Retrospective analysis of veno-occlusive disease/sinusoidal obstruction syndrome in paediatric patients undergoing hematopoietic cell transplantation -a multicentre study

Dristhi Ragoonanan,[a,*] Hisham Abdel-Azim,[b] Aditya Sharma,[c] Saleh Bhar,[d] Jennifer McArthur,[e,l] Renee Madden,[f] April Rahrig,[g] Rajinder Bajwa,[h] Jian Wang,[i] Victoria Sun,[i] Mariah Wright,[h] Rebekah Lassiter,[e,l] Basirat Shoberu,[a] Jitesh Kawedia,[j] Sajad Jawad Khazal,[b] and Kris Michael Mahadeo,[k] Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network

[a]Department of Pediatrics, Stem Cell Transplantation and Cellular Therapy, University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA
[b]Division of Transplant and Cell Therapy, Loma Linda University Cancer Center, Loma Linda, CA 92354, USA
[c]Pediatric Blood and Marrow Transplant, Children's Hospital Los Angeles, University of Southern California Keck School of Medicine, Los Angeles, CA, USA
[d]Texas Children's Hospital, Baylor College of Medicine, Houston, TX 77030, USA
[e]Division of Critical Care, St Jude Children's Research Hospital, Memphis, TN, USA
[f]Department of Bone Marrow Transplantation and Cellular Therapy, St Jude Children's Research Hospital, Memphis, TN, USA
[g]Department of Pediatrics, Division of Stem Cell Transplantation and Cellular Therapy, Riley Hospital for Children, Indianapolis, IN, USA
[h]Division of Hematology/Oncology/BMT, Nationwide Children's Hospital, Columbus, OH, USA
[i]Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston TX 77030, USA
[j]Department of Pharmacy Clinical Programs, The University of Texas MD Anderson Cancer Center, Houston, TX, USA
[k]Pediatric Transplant and Cellular Therapy, Duke University, Durham, NC, USA
[l]Division of Critical Care Medicine, University of Tennessee Health Sciences Center, Memphis, TN, USA

The Lancet Regional Health - Americas 2024;33: 100728

Published Online xxx
https://doi.org/10.1016/j.lana.2024.100728

Summary

Background Sinusoidal obstruction syndrome is a potentially fatal complication following hematopoietic cell transplantation, high-intensity chemotherapies and increasingly seen with calicheamicin based leukemia therapies. Paediatric specific European Society for Blood and Marrow Transplantation (pEBMT) diagnostic criteria have demonstrated benefit in single center studies compared to historic criteria. Yet, the extent to which they have been universally implemented remains unclear.

Methods We conducted a retrospective multi-centre study to examine the potential impact of the Baltimore, modified Seattle and pEBMT criteria on the incidence, severity, and outcomes of sinusoidal obstruction syndrome among paediatric hematopoietic cell transplantation patients.

Findings The incidence of sinusoidal obstruction syndrome in this cohort (n = 488) was higher by pEBMT (21.5%) vs historic modified Seattle (15.6%) and Baltimore (7.0%) criteria ($p < 0.001$). Application of pEBMT criteria identified 44 patients who were not previously diagnosed with sinusoidal obstruction syndrome. Overall, 70.5% of all patients diagnosed with sinusoidal obstruction syndrome ultimately developed very severe disease and almost half of diagnosed patients required critical care support. Overall survival was significantly lower in patients who were diagnosed with sinusoidal obstruction syndrome vs those who were not.

Interpretation Taken together, pEBMT criteria may be a sensitive method for prompter diagnosis of patients who subsequently develop severe/very severe sinusoidal obstruction syndrome. To our knowledge, this is the first multicentre study in the United States (US) to demonstrate that pEBMT guidelines are associated with earlier detection of sinusoidal obstruction syndrome. Since early initiation of definitive treatment for sinusoidal obstruction syndrome has been associated with improved survival in paediatric patients and implementation of pEBMT criteria appears feasible in the US, universal adoption should facilitate prompter diagnosis and lead to improved outcomes of children with sinusoidal obstruction syndrome.

Funding None.

*Corresponding author. Department of Pediatrics, Stem Cell Transplantation and Cellular Therapy, University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030, USA.
E-mail address: DRagoonanan@mdanderson.org (D. Ragoonanan).

Keywords: Veno-occlusive disease; Hematopoietic cell transplantation; Paediatrics; Sinusoidal obstruction syndrome

Research in context

Evidence before this study

Sinusoidal obstruction syndrome or veno-occlusive disease is a life-threatening complication following hematopoietic cell transplantation. The diagnosis of sinusoidal obstruction syndrome is based on a combination of clinical, laboratory and imaging findings which vary based on the diagnostic criteria used, leading to variability in the time to diagnosis and reported incidence of sinusoidal obstruction syndrome. We searched PubMed and Google Scholar for longitudinal studies reporting the incidence and outcome of sinusoidal obstruction syndrome/veno-occlusive disease among paediatric, adolescent, and young adult patients between 1987 and 2023. We used the following search terms: "veno-occlusive disease", "sinusoidal obstruction syndrome", "Baltimore criteria" "Seattle criteria" "Modified Seattle criteria" "Pediatric" "Adolescent and Young Adult" and "pediatric European Society for Blood and Marrow Transplantation (pEBMT) criteria." Retrospective studies in Europe and Asia and a single centre US study have suggested that the pEBMT diagnostic criteria are associated with improved time to diagnosis. Yet, the extent to which pEBMT criteria have been adopted in the US and its potential impact have not been well described.

Added value of this study

In the first multi-centre study to assess its impact in the USA, pEBMT criteria were associated with an earlier time to diagnosis of sinusoidal obstruction syndrome by 2.5-3 days compared to historic criteria of which the majority were severe/very severe grade. Factors associated with increased risk of sinusoidal obstruction syndrome included prior exposure to calicheamicin-conjugated antibodies, busulfan as part of the conditioning regimen and post hematopoietic cell transplantation cyclophosphamide. Busulfan interval dosing may impact the incidence of sinusoidal obstruction syndrome. This highlights an important opportunity for earlier therapeutic intervention for patients with sinusoidal obstruction syndrome.

Implications of all the available evidence

Our findings support emerging evidence that the pEBMT criteria are associated with improved recognition of sinusoidal obstruction syndrome and support more universal implementation of the pEBMT criteria. This may lead to not only earlier diagnosis of sinusoidal obstruction syndrome, but also allowing earlier intervention with definitive treatment, which has been associated with superior patient outcomes.

Introduction

While hematopoietic cell transplantation is a potentially curative therapy for children with some high-risk malignancies and non-malignant genetic disorders, veno-occlusive disease also known as sinusoidal obstruction syndrome remains a potentially fatal complication.[1] Sinusoidal obstruction syndrome remains a clinical diagnosis as confirmation by the historical gold standard of a liver biopsy is often not feasible or recommended, particularly in children, due to its invasive nature and increased risk of morbidity and mortality.[2] As such the incidence of sinusoidal obstruction syndrome is variable depending on the diagnostic criteria used and regardless of criteria used, children are disproportionately affected (20–60% vs 10% in adults).[1,3–6]

In an effort to improve management of sinusoidal obstruction syndrome, the European Society of Blood and Marrow Transplantation (EBMT) introduced new criteria in 2017 for diagnosis and severity grading of sinusoidal obstruction syndrome in paediatric patients.[5] In 2019, the Paediatric Diseases Working Party of the EBMT, the Hematopoietic Cell Transplantation Cancer Immunotherapy Subgroup of the Pediatric Acute Lung Injury and Sepsis Investigators Network and the Supportive Care Committee of the Pediatric Transplantation and Cellular Therapy Consortium adopted the paediatric EBMT (pEBMT) criteria and severity grading by international expert consensus and provided guidance for universal implementation (Supplementary Table S1).[1]

While patients with milder forms of sinusoidal obstruction syndrome may self-resolve with supportive care, 30–40% of patients develop severe/very severe sinusoidal obstruction syndrome with multiorgan dysfunction syndrome and these patients may have a dismal prognosis with mortality of up to 80%.[4,7] Earlier recognition of patients with sinusoidal obstruction syndrome should allow timely initiation of definitive treatment. Among paediatric patients with sinusoidal obstruction syndrome who started defibrotide within 2 days of diagnosis, improved hematopoietic cell transplantation survival at 100 days has been observed.[8]

Studies in Europe and Asia have sought to characterize the application of pEBMT international expert consensus sinusoidal obstruction syndrome criteria and suggest that its application is associated with earlier time to diagnosis.[9,10] A single centre study in the US found that retrospective application of the pEBMT

diagnostic criteria was associated with a higher detection of sinusoidal obstruction syndrome and could have triggered earlier initiation of definitive treatment by 3 days.[6] Among that cohort, 6% of sinusoidal obstruction syndrome cases were retrospectively identified by pEBMT criteria, as they were previously undiagnosed based on the limitations of the historic criteria. Of these previously undiagnosed patients, 42.8% died from multiorgan dysfunction syndrome. Emerging data suggests that application of pEBMT criteria may be a sensitive and specific tool, yet the degree to which the pEBMT criteria have been implemented and its potential impact in the United States (US) remains unclear. With a rapidly expanding therapeutic armamentarium for leukemia (with calicheamicin based therapies) and changing risk profile (during pre and post hematopoietic cell transplantation phases), it is important that universal criteria are used to standardly assess for sinusoidal obstruction syndrome. The pEBMT international expert consensus statement provided guidance for universal implementation, with practical implications particularly for providers in the US.[1] To our knowledge, this is the first paediatric multi-centre study to assess the impact of the pEBMT diagnostic and severity criteria on the incidence, severity and outcomes of sinusoidal obstruction syndrome among paediatric hematopoietic cell transplantation patients in the US in comparison to the modified Seattle and pEBMT criteria.

Methods

This study was reviewed by the PALISI Network Hematopoietic Cellular Therapy-Cancer Immunotherapy Subgroup and approved by the institutional review board at each participating PALISI network site (n = 6); MD Anderson Children's Cancer Center, Children's Hospital Los Angeles, Nationwide Children's Hospital, Riley Hospital for Children, St. Jude Children's Research Hospital and Texas Children's Hospital. Consecutive patients who underwent hematopoietic cell transplantation prior to December 1st, 2019 (with a minimum of 50 patients per site) were included. Patients who were 25 years and younger who were diagnosed and treated for sinusoidal obstruction syndrome were identified via retrospective review of the electronic medical records. The modified Seattle, Baltimore, and pEBMT diagnostic criteria were then all retrospectively applied to these patients and the time to diagnosis of sinusoidal obstruction syndrome was established and compared.[4,11] All three criteria were then also retrospectively applied to remaining subjects during the same time frame at each centre, to identify any hematopoietic cell transplantation patients who may not have been previously diagnosed with sinusoidal obstruction syndrome based upon the diagnostic criteria applied at that time. Consensus pEBMT severity grading was then applied retrospectively to all patients who were identified as having sinusoidal obstruction syndrome (with the exception of delirium screening via the Cornell Assessment of Pediatric Delirium, which was not consistently available).

Data extracted from the electronic medical record included, demographics, primary diagnosis, transplant type, prior history of chemotherapy and radiation therapy, conditioning regimen, previously published risk factors for sinusoidal obstruction syndrome and clinical variables, such as the presence of weight gain, hepatomegaly, ascites, bilirubin levels and transfusion-refractory thrombocytopenia as previously defined[1]. For those meeting sinusoidal obstruction syndrome criteria additional information was collected retrospectively such as coagulopathy, need for respiratory support, continuous renal replacement therapy, paracentesis or thoracentesis, encephalopathy, and, development of multiorgan dysfunction syndrome. Prophylaxis and treatment strategies for sinusoidal obstruction syndrome were also reviewed. STROBE guidelines were followed for this study (Supplementary Table S2).

Role of the funding source

This study was not funded.

Statistical analysis

Continuous variables were summarized using median and range, and categorical variables were summarized using frequency and proportion. Wilcoxon rank-sum test and Fisher's exact test were used to compare the continuous and categorical variables, respectively. Linear mixed regression modelling was used to compare the time to sinusoidal obstruction syndrome using different criteria accounting for the correlation within each patient. The incidence of sinusoidal obstruction syndrome using different criteria was compared using the Cochran's Q test. Logistic regression model was used for analysis of binary outcomes (e.g., sinusoidal obstruction syndrome, multiorgan dysfunction syndrome etc.). Variables with a $p \leq 0.05$ from the univariate analysis, using logistic regression, were included in the multivariable regression models. Bayesian generalized linear model with logit link was used for the multivariable analysis to obtain stable regression coefficients.[12] Multicollinearity was assessed using variance inflation factor (VIF) and variables with high collinearity were removed (i.e., VIF > 5). Accelerated failure time model was used for analysis of overall survival associated with sinusoidal obstruction syndrome and, multiorgan dysfunction syndrome. Different functional forms for the accelerated failure time model were investigated and the best fitted distribution (Weibull) was selected using Akaike information criterion. Overall survival curves for different groups (e.g., patients with and without sinusoidal obstruction

syndrome post-hematopoietic cell transplantation) were estimated using the Kaplan–Meier method. Patients lost to follow up or still alive at the end of observation period were censored. Participating centre was included as a covariate in the regression models (e.g., linear mixed model, logistic, accelerated failure time). Two-sided $p < 0.05$ was considered significant. All analyses were performed in R 3.6.1.[13]

Results

A total of 488 consecutive patients who underwent hematopoietic cell transplantation, during the study period were included from six participating US PALISI Network centers. The median age of patients at time of hematopoietic cell transplantation was 12 years (0.2–25 years) and the demographics and treatment characteristics are summarized in Table 1.

Sixty-one patients were diagnosed with sinusoidal obstruction syndrome during their hematopoietic cell transplantation hospital admission. At that time, the majority of patients were diagnosed using the modified Seattle criteria (n = 45/61; 73.8%), 15 (n = 15/61; 24.6%) patients were diagnosed using the pEBMT criteria and 1 patient (n = 1/61; 1.6%) diagnosed using the Baltimore criteria. When all patients in the cohort were reviewed and the pEBMT criteria was retrospectively applied, an additional 44 patients met criteria for sinusoidal obstruction syndrome, for a total of 105 patients identified with sinusoidal obstruction syndrome in this study (Fig. 1). Among the 44 patients diagnosed with sinusoidal obstruction syndrome retrospectively only, application of pEBMT criteria may have impacted time to diagnosis by as much as 2.5 days. The incidence of multiorgan dysfunction syndrome in this retrospective cohort was 15.9% (n = 7/44), 100 day survival was 88.6% (n = 39/44) and overall survival was 72.7% (n = 32/44).

The overall incidence of sinusoidal obstruction syndrome in this study diagnosed retrospectively was 21.5% (n = 105/488) by the pEBMT criteria, 15.6% (n = 76/488) by the modified Seattle criteria and 7.0% (n = 34/488) using the Baltimore criteria respectively ($p < 0.001$). The pEBMT criteria was associated with the earliest time to diagnosis at a median of 12 (0–53; mean 12.9) days post hematopoietic cell transplantation vs 15 (2–62; mean 16.9) days with the modified Seattle criteria and 14.5 (7–20; mean 13.7) days with the Baltimore criteria respectively ($p < 0.001$, linear mixed model). Among the 76 patients that satisfied both pEBMT and modified Seattle criteria, the median time to diagnosis was 13 (2–53; mean 13.6) days vs 15 (2–62; mean 16.9) days, respectively ($p < 0.001$; linear mixed model). For the 34 patients who satisfied pEBMT and Baltimore criteria, the median time to diagnosis was 10.5 (3–19 mean 10.7) days and 14.5 (7–20; mean 13.7) days post-hematopoietic cell transplantation, respectively ($p < 0.001$; linear mixed model). Fifteen patients (n = 15/105; 14.2%) met criteria for late onset sinusoidal obstruction syndrome (beyond 21 days post hematopoietic cell transplantation) either by modified Seattle or after the pEBMT criteria was applied.

Of the 105 patients with sinusoidal obstruction syndrome by pEBMT criteria, 77 (n = 77/105; 73.3%) patients were anicteric at the time of diagnosis and 42 (n = 42/77; 54.5%) of these, subsequently developed hyperbilirubinemia at a median of 3 (1–26)days later. Thus, 33.3% (n = 35/105) of all patients with sinusoidal obstruction syndrome remained anicteric throughout. As shown in Fig. 2, for the majority of patients, unexplained weight gain on 3 consecutive days of >5% above baseline (n = 84/105; 80.0%) and refractory thrombocytopenia (n = 74/105; 70.5%) were the most common presenting symptoms.

Sub-populations identified with ≥20% incidence for sinusoidal obstruction syndrome are highlighted in Table 2. As there is no evidence to suggest sex significantly predicts the development of sinusoidal obstruction syndrome or has modification effect on the development of sinusoidal obstruction syndrome, stratified analysis based on sex were not performed. Prior exposure to blinatumomab ($p = 0.02$), inotuzumab ($p = 0.01$) and gemtuzumab ($p = 0.01$) were associated with higher incidence of sinusoidal obstruction syndrome using logistic regression model. Of the 22 patients who received prior inotuzumab, 10 (n = 10/22; 45.5%) developed sinusoidal obstruction syndrome. The interval between the last dose of inotuzumab and transplant in patients with sinusoidal obstruction syndrome occurred at a median of 42.5 (26–691) vs 60 (30–169) days in patients without sinusoidal obstruction syndrome, however this difference was not statistically significant. Of note just over half of all the patients who received blinatumomab in this study also received inotuzumab which may partly be responsible for the increased incidence seen in this subpopulation. For the 17 patients with prior exposure to gemtuzumab, 8 developed sinusoidal obstruction syndrome (n = 8/17; 47.1%). We also observed a shorter interval from last dose of gemtuzumab to hematopoietic cell transplantation among patients with sinusoidal obstruction syndrome with a median of 57.5 (32–1153) days vs those without at a median of 73 (33–407) days which was also not statistically significant. On multivariable analysis only, time to platelet and neutrophil engraftment were significant. Patients who developed sinusoidal obstruction syndrome had delayed platelet engraftment a median of 26 (10–115) days vs 18 (8–121) days ($p < 0.001$; logistic regression) in patients who did not develop sinusoidal obstruction syndrome. Similarly, patients who developed sinusoidal obstruction syndrome also had delayed neutrophil engraftment at a median of 14 (8–41) days vs 12 (5–54) days ($p = 0.02$; logistic regression).

One third (n = 173/488; 35.5%) of patients received busulfan as part of their conditioning regimen and a

Characteristic	Patients without SOS (n = 383)	Patients with SOS (n = 105)	All Patients (n = 488)
Sex			
Female	158 (41.3%)	41 (39.0%)	199 (40.8%)
Male	225 (58.7%)	64 (61.0%)	289 (59.2%)
Median age of transplant (years)	12 (0.2–25)	10 (0.4–25)	12 (0.2–25)
Pre- HCT Ferritin > 955 ng/mL			
No	149 (38.9%)	24 (22.9%)	173 (35.5%)
Yes	122 (31.8%)	50 (47.6%)	172 (35.2%)
NA	112 (29.3%)	31 (29.5)	143 (29.3%)
Prior total bilirubin > 2 mg/dL pre HCT			
No	344 (89.8%)	101 (96.2%)	445 (91.2%)
Yes	10 (2.6%)	2 (1.9%)	12 (2.5%)
NA	29 (7.6%)	2 (1.9%)	31 (6.3%)
Pre-transplant diagnosis			
Leukemia/MDS	157 (41.1%)	62 (59.0%)	219 (44.9%)
Lymphoma	61 (15.9%)	8 (7.6%)	69 (14.1%)
Solid tumors	107 (27.9%)	20 (19.1%)	127 (26.0%)
Non-malignant diseases	30 (7.8%)	4 (3.8%)	34 (7.0%)
Immunodeficiency	13 (3.4%)	5 (4.8%)	18 (3.7%)
Other	15 (3.9%)	6 (5.7%)	21 (4.3%)
Donor type			
Autologous	159 (41.5%)	23 (21.9%)	182 (37.3%)
MRD	63 (16.5%)	16 (15.2%)	79 (16.2%)
MUD	95 (24.8%)	44 (41.9%)	139 (28.5%)
MMRD	66 (17.2%)	22 (21.0%)	88 (18.0%)
Stem cell source			
Peripheral blood	218 (56.9%)	45 (42.8%)	263 (53.9%)
Bone marrow	126 (32.9%)	47 (44.8%)	173 (35.5%)
BM + Cord Blood	0 (0%)	1 (1.0)	1 (0.2%)
Cord blood	37 (9.7%)	12 (11.4%)	49 (10.0%)
NA	2 (0.5%)	0 (0.0%)	2 (0.4%)
Conditioning regimen			
MAC	300 (78.4%)	86 (81.9%)	386 (79.1%)
RIC	59 (15.4%)	14 (13.3%)	73 (15.0%)
NMA	22 (5.7%)	5 (4.8%)	27 (5.5%)
None	2 (0.5%)	0 (0.0%)	2 (0.4%)
Busulfan conditioning regimen			
No	253 (66.1%)	62 (59.0%)	315 (64.5%)
Yes	130 (33.9%) Median AUC 16,000 μM min	43 (41.0%) Median AUC 18,912 μM min	173 (35.5%)
Busulfan frequency			
Q6 h	44 (11.5%)	24 (22.9%)	68 (13.9%)
Q24 h	86 (22.5%)	19 (18.1%)	105 (21.5%)
Previous exposure to Inotuzumab			
No	371 (96.9%)	95 (90.5%)	466 (95.5%)
Yes	12 (3.1%)	10 (9.5%)	22 (4.5%)
Previous exposure to Gemtuzumab			
No	374 (97.7%)	97 (92.4%)	471 (96.5%)
Yes	9 (2.3%)	8 (7.6%)	17 (3.5%)
No of Prior HCT			
0	311 (81.2%)	80 (76.2%)	391 (80.1%)
1	53 (13.8%)	21 (20.0%)	74 (15.2%)
2	19 (5.0%)	4 (3.8%)	23 (4.7%)

(Table 1 continues on next page)

Characteristic	Patients without SOS (n = 383)	Patients with SOS (n = 105)	All Patients (n = 488)
(Continued from previous page)			
SOS Prophylaxis			
Urso-deoxycholic acid			
No	96 (25.1%)	9 (8.6%)	105 (21.5%)
Yes	287 (74.9%)	96 (91.4%)	383 (78.5%)
Defibrotide			
No	376 (98.2%)	97 (92.4%)	473 (96.9%)
Yes	7 (1.8%)	8 (7.6%)	15 (3.1%)

SOS: sinusoidal obstruction syndrome, NA: not available, ng: nanogram, mL: milliliter, dl: deciliter, MRD: matched related donor, MUD: matched unrelated donor, MMRD: mismatched related donor, MAC: myeloablative conditioning, RIC: reduced intensity conditioning, NMA: nonmyeloablative, TBI: total body irradiation, µM.min:Micrometre per minute, HCT: hematopoietic cell transplant.

Table 1: **Baseline and treatment characteristics for all patients without and with sinusoidal obstruction syndrome.**

quarter (n = 43/173; 24.9%) of these patients developed sinusoidal obstruction syndrome. On univariate analysis, exposure to busulfan with 6-h interval dosing was associated with a higher incidence of sinusoidal obstruction syndrome compared to those receiving busulfan with 24-h interval dosing (n = 24/68; 35.3% vs n = 19/105; 18.1%) respectively (p = 0.001; logistic regression). Overall survival and 100-day survival were not statistically different between patients receiving busulfan q6 hours vs daily. While patients who developed sinusoidal obstruction syndrome had a higher median exposure of busulfan at 18,912 µM x min vs 16,000 µM x min in patients who did not develop sinusoidal obstruction syndrome, this was not statistically different (p = 0.20; logistic regression). Similarly, patients receiving 6 h interval dosing did have a higher median exposure of busulfan at 19,216 µM x min vs 16,000 µM in the 24-h interval dosing cohort, however this was also not statistically significant (p = 0.12).

Upon retrospective application of pEBMT severity grading, more than half of patients with sinusoidal obstruction syndrome had either severe (n = 25/105; 23.8%) or very severe (n = 30/105; 28.6%) sinusoidal obstruction syndrome at the initial time of diagnosis. Additionally, 44 patients had progressive symptoms and ultimately very severe sinusoidal obstruction syndrome was seen in 74 (n = 74/105; 70.5%) patients (Fig. 3). The median time to progression from mild to very severe disease was 7 (1–22) days, moderate to very severe disease 4 (1–50) days and severe to very severe 6 (2–54) days, respectively. Forty-six patients (n = 46/105; 43.8%) were admitted to the intensive care unit. Indications for

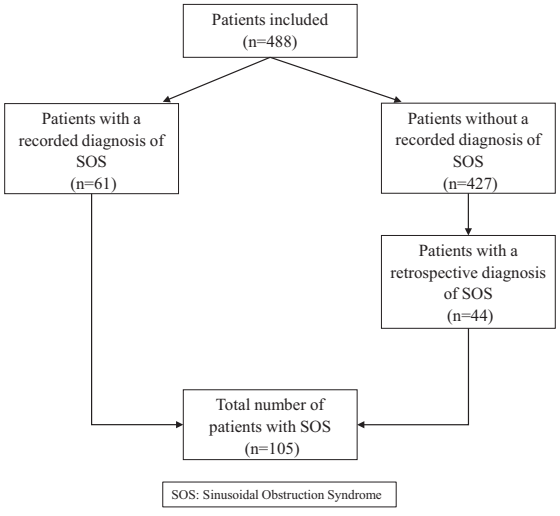

Fig. 1: Identification of patients with sinusoidal obstruction syndrome. 488 patients identified as having received hematopoietic cell therapy during the eligibility period. Among 488 patients, 61 patients were diagnosed with sinusoidal obstruction syndrome by the pEBMT, historic Baltimore and/or the modified Seattle criteria. Retrospective application of the pEBMT, modified Seattle and, Baltimore diagnostic criteria to patients not previously diagnosed with sinusoidal obstruction syndrome identified 44 additional patients, bringing the total number of patients meeting the diagnostic criteria of sinusoidal obstruction syndrome to 105 amongst 488 patients.

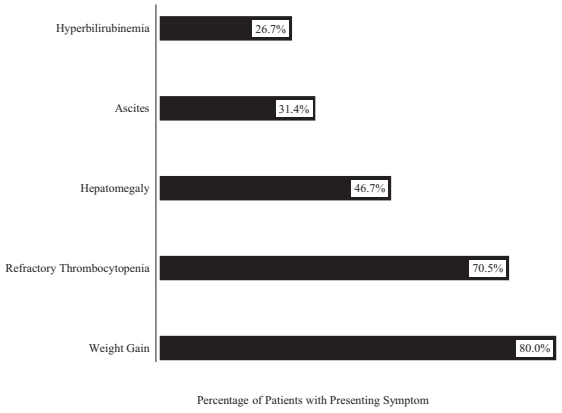

Fig. 2: pEBMT criteria met at time of diagnosis of sinusoidal obstruction syndrome. The most common criteria met at the time of diagnosis of sinusoidal obstruction syndrome by the pEBMT criteria was weight gain, followed by refractory thrombocytopenia, hepatomegaly, ascites and hyperbilirubinemia.

Risk factor	Total number of patients	Patients without SOS	Patients with SOS	p value
Age < 1 year	17	13 (76.5%)	4 (23.5%)	0.77
Thalassemia	3	2 (66.7%)	1 (33.3%)	0.52
MDS/JMML	10	4 (40.0%)	6 (60.0%)	0.03
NB	55	42 (76.4%)	13 (23.6%)	0.73
HLH	4	3 (75.0%)	1 (25.0%)	1.0
CML	4	1 (25.0%)	3 (75.0%)	0.03
AML	83	59 (71.1%)	24 (28.9%)	0.08
Wilms tumor	4	3 (75.0%)	1 (25.0%)	1.0
Immunodeficiency	18	13 (72.2%)	5 (27.8%)	0.56
Inherited bone marrow failure syndrome	8	5 (62.5%)	3 (37.5%)	0.38
Pre transplant ferritin > 955 ng/mL	172	122 (70.9%)	50 (29.1%)	<0.0001
MAC with Busulfan	173	130 (75.1%)	43 (24.9%)	0.08
Blinatumomab	34	21 (61.8%)	13 (38.2%)	0.02
Inotuzumab	22	12 (54.5%)	10 (45.5%)	0.01
Gemtuzumab	17	9 (52.9%)	8 (47.1%)	0.01

SOS: sinusoidal obstruction syndrome, MDS: myelodysplastic syndrome, JMML: juvenile myelomonocytic leukemia, NB: neuroblastoma, HLH: hemophagocytic lymphohistiocytosis, CML: chronic myelogenous leukemia, AML: acute myeloid leukemia ng: nanogram, mL: milliliter, MAC: myeloablative conditioning.

Table 2: **Patient populations at risk for sinusoidal obstruction syndrome.**

intensive care unit admission were; need for mechanical ventilation (n = 39/46; 84.8%) and/or continuous renal replacement therapy (n = 30/46; 65.2%) and/or pressor support (n = 25/46; 54.3%). In total, 39 patients required (n = 39/105; 37.1%) required replacement of coagulation factors and 1 (n = 1/105; 1.0%) underwent liver transplantation.

Three hundred and eighty-three (n = 383/488; 78.5%) patients received ursodiol for sinusoidal obstruction syndrome prophylaxis. Ninety six (n = 96/383; 25.1%) of these developed sinusoidal obstruction syndrome. In this cohort, 15 patients received defibrotide as prophylaxis, 8 (n = 8/15; 53.3%) of which

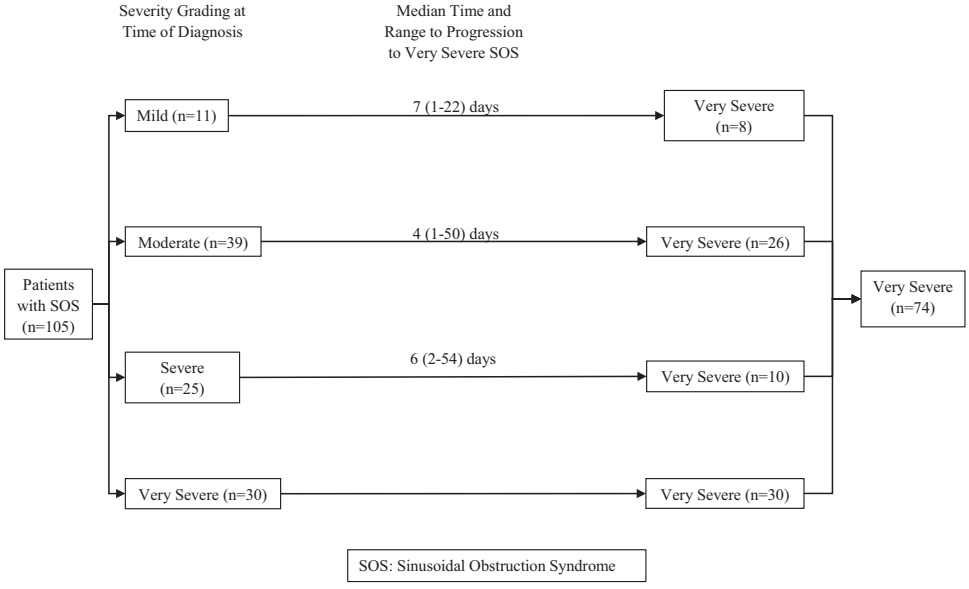

Fig. 3: Patient outcome based on severity grade of sinusoidal obstruction syndrome. All 105 patients diagnosed with sinusoidal obstruction syndrome were classified using the pEBMT severity grading. At the time of diagnosis, 11, 39, 25, and 30 patients were graded as having mild, moderate, severe, and very severe disease, respectively. Of the 11 patients with mild disease, 8 progressed to have very severe disease at a median of 7 (1–22) days. For the 39 patients with moderate disease, 26 progressed to have very severe disease at a median of 4 (1–50) days. Twenty-five patients had severe disease, of which 10 progressed to very severe disease at a median of 6 (2–54) days. Thirty patients were diagnosed with very severe disease at initial diagnosis. A total of 74 out of 105 patients eventually developed very severe sinusoidal obstruction syndrome.

developed sinusoidal obstruction syndrome; moderate (n = 4), severe (n = 1) and very severe disease (n = 3). Patient indications for defibrotide prophylaxis included a combination of neuroblastoma diagnosis (n = 3), prior use of inotuzumab (n = 4), prior use of gemtuzumab (n = 3), age less than 1 year (n = 2), second or greater allogeneic hematopoietic cell transplantation (n = 3), pre-existing liver dysfunction (n = 9) and hyperferritinemia (n = 9). Forty-seven (n = 47/105; 44.8%) patients with sinusoidal obstruction syndrome received treatment with defibrotide, with a median time to initiation of defibrotide of 1 (0–17) days after the diagnosis was made.

Overall survival was significantly better in patients who never developed sinusoidal obstruction syndrome (Fig. 4). For patients with sinusoidal obstruction syndrome, development of multiorgan dysfunction syndrome ($p < 0.0001$; accelerated failure time model) was associated with inferior OS in patients (Fig. 5). Patients were more likely to have multiorgan dysfunction syndrome if they developed sinusoidal obstruction syndrome vs patients who did not have sinusoidal obstruction syndrome; 35.2% (n = 37/105) vs 3.4% (n = 13/383) ($p < 0.0001$). Of the 47 patients treated with defibrotide, 33 (n = 33/47; 70.2%) had complete resolution of sinusoidal obstructione syndrome. Sinusoidal obstruction syndrome resolved at a median of 23 (6–54) days after fulfilling pEBMT criteria. Of the 14 patients who did not have resolution of sinusoidal obstruction syndrome, 13 (n = 13/14; 92.9%) died from multiorgan dysfunction syndrome secondary to sinusoidal obstruction syndrome, and 1 patient (n = 1/14; 7.1%) died from infection. Excluding the eight patients who received defibrotide prophylactically and developed sinusoidal obstruction syndrome, the 100-day survival was 52.6% (n = 10/19) for patients in whom defibrotide was initiated greater than 2 days post diagnosis using the pEBMT criteria and 75% (n = 15/20) in those where defibrotide was initiated within 2 days of diagnosis (p = 0.12). Similarly, patients who started defibrotide within 3 days or less of diagnosis had improved 100-day survival of 77.3% (n = 17/22) vs 41.1% (n = 8/17) (p = 0.051). We did not find a statistical difference in those treated/not treated with defibrotide, but this was outside the scope of this study and we may not have been adequately powered to detect a difference.

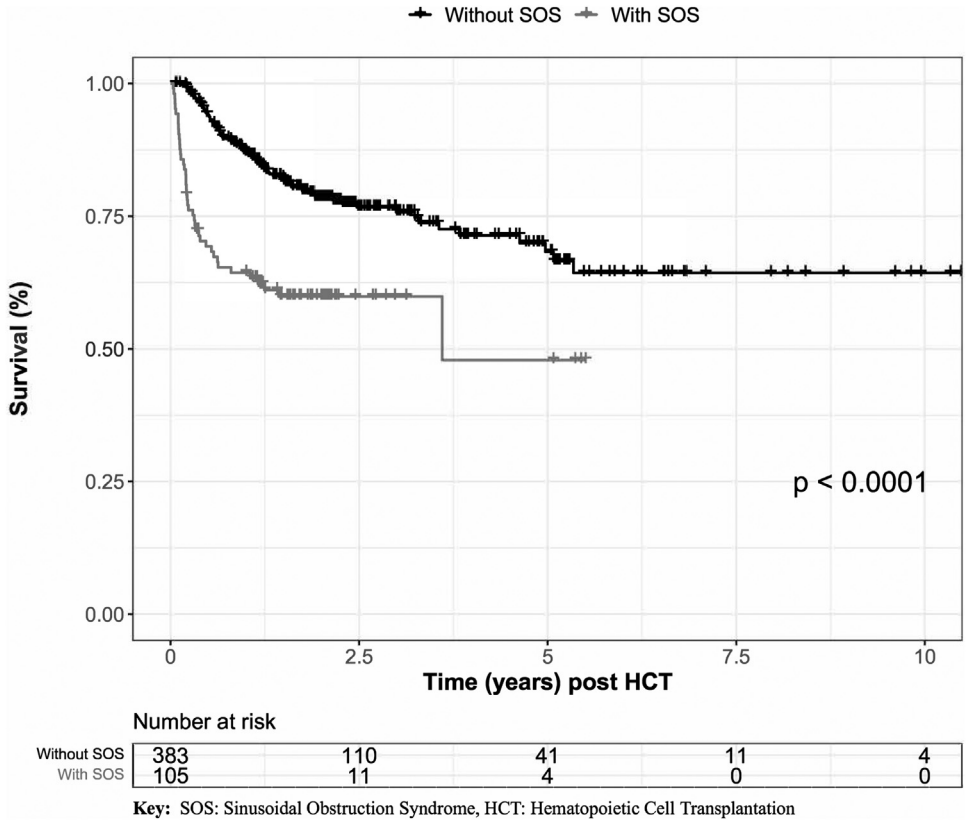

Fig. 4: Overall survival of patients with and without sinusoidal obstruction syndrome post-hematopoietic cell transplantation. Survival was compared amongst 488 patients without sinusoidal obstruction syndrome and patients with sinusoidal obstruction syndrome. Overall survival was inferior in patients who had sinusoidal obstruction syndrome vs those who did not have sinusoidal obstruction syndrome.

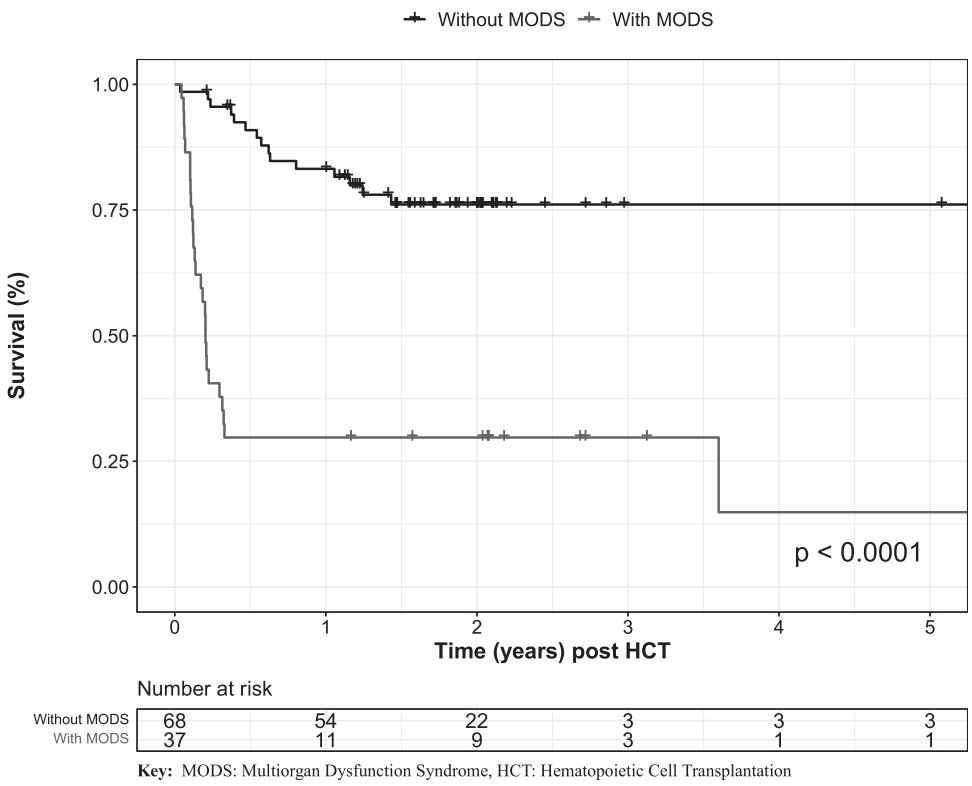

Fig. 5: Overall survival of sinusoidal obstruction syndrome patients with and without multiorgan dysfunction syndrome post-hematopoietic cell transplantation. Survival was compared amongst 105 patients with sinusoidal obstruction syndrome who did and did not develop multiorgan dysfunction syndrome. Overall survival was inferior in sinusoidal obstruction syndrome patients who developed multiorgan dysfunction syndrome vs those who did not have multiorgan dysfunction syndrome.

Discussion

In the recently published open-label, randomized, multicentre, phase 3 trial, defibrotide did not show a benefit in the prophylaxis of sinusoidal obstruction syndrome.[14] Yet, methodological flaws of this study design have limited its generalizability, in particular for paediatric patients.[15] Importantly, variability in adjudication of sinusoidal obstruction syndrome between treating physicians and the study adjudication panel occurred in 26% of cases.[14] Additionally, Corbacioglu et al. previously reported a decrease in the incidence of sinusoidal obstruction syndrome with defibrotide prophylaxis, with an incidence of 12% vs 20% in patients who did and did not receive defibrotide respectively.[16]

Notably, high variability in the diagnosis and grading of sinusoidal obstruction syndrome has been long recognized as a problematic and potentially confounding factor in understanding hematopoietic cell transplantation outcomes among varying studies.[17] In an effort to create more specific diagnostic criteria that account for the features seen in paediatric sinusoidal obstruction syndrome and improve its recognition, the expert consensus pEBMT criteria were introduced. Importantly, these criteria recognize: (i) patients who present with sinusoidal obstruction syndrome beyond 21 days after hematopoietic cell transplantation which has been reported in 15–20% of paediatric cases (ii) individual patients' pre-existing conditions including hyperbilirubinemia (bilirubin >34 μmol/L or >2 mg/dL), presence of hepatomegaly or ascites above baseline (iii) anicteric sinusoidal obstruction syndrome which occurs more frequently in the paediatric and adolescent and young adult population and (iv) refractory thrombocytopenia as an early diagnostic indicator. Further, overall trends of weight gain and rising bilirubin are assessed over consecutive days to avoid acting upon potentially insignificant transient changes and standardized imaging techniques are recommended to evaluate for ascites and hepatomegaly to avoid subjective provider variability.[1,3,5] Leading academic societies have jointly endorsed use of these criteria in an effort to standardize diagnosis and grading of paediatric sinusoidal obstruction syndrome.[1]

In this study, we confirmed a high incidence of sinusoidal obstruction syndrome among paediatric hematopoietic cell transplantation patients (21.5%) and almost half of these patients required critical care

support. Indeed, sinusoidal obstruction syndrome is known to disproportionately affect children.[4,6,7,9] As indications for hematopoietic cell transplantation expand and novel therapies continue to emerge, the rapidly changing pre-hematopoietic cell transplantation therapy armamentarium may also alter the incidence of sinusoidal obstruction syndrome. For example, the calicheamicin-conjugated antibody, inotuzumab is used increasingly among relapsed/refractory paediatric patients with acute lymphoblastic leukemia and is associated with an increased risk of sinusoidal obstruction syndrome post-hematopoietic cell transplantation.[18] In our study, almost half of the patients who were exposed to inotuzumab pre-hematopoietic cell transplantation developed sinusoidal obstruction syndrome. Current guidelines from the National Comprehensive Cancer Network for paediatric acute lymphoblastic leukemia highlight multiple treatment options for patients with relapsed/refractory pre B- acute lymphoblastic leukemia. With the exception of recommending well-designed clinical trials when available, the National Comprehensive Cancer Network does not proscribe one treatment modality vs another. Thus, patient risk factors and clinical status can be weighed in choosing between inotuzumab, blinatumomab and/or immune-effector cell therapies.[19] The Children's Oncology Group AALL 1621 trial, using inotuzumab to treat relapsed/refractory B-Cell acute lymphoblastic leukemia, was halted temporarily when stopping rules were triggered for sinusoidal obstruction syndrome that occurred in 12.5% of all patients and 28.6% of those undergoing hematopoietic cell transplantation.[18] To decrease the risk of sinusoidal obstruction syndrome seen in their research protocol, one group amended their study to give inotuzumab in fractionated doses and increased the interval between inotuzumab and hematopoietic cell transplantation.[20] The group also initiated ursodiol prophylaxis for all patients while receiving inotuzumab. Sequential planning between paediatric leukemia and hematopoietic cell transplantation physicians to address emerging challenges such as this, may improve patient outcomes. A study of defibrotide prophylaxis and/or early initiation of defibrotide for sinusoidal obstruction syndrome may also be informative in this cohort.

Busulfan containing regimens have been previously associated with an increased risk of sinusoidal obstruction syndrome.[21,22] Given its narrow therapeutic window, the introduction of pharmacokinetic monitoring with intravenous busulfan administration was expected to allow dose reduction to mitigate the risk of sinusoidal obstruction syndrome with elevated levels and upward titration when needed for disease control and to avoid graft failures.[21–23] Interestingly, an association of increased sinusoidal obstruction syndrome and pharmacokinetic monitoring was observed in a retrospective analysis in one large cohort. It was speculated that providers were more likely to increase busulfan doses based on available pharmacokinetic information and this may been associated with a higher level of sinusoidal obstruction syndrome.[24] Shorter dose intervals also theoretically provide increased opportunity to adjust busulfan doses as pharmacokinetic results become available, however area under the curve targets are not always achievable.[25] In this study, more than half of the patients (55.8%) received one or more alkylators (cyclophosphamide, melphalan, thiotepa) as part of their conditioning regimen in addition to busulfan and 32.5% of patients received both busulfan and clofarabine. It has been hypothesized that repeated doses of busulfan may inhibit and deplete glutathione-S-transferase leading to the accumulation of toxic metabolites and the simultaneous metabolism of more than one alkylating agent may further potentiate this toxicity.[22] Given the high interpatient and intra-patient pharmacokinetic variability of busulfan, larger studies are needed to validate this finding.

In our US multi-centre study, use of the pEBMT criteria was associated with an earlier median time to sinusoidal obstruction syndrome diagnosis by 2.5-3 days. Earlier time to initiation of definitive treatment with defibrotide for sinusoidal obstruction syndrome has been associated with improved 100-day survival. When defibrotide was initiated within 2 days of diagnosis, improved 100-day survival was observed.[8] Our results support this finding, however was not statistically significant in our study likely impacted by the small sample size. Furthermore, a large proportion of patients in this study with sinusoidal obstruction syndrome had severe or very severe disease at the time of diagnosis. Further research into developing predictive biomarkers and validating non-invasive techniques such as sheer wave elastography may aid in further identifying patients at risk for sinusoidal obstruction syndrome or allowing even earlier diagnosis of sinusoidal obstruction syndrome.[26] Additionally, application of consensus pEBMT criteria identified 44 patients in our cohort, who were previously under-diagnosed. Bazarbachi et al. have recently shown that underdiagnosed sinusoidal obstruction syndrome is a major contributor of multi-organ dysfunction syndrome in patients with acute leukemia undergoing hematopoietic cell transplantation.[27] Overall as the diagnosis of sinusoidal obstruction syndrome is based clinically with some overlapping criteria such as weight gain that can also be seen in patients with other post hematopoietic cell transplantation endotheliopathies, there is the potential risk of overdiagnosis of sinusoidal obstruction syndrome. A relatively low incidence of sinusoidal obstruction syndrome using the pEBMT criteria with similar findings of refractory thrombocytopenia being one of the earliest signs of sinusoidal obstruction syndrome and 80% of patients lacking hyperbilirubinemia on the day of sinusoidal obstruction syndrome diagnosis has also been reported.[28] This further highlights that the

more dynamic pEBMT criteria may facilitate earlier diagnosis. Additionally, in this study however, more than half of the patients initially diagnosed with mild, moderate or severe disease progressed to very severe disease, the pEBMT criteria therefore, may also provide the opportunity to identify these patients at earlier stages of sinusoidal obstruction syndrome before developing multiorgan dysfunction syndrome and allow earlier intervention. Larger prospective studies are needed to further validate these findings.

Guidance for universal implementation by expert consensus pEBMT diagnostic criteria have made standardized application in the US possible. Our manuscript and clinical decision support tools such as mobile phone applications that aid in diagnosis and grading of sinusoidal obstruction syndrome (now available to assist with bedside adjudication) are integral to ongoing implementation science endeavors.[29–31] This study is limited by its retrospective design and number of patients at high-risk for sinusoidal obstruction syndrome. Yet, standardized application of expert consensus pEBMT diagnostic and severity grading for sinusoidal obstruction syndrome appears feasible in US centres. When applied, pEBMT criteria may lead to earlier and improved detection of sinusoidal obstruction syndrome among paediatric patients undergoing hematopoietic cell transplantation. Prompt diagnosis and initiation of definitive treatment of sinusoidal obstruction syndrome have been associated with improved outcomes. Use of expert consensus pEBMT criteria in well-designed prospective studies may improve our understanding of current risk factors for sinusoidal obstruction syndrome and help with validation of predictive biomarkers, definition of optimal prophylaxis strategies and determination of the optimal time to initiation of definitive treatment and its potential impact on patient survival.

Contributors

KMM conceptualized the paper. DR, AS, SB, JM, AR, RB, VS, MW, RL and BS participated in data curation. JW and DR completed formal analysis. DR and KMM wrote the manuscript. JK reviewed and/or edited the manuscript. DR, HAA, AS, SB, JM, RM, AR, RB, SJK and KMM treated patients. All authors reviewed and/or edited the manuscript and made meaningful contributions before submission. DR and KMM directly accessed and verified the data reported in the manuscript and are responsible for the decision to submit the manuscript.

Data sharing statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declaration of interests

RB received honorarium for participation in advisory board for role of radiology in diagnosis of veno-occlusive disease/sinusoidal obstruction syndrome by Jazz Pharmaceuticals. All other authors declare they have no competing interests.

Acknowledgements

We thank our patients and their caregivers, the nursing unit staff for their clinical care.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lana.2024.100728.

References

1 Mahadeo KM, Bajwa R, Abdel-Azim H, et al. Diagnosis, grading, and treatment recommendations for children, adolescents, and young adults with sinusoidal obstructive syndrome: an international expert position statement. *Lancet Haematol*. 2020;7(1):e61–e72.
2 Bajwa RPS, Mahadeo KM, Taragin BH, et al. Consensus report by pediatric acute lung injury and sepsis investigators and pediatric blood and marrow transplantation consortium joint working committees: supportive care guidelines for management of veno-occlusive disease in children and adolescents, Part 1: focus on investigations, prophylaxis, and specific treatment. *Biol Blood Marrow Transplant*. 2017;23(11):1817–1825.
3 Cesaro S, Pillon M, Talenti E, et al. A prospective survey on incidence, risk factors and therapy of hepatic veno-occlusive disease in children after hematopoietic stem cell transplantation. *Haematologica*. 2005;90(10):1396–1404.
4 Coppell JA, Richardson PG, Soiffer R, et al. Hepatic veno-occlusive disease following stem cell transplantation: incidence, clinical course, and outcome. *Biol Blood Marrow Transplant*. 2010;16(2):157–168.
5 Corbacioglu S, Carreras E, Ansari M, et al. Diagnosis and severity criteria for sinusoidal obstruction syndrome/veno-occlusive disease in pediatric patients: a new classification from the European society for blood and marrow transplantation. *Bone Marrow Transplant*. 2018;53(2):138–145.
6 Ragoonanan D, Khazal SJ, Wang J, et al. Improved detection of sinusoidal obstructive syndrome using pediatric-AYA diagnostic criteria and severity grading. *Bone Marrow Transplant*. 2021;56(1):175–184.
7 Carreras E, Diaz-Beya M, Rosinol L, Martinez C, Fernandez-Aviles F, Rovira M. The incidence of veno-occlusive disease following allogeneic hematopoietic stem cell transplantation has diminished and the outcome improved over the last decade. *Biol Blood Marrow Transplant*. 2011;17(11):1713–1720.
8 Richardson PG, Smith AR, Triplett BM, et al. Earlier defibrotide initiation post-diagnosis of veno-occlusive disease/sinusoidal obstruction syndrome improves Day +100 survival following haematopoietic stem cell transplantation. *Br J Haematol*. 2017;178(1):112–118.
9 Kammersgaard MB, Kielsen K, Heilmann C, Ifversen M, Muller K. Assessment of the proposed EBMT pediatric criteria for diagnosis and severity grading of sinusoidal obstruction syndrome. *Bone Marrow Transplant*. 2019;54(9):1406–1418.
10 Yoon JH, Yoo KH, Sung KW, et al. Validation of treatment outcomes according to revised severity criteria from European Society for Blood and Marrow Transplantation (EBMT) for sinusoidal obstruction syndrome/veno-occlusive disease (SOS/VOD). *Bone Marrow Transplant*. 2019;54(8):1361–1368.
11 Jones RJ, Lee KS, Beschorner WE, et al. Venoocclusive disease of the liver following bone marrow transplantation. *Transplantation*. 1987;44(6):778–783.
12 Gelman A, Jakulin A, Pittau MG, Su Y-S. A weakly informative default prior distribution for logistic and other regression models. *Ann Appl Stat*. 2008;2(4):1360–1383.
13 Team RDC. *R: a language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing; 2019. cited. Available from: http://www.R-project.org/. Accessed July 2, 2024.
14 Grupp SA, Corbacioglu S, Kang HJ, et al. Defibrotide plus best standard of care compared with best standard of care alone for the prevention of sinusoidal obstruction syndrome (HARMONY): a randomised, multicentre, phase 3 trial. *Lancet Haematol*. 2023;10(5):e333–e345.
15 Corbacioglu S, Grupp SA, Richardson PG, et al. Prevention of veno-occlusive disease/sinusoidal obstruction syndrome: a never-ending story and no easy answer. *Bone Marrow Transplant*. 2023;58:839–841.
16 Corbacioglu S, Cesaro S, Faraci M, et al. Defibrotide for prophylaxis of hepatic veno-occlusive disease in paediatric haemopoietic stem-cell transplantation: an open-label, phase 3, randomised controlled trial. *Lancet*. 2012;379(9823):1301–1309.
17 Skeens MA, McArthur J, Cheifetz IM, et al. High variability in the reported management of hepatic veno-occlusive disease in children

after hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant*. 2016;22(10):1823–1828.
18 O'Brien MM, Ji L, Shah NN, et al. Phase II trial of inotuzumab ozogamicin in children and adolescents with relapsed or refractory B-cell acute lymphoblastic leukemia: Children's Oncology group protocol AALL1621. *J Clin Oncol*. 2022;40(9):956–967.
19 Jabbour E, Short NJ, Senapati J, et al. Mini-hyper-CVD plus inotuzumab ozogamicin, with or without blinatumomab, in the subgroup of older patients with newly diagnosed Philadelphia chromosome-negative B-cell acute lymphocytic leukaemia: long-term results of an open-label phase 2 trial. *Lancet Haematol*. 2023;10:433–444.
20 Nasnas P, Jabbour E, Short N, et al. A phase II study of mini-hyper-CVD plus inotuzumab ozogamicin, with or without blinatumomab, in older adults with newly diagnosed Philadelphia chromosome-negative B-cell acute lymphoblastic leukemia: updated results and predictors for outcomes. *Blood*. 2022;140(Supplement 1):11679–11682.
21 Bartelink IH, Lalmohamed A, van Reij EM, et al. Association of busulfan exposure with survival and toxicity after haemopoietic cell transplantation in children and young adults: a multicentre, retrospective cohort analysis. *Lancet Haematol*. 2016;3(11):e526–e536.
22 Bognar T, Bartelink IH, Egberts TCG, et al. Association between the magnitude of intravenous busulfan exposure and development of hepatic veno-occlusive disease in children and young adults undergoing myeloablative allogeneic hematopoietic cell transplantation. *Transplant Cell Ther*. 2022;28(4):196–202.
23 ten Brink MH, Zwaveling J, Swen JJ, Bredius RG, Lankester AC, Guchelaar HJ. Personalized busulfan and treosulfan conditioning for pediatric stem cell transplantation: the role of pharmacogenetics and pharmacokinetics. *Drug Discov Today*. 2014;19(10):1572–1586.
24 Strouse C, Zhang Y, Zhang MJ, et al. Risk score for the development of veno-occlusive disease after allogeneic hematopoietic cell transplant. *Biol Blood Marrow Transplant*. 2018;24(10):2072–2080.
25 Zao JH, Schechter T, Liu WJ, et al. Performance of busulfan dosing guidelines for pediatric hematopoietic stem cell transplant conditioning. *Biol Blood Marrow Transplant*. 2015;21(8):1471–1478.
26 A prospective registry of pediatric cellular therapy patients at risk for endothelial dysfunction, sinusoidal obstruction syndrome and/or multi-organ dysfunction syndrome (MODS). cited. Available from: https://clinicaltrials.gov/show/NCT05090345. Accessed July 2, 2024.
27 Bazarbachi AH, Al Hamed R, Labopin M, et al. Underdiagnosed veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) as a major cause of multi-organ failure in acute leukemia transplant patients: an analysis from the EBMT Acute Leukemia Working Party. *Bone Marrow Transplant*. 2021;56(4):917–927.
28 Szmit Z, Gorczynska E, Mielcarek-Siedziuk M, Ussowicz M, Owoc-Lempach J, Kalwak K. Veno-occlusive disease in children and adolescents after hematopoietic stem cell transplantation: did the Modified Seattle Criteria fit the characteristics of pediatric population? *Adv Clin Exp Med*. 2020;29(3):339–344.
29 Anderson DM. SOS/VOD diagnosis and grading: 2023. cited. Available from: https://apps.apple.com/us/app/sos-vod-diagnosis-and-grading/id6444897834. Accessed July 2, 2024.
30 Center DMAC. SOS VOD: 2023. cited. Available from: https://play.google.com/store/apps/details?id=org.mdanderson.vodsos&hl=en_US&gl=US. Accessed July 2, 2024.
31 Wittmeier KD, Klassen TP, Sibley KM. Implementation science in pediatric health care: advances and opportunities. *JAMA Pediatr*. 2015;169(4):307–309.