies including >1 cancer (hematological and non-hematological) [52] Chemotherapy (type of cancer not reported) [42]
Use of imaging Examination of imaging (ultrasound, MRI, radiographs, CT scans) for signs of SOS/VOD	6	Hematological cancers [31,32,34] CRLM [70,73,88,89] Non-hematological cancers [90]

Note: Categories were not mutually exclusive; some studies reported more than 1 method of SOS/VOD diagnosis.

[a] Typically applies to time after HCT; however, it was unclear if it also applies to time after chemotherapy (either from the initiation or end of chemotherapy regimen).

Key: CRLM – colorectal liver metastases; CT, commuted tomography; EBMT – European Society for Blood and Marrow Transplantation; HCT – hematopoietic cell transplantation; MRI, magnetic resonance imaging; SOS – sinusoidal obstruction syndrome; VOD – veno-occlusive disease.

This systematic review was not registered but a full protocol was completed before beginning the study and all changes to the protocol were logged (see supplementary materials). All data collection forms and templates are available on request.

3. Results

Overview of included studies

A total of 3,874 records were screened, of which 452 met the inclusion criteria and were selected for full-text screening. After full-text screening, 92 studies—with a total of 111 publications—were included (Fig. 1). The studies excluded after full-text screening are listed in the supplementary materials with their reasons for exclusion.

The majority (57 %) of the 92 included studies were retrospective cohort studies and 70 % were conducted in the US or Europe. Of the included studies, 75 % had sample sizes of ≤100 people and 7 studies (8 %) recruited more than 1,000 participants. Data collection periods ranged from 1986 to 2021; 30 % began data collection from 2010 onwards and 18 % did not report when they collected data. Full details of all included studies are presented in Additional Table 2 of the supplementary materials.

The results of the methodological quality assessment of the included studies published as full papers varied from some risk of bias to high risk of bias, with many domains categorized as "unclear" due to lack of reporting. Most data sources for the retrospective studies were described in insufficient detail to be able to judge their external validity; case series and case control studies often did not give clear case definitions or inclusion criteria; there was a risk of bias in RCTs due to lack of blinding of outcome assessment and insufficient reporting of randomization and allocation concealment; and there were some concerns about outcome assessment methods in the prospective cohort studies (Additional Fig. 1 in supplementary materials).
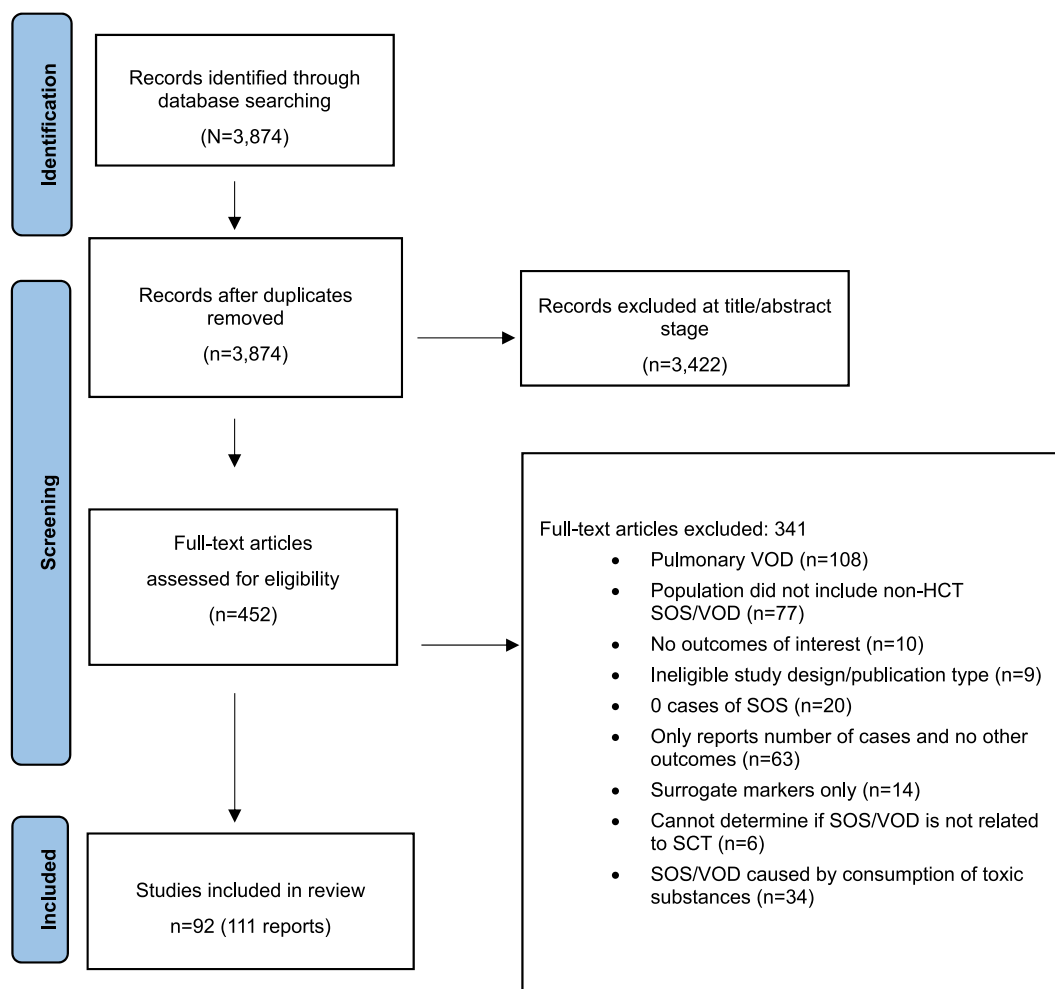

Fig. 1. PRISMA diagram
Key: PRISMA – preferred reporting items for systematic reviews and meta-analyses; VOD – veno-occlusive disease; SCT – stem cell transplant; SOS – sinusoidal obstruction syndrome.

Table 2

Proportions of patients with non-HCT SOS/VOD by initial disease setting and age group.

Initial disease (before/during onset of SOS/VOD)	Range (median) of proportion of patients with non-HCT SOS/VOD		
	Adults	Children	All age groups[a]
ALL	2.8 % to 5.8 % (3.1 %) [33,37,50,100]	0.4 % to 14.8 % (5.8 %) [32,34,38,39,46,54,59,60,101,111]	0.4 % to 14.8 % (4.0 %) [32–34,37–39,46,50,54,59,60,100,101,111]
AML	0.9 % to 33.3 % (6.3 %) [31,36,44,49,51,55,91–94]	3.4 % to 33.3 % (4.2 %) [43,45,95,96,112]	0.9 % to 33.3 % (4.7 %) [31,36,43–45,49,51,55,91–96,98,99,112]
CRLM	–	–	11.1 % to 76.8 % (36.1 %) [61–67,69–79,89,109,110] [b]
Any indication for liver transplant	0.4 % to 10.0 % (3.0 %) [29,35,83,85,87,102,103]	14.3 % (–) [86]	0.3 % to 14.3 % (2.6 %) [29,35,83–87,102–104]
Studies including >1 hematological cancer	–	–	1.5 % to 3.9 % (2.7 %) [24,53]
Studies including >1 non-hematological cancer	15.0 % to 52.9 % (34.0 %) [30,81,82,108]	3.4 % to 60.0 % (7.9 %) [90,113–116]	3.4 % to 60.0 % (17.5 %) [30,81,82,90,108,113–116]
Wilms' tumor	–	1.8 % to 45.1 % (13.1 %) [7,47,57,59,105,106]	–
Liver cancer	–	–	54.5 % (–) [80]
Transfusion-dependent beta-thalassemia	–	11.1 % (–) [117]	–

[a] The category "All age groups" comprises studies in adults, studies in children, studies in mixed-age groups, and studies that did not report the age of the participants.
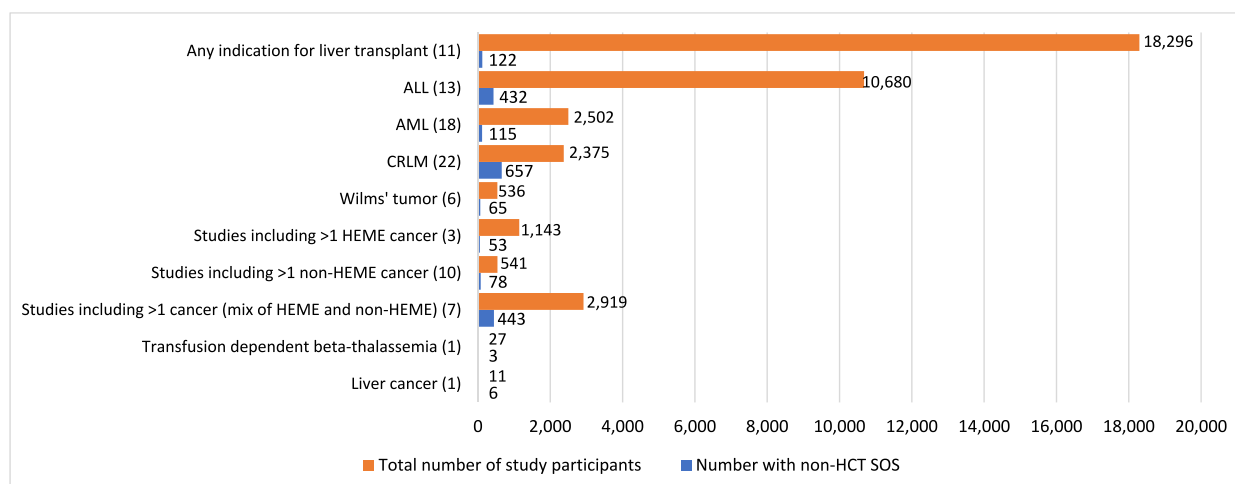
[b] 18/20 included adults only; 2/20 did not report the age of participants. Key: ALL – acute lymphoblastic leukemia; AML – acute myeloid leukemia; CRLM – colorectal liver metastases; SOS – sinusoidal obstruction syndrome; VOD – veno-occlusive disease.

The identified studies reported data relating to diagnosis, epidemiology, clinical burden, and management approaches for non-HCT SOS/VOD. No useable data were identified relating to economic burden or humanistic burden.

The included studies encompassed a range of disease and treatment settings where non-HCT SOS/VOD occurs: hematological and solid tumor cancers, various indications for liver transplant, Wilms' tumor, and transfusion-dependent beta thalassemia. Fig. 2 presents the total number of study participants according to initial disease setting (before or during onset of SOS/VOD) and the total number of SOS/VOD cases in each disease setting.

Diagnosis of non-HCT SOS/VOD

No clinical guidelines were identified for the diagnosis of non-HCT SOS/VOD. Thirty-five of the 92 included studies did not report how SOS/VOD was diagnosed; 26 studies reported using clinical criteria that are used to diagnose SOS/VOD in the transplant setting, namely EBMT, Seattle, and Baltimore criteria. Clinical criteria for diagnosis are generally focused on ascites, weight gain, jaundice, bilirubinemia, and hepatomegaly, although there are differences between the criteria; for instance, thrombocytopenia features as a

Fig. 2. Total numbers of participants and cases of non-HCT SOS/VOD across all studies, by initial disease. Note: Numbers in parentheses indicate the number of studies in each category; includes studies where the entire study sample had SOS/VOD and studies where a proportion of the sample had SOS/VOD. Key: ALL – acute lymphoblastic leukemia; AML – acute myeloid leukemia; CRLM – colorectal liver metastases; HCT – hematopoietic stem cell transplant; HEME – hematological; SOS – sinusoidal obstruction syndrome; VOD – veno-occlusive disease.

diagnostic criterion in the EBMT criteria for children and in the Ponte di Legno criteria but not in other criteria (Table 1).

Diagnosis of SOS/VOD in patients with colorectal liver metastases (CRLM) was distinct from diagnosis of SOS/VOD in other disease settings. Of the 20 studies that described how SOS/VOD was diagnosed in people with CRLM, all of them reported using histological rather than clinical diagnosis, with 16 studies specifying the use of Rubbia-Brandt criteria. Rubbia-Brandt criteria refers specifically to the degree of sinusoidal dilatation and centrilobular involvement and does not take symptoms into account. In addition to its use in patients with CRLM, the Rubbia–Brandt classification was also used to diagnose SOS/VOD in 1 study in patients undergoing liver transplant [29] and another study in patients with unspecified malignant tumors undergoing hepatectomy [30]. None of the studies in patients with hematological cancer reported using Rubbia-Brandt criteria for diagnosing SOS/VOD; 5 studies reported using biopsy in patients with hematological cancers to confirm or diagnose SOS/VOD but there was insufficient detail about the histological criteria that were used [31–34].

In studies that reported using clinical diagnostic criteria and histology in the same patients, there were discrepancies between the 2 approaches. Some patients whose signs and symptoms met clinical diagnostic criteria for SOS/VOD did not always demonstrate abnormal biopsy findings consistent with SOS/VOD and vice versa. In a study of children with ALL, of 10 patients with clinical SOS/VOD and who underwent ultrasound imaging, the findings were definite SOS/VOD in only 4 cases, possible SOS/VOD in 3 cases, and normal findings in 3 cases [34]. Another study, also in children with ALL, reported that 2/8 clinical SOS/VOD cases did not have pathologic evidence of SOS/VOD on biopsy [32]. Conversely, a study in liver transplant patients reported that 7/15 SOS/VOD cases identified by biopsy did not have symptoms at the time of biopsy [35]. This evidence suggests that it is possible to present with no symptoms and have histological SOS/VOD, and it is also possible to have clinical SOS/VOD but no evidence of histological SOS/VOD.

Epidemiology

No population-based epidemiological studies were identified that reported data relating to the incidence of non-HCT SOS/VOD. Non-HCT SOS/VOD cases were most frequently reported in adults and children receiving chemotherapy for hematological cancers, adults receiving chemotherapy for CRLM, adults undergoing liver transplant, and children receiving treatment for Wilms' tumor. The median proportions of non-HCT SOS/VOD by initial treatment received before or during SOS/VOD onset are shown in Fig. 3. The highest median reported was 54.5 % in adults with liver cancer undergoing Y90 radioembolization; however, this study included only 11 patients with liver cancer, 6 of whom were diagnosed with SOS/VOD, based only on histological changes [80].

The proportion of non-HCT SOS/VOD cases in studies investigating patients with acute myeloid leukemia (AML) receiving treatment with GO ranged from 4.2 % to 33.3 % (median: 9.1 %) in adults [31,42,44,46,49,51,55,91–94] and 3 % to 33.3 % (median: 3.8 %) in children [43,45,95,96]. It should be noted that the 2 studies [45,51] reporting rates of the higher rate of 33 % had substantially smaller sample sizes than all other studies and these data appear to be outliers. Additionally, 1 study in children receiving GO
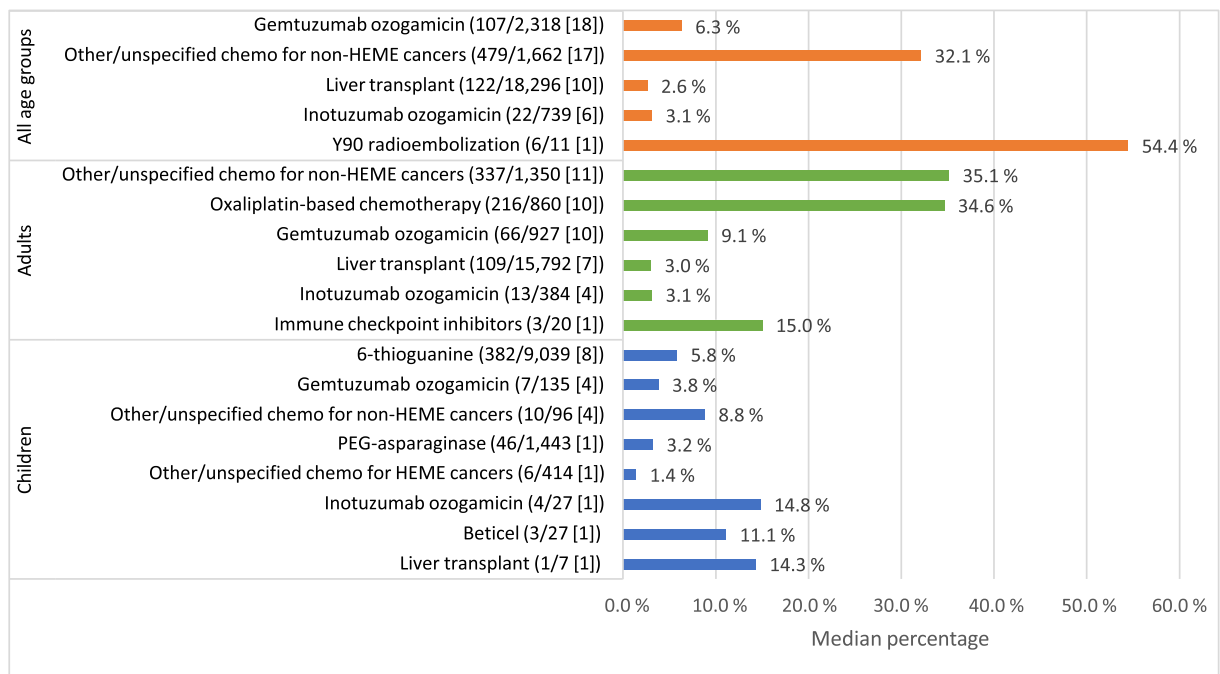
Fig. 3. Median proportion of patients with non-HCT SOS/VOD by initial treatment setting. Note: Numbers in parentheses refer to the numbers of people with SOS/VOD (numerator) within the total number of study participants (denominator). The number of studies appears in square brackets. The category "All age groups" comprises studies in adults, studies in children, studies in mixed-age groups, and studies that did not report the age of the participants. Key: HEME – hematological; SOS – sinusoidal obstruction syndrome; VOD – veno-occlusive disease.

for either AML or myelodysplastic syndrome (MDS) reported 5/129 (4 %) had non-HCT SOS/VOD [53]. Across all studies in patients treated with GO for hematological cancers, regardless of age group, the proportion of non-HCT SOS/VOD cases ranged from 0.9 % to 33.3 % (median: 6.3 %) [31,36,43–45,49,51,53,55,91–93,95–99].

Among adults with acute lymphoblastic leukemia (ALL) receiving treatment with INO, the proportion of non-HCT SOS/VOD cases ranged from 2.8 % to 5.8 % (median: 3.1 %) [33,37,50,100]. One study in children receiving INO for ALL reported 4/27 (14.8 %) [101], and another study reported 5/328 (1.5 %) of all age groups receiving INO for either ALL or non-Hodgkin lymphoma (NHL) had non-HCT SOS/VOD [24]. Across all studies in patients treated with INO for hematological cancers, regardless of age group, the proportion of non-HCT SOS/VOD cases ranged from 1.5 % to 14.8 % (median: 3.1 %) [24,33,37,50,100,101].

Among adults undergoing liver transplant, the proportion of non-HCT SOS/VOD cases ranged from 0.4 % to 10.0 % (median: 3.0 %) [29,35,83,85,87,102,103]. One study in children undergoing liver transplant reported 1/7 (14.3 %) had non-HCT SOS/VOD [86]. Across all studies in liver transplant patients, regardless of age group, the proportion of non-HCT SOS/VOD cases ranged from 0.3 % to 14.3 % (median: 2.6 %) [29,35,83–87,102–104].

Among children treated with vincristine and actinomycin D for Wilms' tumor, the proportion of non-HCT SOS/VOD cases ranged from 11.1 % to 45.1 % (median: 14.3 %) [7,47,57,105,106]. One other study in children with Wilms' tumor treated with vincristine and actinomycin D reported 5/235 (2.1 %) children died of non-HCT SOS/VOD, but it is unclear if this number was the total number of non-HCT SOS/VOD cases or if there were other children in the study with non-HCT SOS/VOD who recovered [107].

In adults with CRLM receiving oxaliplatin-based chemotherapy (OBC), the proportion of non-HCT SOS/VOD cases ranged from 11.2 % to 59.0 % (median: 34.6 %) [61–63,65–68,71,77]. In 2 other studies where OBC was used to treat a range of solid tumor cancers (colorectal, gastric, esophageal, and pancreatic), the proportions of non-HCT SOS/VOD cases were 18/34 (52.9 %) [82] and 12/30 (40 %) [108]. Overall, in patients treated with OBC for solid tumor cancers, the proportion of non-HCT SOS/VOD cases ranged from 11.2 % to 59.0 % (median: 37.5 %) [61–63,65–68,71,77,82,108].

The proportion of CRLM patients who had non-HCT SOS/VOD, regardless of initial treatment regimen, ranged from 11.1 % to 76.8 % (median: 36.1 %) [61–67,69–79,89,109,110]. In hematological cancers, regardless of treatment settings, the proportion of non-HCT SOS/VOD cases ranged from 0.4 % to 14.8 % (median: 4.8 %) in ALL [32–34,37–39,46,50,54,60,100,101,111], 0.9 % to 33.3 % (median: 4.7 %) in AML [31,36,43–45,49,51,55,91–96,98,99,112], 1.5 % to 3.9 % in studies in more than 1 hematological cancer (AML or MDS [53] and ALL or NHL [24]), and 3.4 % to 60.0 % (median: 17.5 %) in studies in more than 1 non-hematological cancer (other than CRLM) [30,81,82,90,108,113–116]. The median proportions of non-HCT SOS/VOD cases by disease setting are shown in
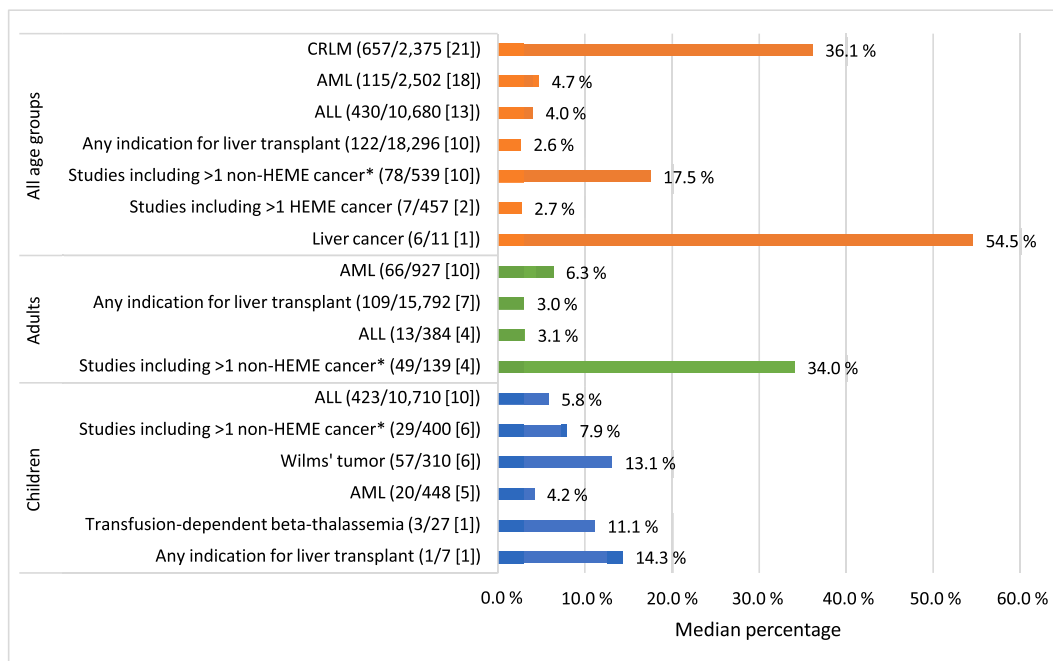

Fig. 4. Median proportions of patients with non-HCT SOS/VOD, by initial disease (before/during onset of SOS/VOD)
Note: Numbers in parentheses refer to the numbers of people with SOS/VOD (numerator) within the total number of study participants (denominator). The number of studies appears in square brackets. The category "All age groups" comprises studies in adults, studies in children, studies in mixed-age groups, and studies that did not report the age of the participants.*Studies including >1 non-hematological cancer: these included adults with esophageal, colorectal, gastric, and pancreas cancers; children with embryonal tumors, metastatic soft tissue sarcoma, Wilms' tumor, clear cell sarcoma of the kidney, and unspecified malignant solid tumors.
Key: ALL – acute lymphoblastic leukemia; AML – acute myeloid leukemia; CRLM – colorectal liver metastases; HCT – hematopoietic stem cell transplant; HEME – hematological; SOS – sinusoidal obstruction; VOD – veno-occlusive disease.

Fig. 4.

The proportions of patients with non-HCT SOS/VOD by age group and initial disease setting are shown in Table 2. In patients with ALL, non-HCT SOS/VOD may occur in a higher proportion of children (0.4 % to 14.8 %; median: 6.8 %) [32,34,38,39,46,54,60,101, 111] than in adults (2.8 % to 5.8 %; median 3.1 %) [33,37,50,100]. In contrast, in AML there may be a higher rate of non-HCT SOS/VOD in adults (0.9 % to 33.3 %; median 6.3 %) [31,36,44,49,51,55,91–94] than in children (3.4 % to 33.3 %; median 4.2 %) [43,45,95,96,112].

In studies comprising more than 1 non-hematological cancer, the range in children was wider but the median proportion of SOS/VOD cases was lower (3.4 % to 60.0 % [median: 7.9 %]) [90,113–116] than in adults (15.0 % to 52.9 % [median: 34.0 %]) [30,81,82, 108]. The narrower range across the studies in adults is likely to due to the greater similarity in population between the adults-only studies, where almost half of the included patients had colorectal, pancreatic, and gastric cancers treated with OBC [82,108], and all non-HCT SOS/VOD cases were diagnosed based on histology. In contrast, the studies in children with non-hematological cancers had more heterogeneous populations and the methods of non-HCT SOS/VOD diagnosis were not reported.

Five studies reported the percentage of patients with non-HCT SOS/VOD as a proportion of all types of SOS/VOD, including SOS/VOD following HCT. The proportion of non-HCT SOS/VOD cases ranged from 5.8 % to 33.8 % (median: 12.8 %) [42,52,56,58,118]. In 2 of these 5 studies, no details were reported regarding the initial disease and treatment setting, except that the participants were being treated for cancer with chemotherapy. In another 2 studies investigating 710 [58] and 798 [56] patients, respectively, all of whom received defibrotide for any kind of SOS/VOD, 11 % [58] and 6 % [56], respectively, had non-HCT SOS/VOD. In the remaining study, investigating 71 patients who were all treated for any kind of SOS/VOD in the intensive care unit, 14 % had non-HCT SOS [42].

Presentation of non-HCT SOS/VOD

Evidence relating to the clinical characteristics and presentation of non-HCT SOS/VOD was reported inconsistently across the included studies. The proportions of patients presenting with each of the key symptoms of ascites, hepatomegaly, and hyper-bilirubinemia were reported in 11 studies [6,20,29,35,47,49,51,55,84,104,112] (see additional Table 3 in supplementary materials).

Time to onset of non-HCT SOS/VOD was reported infrequently across the included studies and it varied considerably according to disease and treatment setting (Table 3). None of the studies in patients with SOS/VOD following treatment for CRLM reported time to SOS/VOD onset. In liver transplant patients, time to onset ranged from 2.4 to 65 months post-treatment; however, in the 2 largest liver transplant studies, including over 12,000 and 1,000 patients respectively, the median time to onset of SOS/VOD after liver transplant was 2 months [29,87]. In the studies reporting time to SOS/VOD onset in AML patients treated with GO, most patients had onset within 3 weeks, but some developed SOS/VOD as long as 4 months after treatment initiation [43,45,95,98]. In children treated with 6-thioguanine for ALL, time to onset of SOS/VOD ranged from 17 days to 18 months [34,46,54,111]. In patients receiving vincristine and actinomycin D for Wilms' tumor, the range of time to onset was shorter, at 9 days to 4 months [57,105,106]; and only 1 study in ALL patients treated with INO reported time to SOS/VOD onset (16 days) [33].

Ascites was reported in 40 % to 100 % of non-HCT SOS/VOD cases in patients treated for AML [33,49,51], ALL [6,32,34,38,112], liver transplant [84,87,104,119], and Wilms' tumor [47]. In patients with CRLM, 0 % to 55 % of non-HCT SOS/VOD cases presented with ascites [66,67,70]. Hepatomegaly was reported in 39 % to 100 % of non-HCT SOS/VOD cases in AML [33,49,51], and ALL [6,32, 34,46,111,112] in CRLM [70,88] and liver transplant patients [84,104]. Hyper-bilirubinemia was reported in 72 % to 100 % of non-HCT SOS/VOD cases in ALL [6,46,111,112], 20 % to 100 % in AML [33,49,51] and 43 % in liver transplant patients [104]. None of the studies in CRLM reported any data on hyperbilirubinemia. Two studies in liver transplant patients reported that none of the non-HCT SOS/VOD cases presented with the triad of hepatomegaly, ascites, and jaundice [29,35].

Thrombocytopenia, which features in the EBMT and Ponte di Legno diagnostic criteria—but not in the more widely used modified Seattle and Baltimore criteria—occurred in 62 % to 90 % of non-HCT SOS/VOD cases in the 10 studies that reported it. The disease settings were ALL [34,46,54,112], Wilms' tumor [47], studies in more than 1 cancer (hematological and non-hematological) [41,56, 59], and studies in more than 1 non-hematological cancer [20,90].

Disease severity and mortality

Various criteria with differing definitions of severity categories were used to grade the severity of non-HCT SOS/VOD across the

Table 3
Time to onset of non-HCT SOS/VOD.

Initial disease and treatment setting (before/during SOS/VOD onset)	Time to onset after initial treatment initiation (range)
Liver transplant	1–65 months [29,35,84,103,104]
AML treated with GO	7–47 days [43,45,95,98]
6-thioguanine for ALL	17 days to 18 months [34,46,54,111]
Vincristine and actinomycin D for Wilms' tumor	9 days to 4 months [57,105,106]
ALL treated with INO	16 days [33]
Chemotherapy-treated CLRM	Not reported

Key: ALL – acute lymphoblastic leukemia; AML – acute myeloid leukemia; CRLM – colorectal liver metastases; GO – gemtuzumab ozogamicin; HCT – hematopoietic cell transplantation; SOS – sinusoidal obstruction syndrome; VOD – veno-occlusive disease.

included studies. In people with CRLM, Rubbia–Brandt criteria (based on the extent of centrilobular involvement) was used to grade the severity of non-HCT SOS/VOD, as well as to diagnose non-HCT SOS/VOD. In other disease settings, the severity of non-HCT SOS/VOD was graded with McDonald, Ponte di Legno, or EBMT criteria. Severity according to McDonald criteria is based on time taken to resolve non-HCT SOS/VOD and whether or not treatment is required; Ponte di Legno severity grading is based on bilirubin level, extent of weight gain, and presence of renal failure or hepatic encephalopathy; and the EBMT severity grading is based on time since first clinical symptoms, levels of bilirubin transaminases, and extent of weight gain.

The proportions of severe cases SOS/VOD and/or multi-organ failure and the numbers of deaths due to non-HCT SOS/VOD are shown in Table 4. The highest rates of severe disease were reported in patients with Wilms' tumor (range: 40 % to 100 %) and AML (range: 33 % to 43 %). Deaths attributed to non-HCT SOS/VOD were reported in 0 % to 100 % of non-HCT SOS/VOD cases in AML patients [36,44,45,51,92,94,96], 0 % to 67 % of cases in ALL patients [32,37,38,60,100,101,111,112], 0 % to 29 % of cases in liver transplant patients [29,35,84,86,120], and 0 % to 25 % in studies reporting SOS/VOD in more than 1 non-hematological cancer [20, 58,82,116]. Only 1 study reported non-HCT SOS/VOD mortality in people with CRLM, which was 0 % [75]. None of the studies reported mortality stratified by severity of SOS/VOD. One study reported that 1 of 2 deaths due to SOS/VOD was confirmed by liver biopsy. None of the other studies reporting SOS/VOD mortality described confirmation by biopsy or autopsy, although 2 of these studies reported that the diagnosis of SOS/VOD had been confirmed by liver biopsy [35,84].

Treatments for non-HCT SOS/VOD

While many studies reported no information about how SOS/VOD cases were managed, where SOS/VOD treatment was reported there was a wide variety of approaches (see Additional Table 4 in supplementary materials). Defibrotide, switching or pausing chemotherapy, and supportive care (eg, fluid restriction, blood product support) were the most frequently reported.

Twenty-four studies reported the use of defibrotide to treat non-HCT SOS/VOD, and a further 2 explicitly reported that no patients received defibrotide; these were 1 study in patients with ALL [54] and another in liver transplant patients [35]. None of the studies in people with CRLM reported using defibrotide to manage SOS/VOD; it is not certain if this is because defibrotide was not used for SOS/VOD cases in people with CRLM or if it was used but not reported. Outcome data related to defibrotide treatment was reported in 14 of 24 studies (58 %). Eight studies reported that everyone who received defibrotide recovered from non-HCT SOS/VOD [33,37,59, 87,93,94,98,121] and another 3 reported recovery rates of 50 % [20], 83 % [92], and 94 % [38] after defibrotide. Five studies reported the number of deaths due to non-HCT SOS/VOD following defibrotide; in total, there were 43 deaths among 226 people treated with defibrotide [20,38,52,56,58]. Except for 1 study in patients with ALL [38], all deaths following defibrotide were reported in studies that included mixed populations of people with hematological and non-hematological cancers.

In 10 studies reporting the use of supportive care to manage non-HCT SOS/VOD, 2 reported recovery rates of 5/6 (83 %) [40], and 4/5 (80 %) [20]. One study described fluid restriction, furosemide administration, plasma and platelet transfusions, antibiotics, and other measures that were personalized for each individual [20]. The other study did not describe details of the supportive care the

Table 4
Severity and mortality in non-HCT SOS/VOD.

Initial disease setting (before/during SOS/VOD onset)	Range (median) with severe non-HCT SOS/VOD and/or multi-organ failure (as a proportion of non-HCT SOS/VOD cases)	Mortality: range (median) (as a proportion of non-HCT SOS/VOD cases)
ALL	10 % to 20 % (15 %) [54,60]	**0 % to 67 % (3.0 %)** 8/268 (7 studies) [6,32,37,38,100, 101,111]
AML	33 % to 43 % (38 %) [36,44]	**0 % to 100 % (31.4 %)** 21/75 (8 studies) [36,44,45,51,92,94, 96,112]
CRLM	0 % to 35.4 %[a] (11 %) [62,64,66–74,109]	**0 % (—)** 0/57 (1 study) [75]
Any indication for liver transplant	14 % (—) [84]	**0 % to 29 % (7.3 %)** 7/62 (5 studies) [29,35,84,86,120]
Studies including >1 non-hematological cancer	31 % to 70 %[b] (38 %) [30,41,58]	**0 % to 25 % (10 %)** 21/103 (4 studies) [20,58,82,116]
Wilms' tumor	40 % to 100 % (71.4 %) [47,105,106]	**0 % (—)** 0/1 (1 study) [57]
Liver cancer	NR	NR
Transfusion-dependent beta-thalassemia	NR	NR
Studies including >1 cancer (hematological and non-hematological)	Multi-organ failure: 32.6 % to 46.3 % (39.6 %) [52,56,118] Severe SOS/VOD: 89.1 % (—) [56]	**0 % to 25.6 % (13.6 %)** 24/150 (3 studies) [41,52,56]

[a] Includes 1 study that reported people with moderate or severe SOS/VOD in a single category; without the data from this study, the median proportion with severe SOS/VOD is 8 % (range: 0%–35 %).

[b] Includes 1 study that reported people with moderate or severe SOS/VOD in a single category; without the data from this study, the median proportion with severe SOS/VOD is 59 % (range: 48%–70 %). Key: ALL – acute lymphoblastic leukemia; AML – acute myeloid leukemia; CRLM – colorectal liver metastases; HCT – hematopoietic cell transplantation; NR – not reported; SOS – sinusoidal obstruction syndrome; VOD – veno-occlusive disease; WT – Wilms' tumor.

patients received but it is important to note that half of the SOS episodes were treated with defibrotide in addition to supportive care, although the study does not report whether the individual who did not recover had been treated with or without defibrotide [40]. Neither of the 2 studies reporting outcomes of supportive care for non-HCT SOS/VOD provided details of the severity of the SOS cases. In 6 studies that reported switching or pausing chemotherapy to manage non-HCT SOS/VOD, 2 reported no outcomes [46,115], and 1 reported no deaths and no instances of liver failure but included no specific details relating to recovery from SOS/VOD [82]. In 3 studies, 100 % of patients whose chemotherapy was switched or paused recovered from SOS/VOD [34,111,116], although 2/6 patients then went on to experience ALL relapse [111]. Severity of non-HCT SOS/VOD was reported in 2 of the 6 studies where patients were treated with switching or pausing chemotherapy: 100 % of cases were mild in 1 study [34] and 72 % were mild or moderate in another [82].

Safety data for non-HCT SOS/VOD treatments were reported in only 4 studies, 2 of which reported no adverse events: 2 children with Wilms' tumor who had severe SOS/VOD treated with N-acetylcysteine [106] and 4 children with ALL who had severe SOS/VOD treated with defibrotide [59]. Another study investigating the usage and safety of defibrotide reported that 22/88 (25 %) of SOS/VOD cases experienced adverse events possibly related to defibrotide [52]. These included mouth hemorrhage, pulmonary hemorrhage, hematochezia, nausea, encephalopathy, epistaxis, and hypotension. Additionally, 1 death was judged to be possibly related to defibrotide. In children and adults with non-HCT SOS/VOD following GO or INO, 7/46 (15 %) had at least 1 serious adverse event associated with defibrotide [56]. Four patients had infection and 4 experienced hemorrhage, while none had coagulopathy, immunogenicity, septicemia, injection-site reactions, or thromboembolic events [56]. No other studies reported adverse events related to treatments for non-HCT SOS/VOD.

4. Discussion

This systematic review identifies a substantial body of evidence, from 92 studies, to indicate that SOS/VOD occurs in a wide range of disease and treatment contexts outside the HCT setting. The diversity of diagnostic methods means that the true incidence of non-HCT SOS/VOD remains uncertain; in the HCT-specific setting, similar variations in diagnostic criteria have been identified as a potential barrier to measuring the incidence of the disease [3]. Nevertheless, the current evidence indicates that non-HCT SOS/VOD occurs in approximately 5 % of patients treated for ALL or AML, 3 % of liver transplant patients, and 35 % of oxaliplatin-treated CRLM patients. Across all age groups, GO was the most frequently reported cancer therapy received by patients at the time of onset of non-HCT SOS/VOD [122]. There is some evidence to suggest that lower dosages of GO can reduce the risk of SOS/VOD following HCT [122]; however, the studies included in this systematic review did not report sufficient detail of the dosages administered to conclude that higher rates of SOS/VOD are associated with higher GO dosage. In children, 6-thioguanine was the most frequently reported therapy associated with the onset of SOS/VOD. Similar to GO, there is some suggestion that the risk of SOS/VOD with 6-thioguanine may increase with higher doses [123], but there are insufficient data from the included studies in the non-HCT setting to confirm this.

The identified literature highlights the lack of consensus on diagnostic criteria for non-HCT SOS/VOD. Clinical criteria intended for diagnosing SOS/VOD in the HCT population are widely used for non-HCT SOS/VOD but there appears to be uncertainty whether these criteria are equally appropriate in both the HCT and non-HCT SOS/VOD settings. A notable distinction in diagnosing non-HCT SOS/VOD is the use of Rubbia-Brandt histology-based diagnostic criteria in patients with CRLM. Despite a higher incidence of non-HCT SOS, there were lower rates of severe disease and death from SOS/VOD in patients with CRLM. The higher rates of non-HCT SOS/VOD in patients with CRLM appear to be driven by the histology-based diagnosis of SOS/VOD performed in this population, where diagnosis does not take clinical symptoms into account.

In other disease settings, diagnosis tends to be based on clinical criteria which are predominantly focused on symptoms of ascites, hepatomegaly, and hyperbilirubinemia. The identified studies reported sparse data relating to the numbers of patients experiencing the SOS/VOD symptom triad but it is not certain if this is due to the absence of those symptoms in patients with non-HCT SOS/VOD or due to lack of reporting. Considering the variety of methods used to diagnose non-HCT SOS/VOD, it is possible that many patients experienced broadly similar signs and symptoms but that these data were not sought or reported. Furthermore, there is some evidence that patients whose signs and symptoms meet clinical diagnostic criteria for non-HCT SOS/VOD do not always demonstrate histological findings consistent with SOS/VOD and vice versa; therefore, it is possible to present with no symptoms and have histological SOS/VOD, and it is also possible to have clinical SOS/VOD but no evidence of histological SOS/VOD. Prior to 2016, a similar challenge existed for diagnosing SOS/VOD in the HCT setting, due to pre-dated criteria that lacked sensitivity and specificity. The EBMT criteria was therefore developed to address this need in HCT and has gained significant momentum, making an impact on diagnosis and management of SOS in the HCT setting [13].

Similar to the variation in diagnostic approaches, definitions of severe non-HCT SOS/VOD were diverse. Non-HCT SOS/VOD appears to carry a substantial risk of severe disease and death with estimates of the proportion of cases with severe disease ranging from 11 % to 70 %. Mortality rates ranged from 3 % to 37 %, which is lower than the mortality reported in severe cases of SOS/VOD following HCT [3], but since the data for deaths due to non-HCT SOS/VOD are based on a small number of studies with small sample sizes, there remains some uncertainty about the true mortality rate. Additionally, given the variety of definitions used in the literature to categorize severe disease, it is unclear how reliable the estimates of severe cases are.

Evidence related to the management of non-HCT SOS/VOD is relatively sparse. Off-label defibrotide was the most frequently used SOS/VOD-specific treatment and the reported high rates of recovery from non-HCT SOS/VOD suggest that it is effective, although with some risk of adverse events. Other studies of defibrotide in predominantly HCT-related SOS/VOD have reported day +100 survival rates of 43 % [124] to 50 % [125] and 65 % [124] to 69 % [125] in HCT patients with and without multiorgan failure [124], 58 % [126] to 61 % [127] in severe SOS/VOD cases post-HCT, 83 % in mild/moderate SOS/VOD post-HCT [127], and 71 % [128] in

predominantly HCT-related SOS/VOD. While the studies included in this systematic review do not provide granular detail to allow for meaningful analysis of defibrotide-treated patients with and without multiorgan failure, or with severe, moderate, and mild SOS/VOD, the evidence presented here indicates that defibrotide shows promise as an effective treatment for non-HCT SOS/VOD.

Since the included studies cover a period starting before defibrotide's FDA approval in 2016 for HCT-specific SOS/VOD, the fact that more than a fifth of the included studies reported using defibrotide for non-HCT SOS/VOD suggests that there is a strong demand for treatments for this condition. There is some limited evidence that managing non-HCT SOS/VOD by switching or pausing chemotherapy is effective in mild cases but data relating to the risk for cancer outcomes, especially relapse-free survival were not reported.

Limitations

While we included a large number of studies with data relevant to non-HCT SOS/VOD, no population-based studies were identified whose primary objective was to measure the incidence of non-HCT SOS/VOD. This is an important limitation of the epidemiological evidence on non-HCT SOS/VOD. Since much of the evidence presented here is based on studies with a focus other than non-HCT SOS/VOD, our findings are limited by the reporting of primary data in the included studies. For instance, it may be that HCT in earlier lines of therapy has some impact on the risk of developing non-HCT SOS/VOD but the included studies were lacking this level of detail. Additionally, SOS/VOD prophylaxis was outside the scope of this study and merits further investigation in future studies on SOS/VOD in the non-HCT setting.

Notwithstanding our comprehensive searches of bibliographic databases and grey literature sources, relevant studies may have been missed where SOS/VOD was not mentioned in the title or abstract. Furthermore, the identified studies include predominantly European and North American populations therefore it is uncertain the extent to which these findings can be generalized to other populations.

5. Conclusions

Non-HCT SOS/VOD occurs in diverse disease conditions, therefore guidelines on diagnosis and management of non-HCT SOS/VOD are needed to be able to optimally identify and treat the condition in clinical practice. Large population-based studies would help to identify which patient groups are most at risk of developing non-HCT SOS/VOD and which patients are most severely affected. Greater awareness by clinicians of the existence of SOS/VOD outside the HCT setting is crucial; more recognition of the condition will help patients receive appropriate care and treatment, thereby saving lives. Currently, the only treatment for non-HCT SOS/VOD that has approval anywhere in the world is defibrotide, which was approved in Japan in 2019 for SOS/VOD regardless of disease severity or HCT. In other countries, defibrotide is approved only in the HCT setting for severe disease or SOS/VOD with renal or pulmonary dysfunction, but the evidence presented here suggests it is also used for non-HCT SOS/VOD. Further evidence from clinical trials and real-world studies is needed to investigate the effectiveness of defibrotide and other treatments for non-HCT SOS/VOD.

Data availability statement

All of the references used in this manuscript were published in the public domain.

CRediT authorship contribution statement

Lin Fan: Writing – review & editing, Methodology, Formal analysis. **Fiona Stewart:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Kimberly Ruiz:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Darsh Devani:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Nicole Fusco:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Malia Gill:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Vian Amber:** Writing – review & editing, Formal analysis. **Wayne Su:** Writing – review & editing, Formal analysis. **Alexandra Gangi:** Writing – review & editing, Formal analysis. **Raj Hanvesakul:** Writing – review & editing, Methodology, Formal analysis.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: **Lin Fan** is an employee of and holds stock ownership and/or stock options in Jazz Pharmaceuticals. **Fiona Stewart** is employed by Cencora, which received funds from Jazz Pharmaceuticals to support this research. **Kimberly Ruiz** is employed by Cencora, which received funds from Jazz Pharmaceuticals to support this research. **Darsh Devani** was employed by Cencora, which received funds from Jazz Pharmaceuticals to support this research, during the time the study was conducted. **Nicole Fusco** is employed by Cencora, which received funds from Jazz Pharmaceuticals to support this research. **Malia Gill** is employed by Cencora, which received funds from Jazz Pharmaceuticals to support this research. **Vian Amber** is an employee of and holds stock ownership and/or stock options in

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e36883.

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