Assessment of the proposed EBMT pediatric criteria for diagnosis and severity grading of sinusoidal obstruction syndrome

Kammersgaard, Marte B.; Kielsen, Katrine; Heilmann, Carsten; Ifversen, Marianne; Müller, Klaus

Published in:
Bone Marrow Transplantation

DOI:
10.1038/s41409-018-0426-8

Publication date:
2019

Document version
Publisher's PDF, also known as Version of record

Document license:
CC BY

Citation for published version (APA):
Kammersgaard, M. B., Kielsen, K., Heilmann, C., Ifversen, M., & Müller, K. (2019). Assessment of the proposed EBMT pediatric criteria for diagnosis and severity grading of sinusoidal obstruction syndrome. Bone Marrow Transplantation, 54(9), 1406-1418. https://doi.org/10.1038/s41409-018-0426-8
Assessment of the proposed EBMT pediatric criteria for diagnosis and severity grading of sinusoidal obstruction syndrome

Marte B. Kammersgaard1,2 · Katrine Kielsen1,2 · Carsten Heilmann2 · Marianne Ifversen2 · Klaus Müller1,2

Received: 16 April 2018 / Revised: 5 December 2018 / Accepted: 10 December 2018 / Published online: 25 January 2019
© The Author(s) 2019. This article is published with open access

Abstract
Sinusoidal obstruction syndrome (SOS), also known as veno-occlusive disease (VOD; hereafter referred to as SOS), is a potentially life-threatening complication of allogeneic hematopoietic stem cell transplantation (HSCT). We assessed the proposed pediatric EBMT criteria along with the Baltimore and modified Seattle criteria in a population-based cohort. Eighty-seven children (1.1–17.3 years) undergoing myeloablative HSCT from 2010 to 2017 were consecutively included at the Danish National Transplantation Center. In total, 39 (44.8%) patients fulfilled the EBMT criteria and 30 patients (35%) fulfilled the criteria for severe or very severe SOS. Nine (10.3%) patients fulfilled the modified Seattle criteria while none met the Baltimore criteria. Patients fulfilling the EBMT criteria for SOS had longer primary admission (31 days (23–183) vs. 27 days (17–61), \( p = 0.001 \)), were treated more intensively with diuretics within the first 3 months (29 days (0–90) vs. 3.5 days (0–90), \( p < 0.0001 \)), and had a longer time to stable platelet counts >50 × 10⁹/L (32 days (16–183) vs. 23 days (14–101), \( p < 0.0001 \)). Two patients, fulfilling neither Baltimore nor Seattle criteria, but selectively fulfilling EBMT criteria, died of treatment-related acute inflammatory complications within 1 year post-HSCT. In conclusion, application of the pediatric EBMT diagnostic and severity criteria may be helpful in identifying patients at increased risk of severe treatment-related complications and mortality, although with a risk of over-diagnosing SOS.

Introduction
Sinusoidal obstruction syndrome (SOS), also known as veno-occlusive disease (VOD; hereafter referred to as SOS), is a potentially life-threatening complication of allogeneic hematopoietic stem cell transplantation (HSCT) [1]. The initiating pathogenic step is damage to sinusoidal endothelial cells in the hepatic acinus, initiated by toxic metabolites of the conditioning regimen. This may lead to vascular occlusion, capillary leakage and hepatocellular necrosis, causing fluid overload, consumptive and transfusion-refractory thrombocytopenia and hyperbilirubinemia [2–4]. Most cases resolve within weeks, but a variable percentage of up to 30–60% have been reported to progress to multi-organ dysfunction/failure (MOD/MOF) with a mortality rate of >80% [3, 5–7].

The reported incidence of SOS in children is variable and partly related to the diagnostic criteria applied, reportedly ranging from 20% to 60% in high-risk populations after allogeneic HSCT [5, 7–10]. Transplant-related risk factors include second myeloablative transplantation, unrelated and HLA-mismatched donor, high-dose or unfractionated total body irradiation (TBI) and conditioning with high-dose busulfan and cyclophosphamide [4, 9–11]. Furthermore, acute graft-versus-host disease (GvHD) and previous hepatic disease are risk factors [4, 10, 12]. In addition, a number of pediatric factors such as young age and low weight as well as certain genetic diseases are associated with increased incidence of SOS [4, 5, 7, 9, 10, 13].

Until recently, SOS has been diagnosed using the Seattle [14] and Baltimore [15] criteria in both children and adults, with modification of the Seattle criteria to require a 5% weight gain in children [5]. However, the use of similar criteria for children and adults is challenged by age-related differences in the clinical presentation. In 15–20% of cases, children present with SOS later than a month after HSCT [7, 9], which is rare in adults [16], and while hyperbilirubinemia is an indispensable requirement in the Baltimore...
criteria, anicteric SOS has been reported in about one-third of children, including those experiencing severe SOS [5]. If hyperbilirubinemia is present at an early stage, it is often pre-existing, caused by the primary diagnosis, or it may occur late in a severe case of SOS [7, 17, 18].

Accordingly, pediatric diagnostic criteria for SOS have been suggested by a working group under the European Society for Blood and Marrow Transplantation (EBMT). In these new criteria, the time-restriction of the Seattle and Baltimore criteria has been omitted, and hyperbilirubinemia and weight gain are evaluated based on individual baselines, taking pre-existing clinical conditions into account. To avoid potentially misleading insignificant changes, weight gain and increase in bilirubin are assessed over 3 consecutive days and imaging techniques for ascites and hepatomegaly are recommended to improve sensitivity and specificity of the criteria [7]. Finally, transfusion refractory thrombocytopenia (RT) has been added as a criterion (Table 2) [16, 19–21].

Clinical studies indicate that defibrotide is effective for treatment of SOS in children [5, 6, 22, 23], especially after early intervention [24, 25], underlining the need for early diagnosis of SOS. Since the proposed pediatric SOS criteria are based on expert opinion like the Seattle and Baltimore criteria, empirical studies are needed to assess their validity and their applicability in the clinic. The Seattle and Baltimore criteria have a reported specificity of 95% and 89%, respectively [14, 15], with a low sensitivity of 56% [26], though this is mainly based on studies in adult HSCT which cannot directly be applied to children due to differences in clinical presentation of SOS.

The purpose of this retrospective study was to assess the new pediatric EBMT diagnostic criteria and severity grading along with the classical Baltimore and modified Seattle criteria in a clinical study.

Patients and methods

Study population

In this population-based study, 87 children (1–18 years of age) undergoing allogeneic HSCT were consecutively recruited at Copenhagen University Hospital Rigshospitalet, Denmark, from June 2010 to December 2012 and from March 2015 to June 2017, for studies of toxicities and immune reconstitution as described previously [27–30]. One patient was excluded due to death from fungal infection on day +9 without signs of SOS. Written informed consent was obtained from all included patients and/or their legal guardians after approval by the local ethics committee (H-1-2010-009 and H-7-2014-016). The patients were followed for 1 year post-transplant with an average follow-up time of 314 days (56–365). Thirteen patients did not complete a full year of follow-up due to relapse (n = 6), graft rejection (n = 4), or treatment-related death (n = 3).

The clinical characteristics are listed in Table 1. Diagnoses were malignant (n = 51) or benign diseases (n = 36). Donors were either matched siblings (MSD) (n = 22), matched unrelated donors (MUD) (n = 41), mismatched unrelated donors (MMUD) (n = 10), haploidentical (n = 6), or umbilical cord blood (UCB) (n = 8). Stem cell sources were bone marrow (BM) (n = 69), peripheral blood stem cells (PBSC) (n = 10), or UCB grafts (n = 8). Conditioning regimens were TBI-based (n = 21), busulfan-based (n = 42), or other chemotherapy-based regimens (n = 24).

Four patients (4.6%) had a baseline bilirubin above normal range. Twenty-five patients (28.7%) had a high risk of developing SOS due to prior HSCT, allogeneic HSCT for leukemia beyond the second relapse, diagnoses of adenoleukodystrophy, osteopetrosis or macrophage activation syndrome or conditioning with busulfan and melphalan, while no patients presented with pre-existing liver disease or received ozogamicin-coupled monoclonal antibodies (gemtuzumab or ozogamicin) [5]. Defibrotide was given as SOS-prophylaxis to certain high-risk patients by the clinician in charge based on a general clinical assessment, and most frequently after the approval in 2016.

Assessment of criteria

Clinical parameters were retrospectively registered from the patient’s medical records for the first year following HSCT. The applied pediatric EBMT criteria are stated in Table 2.

Some of the EBMT criteria required supplementary specifications not detailed in the article by Corbacioglu et al. [7]. In the present study, bilirubin was considered increased if either above normal range for the patient’s age and sex or if higher than 4 times the baseline value, as this combination appeared to result in a consistent assessment of rise in bilirubin. Further, baseline bilirubin was defined as the average of the last 2–3 values measured prior to conditioning. Refractory consumptive RT was defined as the need for otherwise unexplained platelet transfusions daily for ≥3 days to keep platelet counts above transfusion levels (20 × 10^9/L). Bilirubin and platelet counts were measured at least once daily as a routine procedure during hospitalization, and patients were weighed at least once daily during the admission to monitor hydration. For patients fulfilling EBMT criteria at more than one occasion, only data related to the first time point of SOS were applied in this analysis.

In this study, patients were severity graded for maximum grade of SOS by applying the pediatric EBMT severity grading criteria [7]. These criteria categorize SOS as mild, moderate, severe, or very severe (grade I–IV) based on the
extent of the following parameters: duration of persistent RT, rise of liver biomarkers, rise and kinetics of bilirubin, amount of ascites, and impaired coagulation as well as signs of SOS.

Table 1: Patient and transplant characteristics

| Characteristic                          | n = 87 |
|----------------------------------------|--------|
| Males                                  | 49 (56.3%) |
| Age at transplantation (years), median (range) | 7.8 (1.1–17.3) |
| Donors                                 | 22.9 (0.0–58.4) |
| Disease at transplantation, no. (%)    |        |
| Acute lymphoblastic leukemia           | 27 (31.0%) |
| Acute myeloid leukemia                 | 11 (12.6%) |
| Myelodysplastic syndrome               | 5 (5.7%) |
| Other malignancies                     | 8 (9.2%) |
| Severe aplastic anemia                 | 7 (8.0%) |
| Thalassemia                            | 3 (3.4%) |
| Hemophagocytic lymphohistiocytosis     | 2 (2.3%) |
| X-linked lymphoproliferative syndrome  | 2 (2.3%) |
| Pediatric immunodeficiency syndromes   | 12 (13.8%) |
| Infantile osteopetrosis                | 1 (1.1%) |
| Other benign disorders                  | 9 (10.3%) |
| Donor type, no. (%)                    |        |
| Matched sibling donor (10/10)          | 22 (25.3%) |
| Matched unrelated donor (10/10)        | 41 (47.1%) |
| Mismatched unrelated donor (9/10)      | 10 (11.5%) |
| Umbilical cord blood (8/10)            | 8 (9.2%) |
| Haploidentical donor                   | 6 (6.9%) |
| Stem cell source, no. (%)              |        |
| Bone marrow                            | 69 (79.3%) |
| Peripheral blood stem cells            | 10 (11.5%) |
| Umbilical cord blood                   | 8 (9.2%) |
| Conditioning regime, no. (%)           |        |
| TBI (1200 cGy) + VP16 or CY            | 17 (19.5%) |
| TBI (200 cGy) + CY                     | 4 (4.6%) |
| BU + CY + VP16                         | 10 (11.5%) |
| BU + CY + MEL                          | 15 (17.2%) |
| BU + other                             | 17 (19.5%) |
| Other chemotherapy-based conditioning  | 24 (27.6%) |
| ATG as part of conditioning regimen, no. (%) | 67 (77.0%) |
| Ciclosporin as GvHD prophylaxis, no. (%) | 79 (90.8%) |
| HSCT no.                               |        |
| 1                                      | 85 (97.7%) |
| 2                                      | 2 (2.3%) |
| Baseline bilirubin, median (range)     | 5.6 (2.2–43.0) |
| High risk of SOS, no. (%)              | 25 (28.7%) |
| Defibrotide prophylaxis, no. (%)       | 5 (5.7%) |

Table 2: Criteria for the diagnosis of SOS

| Location                                    | Seattle criteriaa | Baltimore criteria | EBMT pediatric criteria |
|---------------------------------------------|-------------------|-------------------|------------------------|
| Presence before day 20 after HSCT          | Bilirubin ≥24 µmol/L from baseline | Weight gain >5% from baseline | Weight gain >5% from baseline |
| Presence before day 21 after HSCT          | Bilirubin ≥24 µmol/L or rising bilirubin from a baseline value on 3 consecutive days | A weight gain >5% above baseline value or otherwise unexplained weight gain on 3 consecutive days despite the use of diuretics | Unexplained consumptive and transfusion-refractory thrombocytopenia |
| Presence before day 22 of the following:   | Bilirubin ≥34 µmol/L within 72 h or rising bilirubin from a baseline value on 3 consecutive days | Hepatomegaly (best if confirmed by imaging) above baseline valuec | Hepatomegaly (best if confirmed by imaging) above baseline valuec |
| Haplodependent donor                       |                   |                   |                        |
| Bone marrow                                | 69 (79.3%)        |                   |                        |
| Peripheral blood stem cells                | 10 (11.5%)        |                   |                        |
| Umbilical cord blood                       | 8 (9.2%)          |                   |                        |
| ATG as part of conditioning regimen, no. (%) | 67 (77.0%)        |                   |                        |
| Ciclosporin as GvHD prophylaxis, no. (%)   | 79 (90.8%)        |                   |                        |

TBI: total body irradiation; BU: busulfan; CY: cyclophosphamide; MEL: melphalan; VP16: etoposide; ATG: anti-thymocyte globulin; GvHD: graft-versus-host disease; HSCT: hematopoietic stem cell transplantation.

SOS: sinusoidal obstruction syndrome; GvHD: graft-versus-host disease; HSCT: hematopoietic stem cell transplantation.
of renal, pulmonary, or CNS organ dysfunction [7]. Of liver transaminases, only alanine aminotransferase (ALT) was available in all patients. International Normalized Ratio and coagulation factors II, VII, and X (both measured with ACL TOP), as well as need for fresh frozen plasma, were used to evaluate impaired coagulation. Oxygen requirement and new onset cognitive impairment were registered from medical records to assess pulmonary and CNS dysfunction, respectively. Due to scarce data on estimated glomerular filtration rate (eGFR) based on EDTA clearance, eGFR was calculated based on cystatin C (n = 31) [31] or creatinine (n = 8) [32]. Creatinine was measured at least daily during hospitalization (with Cobas 8000 c702), and Cystatin C was measured when indicated by the clinical condition and at least weekly for most of the period from August 2012 (with Cobas 8000 c502).

Statistical analyses

The Mann–Whitney- U test, Wilcoxon rank sum test, or Kruskal–Wallis rank sum test were used to calculate differences between continuous variables. Fisher’s exact test was used for categorical variables.

Kaplan–Meier estimates with log-rank test were applied for overall survival, transplant-related mortality, relapse, duration of primary admission, admission to the intensive care unit (ICU), acute and chronic GvHD, time to neutrophil engraftment, and time to stable platelet counts >50 × 10^9/L.

A two-sided p-value <0.05 was considered statistically significant. All statistical analyses were performed using R statistical software version 3.4.2 (The R Foundation for Statistical Computing, Vienna, Austria) and R studio (R Studio, Boston, MA, USA).

Results

Incidence of SOS

Thirty-nine (44.8%) patients fulfilled the EBMT criteria, while 9 (10.3%) patients fulfilled the modified Seattle criteria. Of the patients fulfilling the Seattle criteria, 8 out of 9 also fulfilled the EBMT criteria (Fig. 1), while one patient only fulfilled the modified Seattle criteria with upper right quadrant pain and bilirubin ≥34 µmol/L. None of the patients met the Baltimore criteria. Three patients were treated with defibrotide: one fulfilling Seattle criteria, one on suspicion of late onset SOS, and one with suspected pulmonary VOD.

Median time to diagnosis was 6 days from HSCT (0–54 days) with EBMT criteria, and 6 days (1–13 days) with Seattle criteria. For the 8 patients fulfilling both Seattle and EBMT criteria, EBMT criteria were in average fulfilled 3 days earlier than Seattle criteria. Patients fulfilling the EBMT criteria presented with rising bilirubin (n = 33, 84.6%), consumptive RT (n = 31, 79.5%), weight gain (n = 26, 66.7%), ultrasound-confirmed hepatomegaly (n = 1, 2.6%), and ultrasound-confirmed ascites (n = 1, 2.6%). Four patients fulfilled EBMT criteria at two separate time points.

When grading the patients according to the pediatric EBMT severity criteria, 13 (14.9%) were classified as grade IV, 17 (19.5%) as grade III, 6 (6.9%) as grade II, and 3 (3.4%) as grade I SOS.

Patient characteristics and development of SOS

Grade III–IV SOS was associated with malignant diagnoses and conditioning with busulfan plus cyclophosphamide (p = 0.039 and p = 0.015, respectively). There were no associations with recipient age, donor type, stem cell source, conditioning with TBI, or baseline levels of bilirubin (Tables 3 and 4). Patients with malignant diseases received TBI-based conditioning or conditioning with cyclophosphamide plus busulfan plus/minus etoposide or melphalan more commonly than patients with benign diseases (p < 0.0001 and p = 0.0006, respectively).

Defibrotide (25 mg/kg/day) was given to five patients as prophylaxis due to diagnoses with increased risk of SOS (n = 3) or pre-existing liver disease (n = 2) with a median length of treatment of 35 days (31–40 days). Three patients on defibrotide prophylaxis developed grade III–IV SOS according to EBMT criteria.
Table 3 (continued)

| Patient and transplant characteristics | Grade 0 | Grade I–II | Grade III–IV |
|---------------------------------------|---------|-----------|-------------|
| Total number of patients, no. (%)     | 48 (55.2%) | 9 (10.3%) | 30 (34.5%) |
| Males                                 | 28 (57.1%) | 5 (10.2%) | 16 (32.7%) |
| Age at transplantation (years), median (range) | 7.5 (1.1–16.6) | 3.4 (1.2–13.4) | 9.1 (1.2–17.3) |
| Recipients                            | 23.1 (0.0–58.4) | 22.6 (5.5–45.4) | 20.2 (0.0–51.4) |
| Donors                                | 11 (40.7%) | 3 (11.1%) | 13 (48.1%) |
| Disease at transplantation, no. (%)   | 4 (80.0%) | 0 (0.0%) | 1 (20.0%) |
| Acute lymphoblastic leukemia           | 3 (27.3%) | 1 (9.1%) | 7 (63.6%) |
| Acute myeloid leukemia                 | 3 (27.3%) | 1 (9.1%) | 7 (63.6%) |
| Myelodysplastic syndrome              | 0 (0.0%) | 0 (0.0%) | 1 (100.0%) |
| Other malignancies                    | 5 (62.5%) | 1 (12.5%) | 2 (25.0%) |
| Severe aplastic anemia                | 6 (85.7%) | 0 (0.0%) | 1 (14.3%) |
| Thalassemia                           | 3 (100.0%) | 0 (0.0%) | 0 (0.0%) |
| Hemophagocytic lymphohistiocytosis    | 1 (50.0%) | 0 (0.0%) | 1 (50.0%) |
| X-linked lymphoproliferative syndrome | 2 (100%) | 0 (0.0%) | 0 (0.0%) |
| Pediatric immunodeficiency syndromes  | 8 (66.7%) | 3 (25%) | 1 (8.3%) |
| Infantile osteopetrosis               | 0 (0.0%) | 0 (0.0%) | 1 (100.0%) |
| Other benign disorders                | 5 (55.6%) | 1 (11.1%) | 3 (33.3%) |
| Donor type, no. (%)                   | 10 (45.5%) | 4 (18.2%) | 8 (36.4%) |
| Matched sibling donor (10/10)         | 25 (61.0%) | 3 (7.3%) | 13 (31.7%) |
| Mismatched unrelated donor (9/10)     | 5 (50.0%) | 1 (10.0%) | 4 (40.0%) |
| Umbilical cord blood (8/10)           | 4 (50.0%) | 0 (0.0%) | 4 (50.0%) |
| Haploidentical donor                  | 4 (66.7%) | 1 (16.7%) | 1 (16.7%) |
| Stem cell source                      | 39 (56.5%) | 8 (11.6%) | 22 (31.9%) |
| Bone marrow                           | 5 (50.0%) | 1 (10.0%) | 4 (40.0%) |
| Umbilical cord blood                  | 4 (50.0%) | 0 (0.0%) | 4 (50.0%) |
| Conditioning regime, no. (%)          | 10 (58.8%) | 1 (5.9%) | 6 (35.3%) |
| TBI (1200 cGy) + VP16 or CY           | 4 (100.0%) | 0 (0.0%) | 0 (0.0%) |
| TBI (200 cGy) + CY                    | 3 (30.0%) | 1 (10.0%) | 6 (60.0%) |
| BU + CY + VP16                        | 5 (33.3%) | 2 (13.3%) | 8 (53.3%) |
| BU + CY + MEL                         | 8 (47.1%) | 1 (5.9%) | 8 (47.1%) |

**SOS and duration of primary admission**

Next, we evaluated the course of HSCT in patients with SOS defined by the EBMT criteria in comparison with patients not fulfilling these criteria. Patients fulfilling grade III–IV SOS had a longer duration of their primary admission (31 days (23–183) vs. 27 days (17–61), p = 0.001) than patients without SOS. In contrast, the duration of stay in hospital did not differ between patients with milder degrees of SOS and patients with no SOS (Fig. 2a). The number of patients admitted to the ICU was too low (n = 3) for assessment of any association with the pediatric EBMT criteria.

**Use of diuretics**

Patients fulfilling the pediatric EBMT SOS criteria received diuretics for more days post-HSCT within the first 3 months (29 days (0–90) vs. 3.5 days (0–90), p < 0.0001). These differences were significant both for grade III–IV SOS and grade I–II SOS compared with patients without SOS (p < 0.0001 and p = 0.0022, respectively) (Fig. 2b).

**Engraftment and GvHD**

Time to neutrophil engraftment did not differ between patients with and without SOS. However, stable platelet counts >50 × 10^9/L were achieved later in patients with grade III–IV SOS compared to patients without SOS (31 days (17–183) vs. 22 days (14–101), p = 0.0003), while no significant difference was seen for patients with milder SOS (Fig. 2c).
| Patient ID | Sex | Age at transplantation (years) | Diagnosis | Donor type | Stem cell source | HSCT, no. | Conditioning | High risk of SOS | Delibirrote prophylaxis pre-transplant (day) | Grade of EBMT SOS (day) | Modified Seattle SOS (day) | Baltimore SOS (day) | Delibirrote treatment (day) | Cause of death (day post-HSCT) |
|------------|-----|------------------------------|-----------|------------|-----------------|----------|-------------|---------------|---------------------------------|------------------------|-------------------------|---------------------|--------------------------|-----------------------------|
| 17         | Male| 11.5                         | Acute myeloid leukemia | SIB        | BM              | 1        | BU + CY + MEL | Yes           | -                               | IV (+5)                | -                       | -                    | -                        | -                           |
| 23         | Male| 13.7                         | Myelodysplastic syndrome | UCB        | UCB             | 1        | BU + CY + MEL | -             | -                               | IV (0)                 | -                       | -                    | -                        | -                           |
| 24         | Male| 13.9                         | Acute myeloid leukemia | SIB        | BM              | 1        | BU + CY + MEL | Yes           | -                               | IV (0)                 | Yes (+1)                | -                    | -                        | -                           |
| 34         | Male| 12.6                         | Congenital sideroblastic anemia | MUD        | BM              | 1        | BU + CY + ATG | -             | -                               | IV (+4)                | Yes (+4)                | -                    | -                        | -                           |
| 41         | Male| 3.4                          | Acute lymphoblastic leukemia | MMUD       | BM              | 1        | BU + THIO + FLU + ATG | -            | -                               | IV (+4)                | -                       | -                    | -                        | -                           |
| 44         | Female| 8.3                          | Acute myeloid leukemia | MUD        | BM              | 1        | BU + CY + MEL + ATG | Yes           | -                               | IV (+3)                | -                       | -                    | Yes (+144)               | PVOD with pulmonary failure (+183) |
| 46         | Female| 7.8                          | Metachromatic leukodystrophy | UCB        | UCB             | 1        | BU + FLU + ATG | -             | -                               | IV (+4)                | Yes (+6)                | -                    | -                        | -                           |
| 52         | Male| 14.6                         | Acute lymphoblastic leukemia | MUD        | BM              | 1        | TBI (12 Gy) + VP16 + ATG | -            | -                               | IV (+5)                | -                       | -                    | -                        | -                           |
| 68         | Male| 9.9                          | Acute lymphoblastic leukemia | MUD        | BM              | 1        | TBI (12 Gy) + VP16 + ATG | -            | -                               | IV (0)                 | -                       | -                    | -                        | -                           |
| 69         | Female| 15.8                         | Acute myeloid leukemia | SIB        | BM              | 1        | BU + CY + MEL | Yes           | -                               | IV (+8)                | -                       | -                    | -                        | -                           |
| 75         | Female| 14.3                         | Acute myeloid leukemia | MUD        | BM              | 1        | BU + CY + MEL + ATG | Yes           | -                               | IV (+4)                | Yes (+13)               | -                    | -                        | -                           |
| 80         | Female| 15.2                         | Acute myeloid leukemia | SIB        | BM              | 1        | BU + CY + MEL | Yes           | -                               | IV (+8)                | -                       | -                    | -                        | -                           |
| 86         | Male| 13.6                         | Chronic myeloid leukemia | MUD        | BM              | 1        | BU + CY + ATG | -             | -                               | IV (+54)               | -                       | -                    | Multi-organ failure (+111) | -                           |
| 1          | Male| 3.6                          | Acute lymphoblastic leukemia | MUD        | PBSC            | 1        | BU + CY + ATG | -             | -                               | III (+11)               | -                       | -                    | -                        | -                           |
| 5          | Female| 1.2                          | Hemophagocytic lymphohistiocytosis | MUD        | BM              | 1        | BU + CY + ATG | Yes           | Yes (-9)                         | III (+5)                | Yes (+12)               | -                    | -                        | -                           |
| 11         | Female| 2.1                          | Acute lymphoblastic leukemia | UCB        | UCB             | 1        | BU + CY + MEL + ATG | Yes           | -                               | III (+8)               | -                       | -                    | -                        | -                           |
| 12         | Female| 11.6                         | Infantile osteopetrosis | SIB        | BM              | 1        | BU + FLU | Yes           | -                               | III (+7)               | -                       | -                    | -                        | -                           |
| 19         | Male| 5.1                          | Acute lymphoblastic leukemia | MUD        | BM              | 1        | TBI (12 Gy) + VP16 + ATG | -            | -                               | III (+6)               | -                       | -                    | -                        | -                           |
| 21         | Male| 14.3                         | Acute lymphoblastic leukemia | MUD        | BM              | 1        | TBI (12 Gy) + VP16 + ATG | Yes           | -                               | III (+8)               | -                       | -                    | -                        | -                           |
| 33         | Male| 5.7                          | Acute lymphoblastic leukemia | MMUD       | BM              | 1        | TBI (12 Gy) + VP16 + ATG | -            | -                               | III (+7)               | -                       | -                    | -                        | -                           |
| 48         | Female| 4.0                          | Acute myeloid leukemia | MMUD       | BM              | 1        | BU + CY + MEL + ATG | Yes           | -                               | III (+43)              | -                       | Yes (+43)             | -                        | -                           |
| Patient ID | Sex | Age at transplantation (years) | Diagnosis | Donor type | Stem cell source | HSCT, no. | Conditioning | High risk of SOS | Delirubiotide prophylaxis pre-transplant (day) | Grade of EBMT SOS (day) | Modified Seattle SOS (day) | Baltimore SOS (day) | Delirubiotide treatment (day) | Cause of death (day post-HSCT) |
|-----------|-----|-----------------------------|-----------|------------|-----------------|----------|-------------|----------------|----------------------------------|------------------------|------------------------|----------------|-------------------------|---------------------------|
| 56        | Male | 3.8                         | Kostmann agranulocytosis | MUD       | PBSC            | 1        | BU + FLU + ATG | -              | Yes (−6)                        | III (13)               | -                      | -                        | -                       | -                       | Relapse of leukemia (174) |
| 62        | Female | 8.0                        | Acute lymphoblastic leukemia | SB         | BM              | 1        | BU + THIO + FLU | -              | -                                | III (10)               | Yes (6)                | Yes (13)                | -                       | -                       | -                       |
| 63        | Female | 7.9                        | Acute lymphoblastic leukemia | Haplo      | PBSC            | 1        | BU + THIO + FLU + ATG | -              | -                                | III (−6)               | -                      | -                        | -                       | -                       | -                       |
| 70        | Female | 2.9                        | Diamond-Blackfan anemia    | MUD       | BM              | 1        | THIO + FLU + ATG | -              | Yes (−7)                       | III (−7)               | -                      | -                        | -                       | -                       | -                       |
| 77        | Male | 12.4                       | Acute lymphoblastic leukemia | MUD       | BM              | 1        | BU + THIO + FLU + ATG | -              | -                                | III (−6)               | -                      | -                        | -                       | -                       | -                       |
| 79        | Female | 15.2                       | Severe aplastic anemia     | SB         | BM              | 1        | CY + ATG        | -              | -                                | III (−2)               | -                      | -                        | -                       | -                       | -                       |
| 82        | Male | 2.6                        | Juvenile chronic myeloid leukemia | SB         | BM              | 1        | BU + CY + MEL  | Yes         | -                                | III (−1)               | -                      | -                        | -                       | -                       | -                       |
| 84        | Male | 17.3                       | Acute lymphoblastic leukemia | MMUD      | PBSC            | 1        | TBI (12 Gy) + VP16 + ATG | Yes         | -                                | III (0)                | -                      | -                        | -                       | -                       | -                       |
| 85        | Female | 2.5                        | Acute lymphoblastic leukemia | SB         | UCB             | 1        | BU + THIO + FLU | -              | -                                | III (−33)              | -                      | -                        | -                       | -                       | -                       |
| 16        | Female | 8.0                        | Acute lymphoblastic leukemia | SB         | BM              | 1        | TBI (12 Gy) + VP16 | -              | -                                | II (17)                | -                      | -                        | -                       | -                       | -                       |
| 35        | Male | 2.2                        | Juvenile chronic myeloid leukemia | SB         | BM              | 1        | BU + CY + MEL  | Yes         | -                                | II (17)                | -                      | -                        | -                       | -                       | -                       |
| 37        | Female | 3.3                        | Acute lymphoblastic leukemia | MUD       | BM              | 1        | BU + CY + VP16 + ATG | -              | -                                | II (10)                | -                      | -                        | -                       | -                       | -                       |
| 38        | Male | 11.9                       | Severe combined immunodeficiency | MMUD     | BM              | 1        | BU + FLU + ATG | -              | -                                | II (11)                | -                      | -                        | -                       | -                       | -                       |
| 57        | Male | 3.4                        | Acute myeloid leukemia      | SB         | BM              | 1        | BU + CY + MEL  | Yes         | -                                | II (5)                 | -                      | -                        | -                       | -                       | -                       |
| 73        | Female | 7.6                        | Erythroblastic anemia       | MUD       | BM              | 1        | THIO + FLU + ATG | -              | -                                | II (5)                 | -                      | -                        | -                       | -                       | -                       |
| 3         | Female | 3.6                        | Severe combined immunodeficiency | SB         | BM              | 2        | FLU + TBIO | Yes         | I (6)                           | -                      | -                      | -                        | -                       | -                       | -                       |
| 39        | Male | 2.0                        | Leukocyte adhesion deficiency | MUD       | BM              | 1        | FLU + TBIO + ATG | -              | -                                | I (10)                 | -                      | -                        | -                       | -                       | -                       |
| 66        | Female | 13.4                      | Acute lymphoblastic leukemia | Haplo      | PBSC            | 2        | MEL + THIO + FLU + ATG | Yes         | -                                | I (5)                  | -                      | -                        | -                       | -                       | -                       |
| 2         | Female | 7.5                        | Acute myeloid leukemia      | UCB       | UCB             | 1        | BU + CY + ATG | Yes         | -                                | -                      | -                      | -                        | -                       | -                       | -                       |
| 4         | Female | 11.6                       | Acute lymphoblastic leukemia | MUD       | BM              | 1        | CY + VP16 + ATG | -              | -                                | -                      | -                      | -                        | -                       | -                       | -                       |
| 6         | Female | 15.4                       | Blastic plasmacytoid dendritic cell leukemia | MUD       | BM              | 1        | TBI (12 Gy) + CY + ATG | -              | -                                | -                      | -                      | -                        | -                       | -                       | -                       |
| 7         | Male | 13.1                       | Severe aplastic anemia      | MUD       | BM              | 1        | -              | -              | -                                | -                      | -                      | -                        | -                       | -                       | -                       |
| Patient ID | Sex  | Age at transplantation (years) | Diagnosis                          | Donor type | Stem cell source | HSCT, no. | Conditioning | High risk of SOS | Delibrotide prophylaxis pre-transplant (day) | Grade of EBMT SOS (day) | Modified Seattle SOS (day) | Grade of SOS | Delibrotide treatment (day) | Cause of death (day post-HSCT) |
|------------|------|-------------------------------|-----------------------------------|------------|-----------------|-----------|--------------|-----------------|--------------------------------|--------------------------|-------------------------------|---------------|--------------------------|---------------------------|
| 8          | Male | 6.2                           | Acute lymphoblastic leukemia      | MUD        | BM              | 1         | TBI (12 Gy)  | -               | -                              | -                        | -                            | -             | -                        | -                         |
| 9          | Male | 1.1                           | Acute lymphoblastic leukemia      | MUD        | BM              | 1         | BU + CY + VP16 + ATG | -               | -                              | -                        | -                            | -             | -                        | Relapse of leukemia (+266) |
| 10         | Male | 5.8                           | Diffuse large cell lymphoma       | SBI        | BM              | 1         | TBI (12 Gy) + VP16 | -               | -                              | -                        | -                            | -             | -                        | Relapse of lymphoma (+82) |
| 13         | Male | 1.6                           | Hyper IgM syndrome               | MUD        | BM              | 1         | BU + FLU + ATG     | -               | -                              | -                        | -                            | -             | -                        | -                         |
| 14         | Male | 1.6                           | Hyper IgM syndrome               | MUD        | BM              | 1         | BU + FLU + ATG     | -               | -                              | -                        | -                            | -             | -                        | -                         |
| 15         | Female | 1.3                          | Hurler syndrome                  | MUD        | BM              | 1         | BU + CY + ATG     | -               | -                              | -                        | -                            | -             | -                        | -                         |
| 18         | Female | 11.0                         | Myelodysplastic syndrome         | MUD        | BM              | 1         | BU + CY + ATG     | -               | -                              | -                        | -                            | -             | -                        | -                         |
| 20         | Male | 4.2                           | Hyper IgM syndrome               | MUD        | BM              | 1         | BU + FLU + ATG     | -               | -                              | -                        | -                            | -             | -                        | -                         |
| 22         | Female | 15.8                         | Duncans syndrome                | MUD        | BM              | 1         | FLU + TRBO + ATG   | -               | -                              | -                        | -                            | -             | -                        | -                         |
| 23         | Female | 11.2                         | Severe aplastic anemia           | MMUD       | BM              | 1         | TBI (2 Gy) + CY + ATG | -               | -                              | -                        | -                            | -             | -                        | -                         |
| 26         | Female | 1.4                          | Juvenile chronic myeloid leukemia| UCB        | UCB             | 1         | BU + CY + MEL + ATG | Yes             | -                              | -                        | -                            | -             | -                        | -                         |
| 27         | Male | 7.8                           | Severe aplastic anemia           | MMUD       | BM              | 1         | TBI (2 Gy) + CY + ATG | -               | -                              | -                        | -                            | -             | -                        | -                         |
| 28         | Male | 10.2                          | Acute myeloid leukemia           | MUD        | BM              | 1         | BU + CY + MEL + ATG | Yes             | -                              | -                        | -                            | -             | -                        | -                         |
| 29         | Male | 7.6                           | Severe aplastic anemia           | MUD        | BM              | 1         | TBI (2 Gy) + CY + ATG | -               | -                              | -                        | -                            | -             | -                        | -                         |
| 30         | Female | 4.7                          | Myelodysplastic syndrome         | MUD        | BM              | 1         | BU + CY + MEL + ATG | Yes             | -                              | -                        | -                            | -             | -                        | -                         |
| 31         | Female | 8.5                          | Myelodysplastic syndrome         | MUD        | BM              | 1         | CY + FLU + ATG     | -               | -                              | -                        | -                            | -             | -                        | -                         |
| 32         | Male | 8.3                           | Acute lymphoblastic leukemia      | MUD        | BM              | 1         | TBI (12 Gy) + VP16 + ATG | -               | -                              | -                        | -                            | -             | -                        | -                         |
| 36         | Male | 12.0                          | Fanconi anemia                   | MUD        | BM              | 1         | CY + FLU + ATG     | -               | -                              | -                        | -                            | -             | -                        | -                         |
| 40         | Male | 5.7                           | Acute lymphoblastic leukemia      | MUD        | BM              | 1         | TBI (12 Gy) + VP16 + ATG | -               | -                              | -                        | -                            | -             | -                        | -                         |
| 42         | Female | 9.1                          | Sickle Thalassemia major         | SBI        | BM              | 1         | THIO + FLU + ATG   | -               | -                              | -                        | -                            | -             | -                        | -                         |
| 43         | Male | 4.4                           | Burkitt’s lymphoma               | Haplo      | PBSC            | 1         | MEL + THIO + ATG   | -               | -                              | -                        | -                            | -             | -                        | Relapse of lymphoma (+89) |
| 45         | Male | 16.6                          | Acute lymphoblastic leukemia      | MUD        | PBSC            | 1         | TBI (12 Gy) + VP16 + ATG | -               | -                              | -                        | -                            | -             | -                        | -                         |
| 47         | Female | 7.1                          | Fanconi anemia                   | UCB        | UCB             | 1         | -                | -               | -                              | -                        | -                            | -             | -                        | -                         |
| Patient ID | Sex  | Age at transplantation (years) | Diagnosis                                | Donor type | Stem cell source | HSCT, no. | Conditioning | High risk of SOS | Delirium prophylaxis pre-transplant (day) | Grade of EBMT SOS (day) | Modified Seattle SOS (day) | Baltimore SOS (day) | Delirium treatment (day) | Cause of death (day post-HSCT) |
|------------|------|-------------------------------|------------------------------------------|------------|------------------|-----------|--------------|------------------|------------------------------------------|----------------------------|--------------------------|-----------------|--------------------------|-----------------------------|
| 49         | Male | 5.7                           | Acute lymphoblastic leukemia             | MUD        | BM               | 1         | CY + FLU + ATG | TBI (12 Gy) + VP16 + ATG | -                         | -                          | -                         | -               | -                         | -                          |
| 50         | Male | 13.0                          | SHOX syndrome                            | SB         | BM               | 1         | FLU + TREO    | -                | -                         | -                          | -                         | -               | -                         | -                          |
| 51         | Female | 7.3                          | Chronic granulomatous disease            | MMUD       | BM               | 1         | BU + FLU + ATG | -                | -                         | -                          | -                         | -               | -                         | -                          |
| 53         | Male  | 7.4                           | Acute lymphoblastic leukemia             | SB         | BM               | 1         | TBI (12 Gy) + VP16 | -                | -                         | -                          | -                         | -               | -                         | -                          |
| 54         | Male  | 3.2                           | Acute myeloid leukemia                    | MUD        | BM               | 1         | BU + CY + MEL + ATG | Yes             | -                         | -                          | -                         | -               | -                         | -                          |
| 55         | Male  | 7.3                           | Acute lymphoblastic leukemia             | SB         | BM               | 1         | TBI (12 Gy) + VP16 | -                | -                         | -                          | -                         | -               | -                         | -                          |
| 58         | Female | 12.8                         | Myelodysplastic syndrome                  | MUD        | BM               | 1         | THIO + FLU + ATG | -                | -                         | -                          | -                         | -               | -                         | -                          |
| 59         | Female | 13.9                         | Severe aplastic anemia                   | MUD        | BM               | 1         | TBI (2 Gy) + CY + ATG | -                | -                         | -                          | -                         | -               | -                         | -                          |
| 60         | Male  | 6.9                           | Fanconi anemia                            | SB         | BM               | 1         | CY + FLU + ATG | -                | -                         | -                          | -                         | -               | -                         | -                          |
| 61         | Male  | 3.9                           | Acute lymphoblastic leukemia             | Haplo      | PBSC             | 1         | BU + THIO + FLU + ATG | -                | -                         | -                          | -                         | -               | -                         | -                          |
| 64         | Female | 4.5                           | Congenital anemia                         | MUD        | BM               | 1         | THIO + FLU + ATG | -                | -                         | -                          | -                         | -               | -                         | -                          |
| 65         | Female | 1.5                           | Hemophagocytic lymphohistiocytosis        | MUD        | BM               | 1         | FLU + TREO + ATG | Yes             | Yes (~2)                  | -                          | -                         | -               | -                         | -                          |
| 67         | Male  | 2.9                           | X-linked lymphoproliferative syndrome     | SB         | BM               | 1         | BU + FLU      | Yes (~8)        | -                         | -                          | -                         | -               | -                         | -                          |
| 71         | Female | 7.1                           | Large cell anaplastic lymphoma            | SB         | BM               | 1         | TBI (12 Gy) + VP16 | -                | -                         | -                          | -                         | -               | -                         | -                          |
| 72         | Male  | 16.4                          | Acute lymphoblastic leukemia             | Haplo      | PBSC             | 1         | BU + THIO + FLU + ATG | -                | -                         | -                          | -                         | -               | -                         | -                          |
| 74         | Female | 10.6                          | Fanconi anemia                            | MMUD       | BM               | 1         | CY + FLU + ATG | -                | -                         | -                          | -                         | -               | -                         | -                          |
| 76         | Male  | 14.4                          | Severe aplastic anemia                   | MMUD       | BM               | 1         | CY + FLU      | -                | -                         | -                          | -                         | -               | -                         | -                          |
| 78         | Male  | 8.2                           | Adrenoleukodystrophy                     | Haplo      | PBSC             | 1         | CY + THIO + FLU | Yes             | -                         | -                          | -                         | -               | -                         | Progression of disease (+241) |
| 81         | Male  | 8.2                           | X-linked lymphoproliferative syndrome     | UCB        | UCB              | 1         | BU + FLU + ATG | -                | -                         | -                          | -                         | -               | -                         | -                          |
| 83         | Male  | 10.1                          | Sickle Thalassemia major                 | SB         | BM               | 1         | THIO + FLU + ATG | -                | -                         | -                          | -                         | -               | -                         | -                          |
| 87         | Female | 16.1                          | Sickle Thalassemia major                 | SB         | BM               | 1         | THIO + FLU + ATG | -                | -                         | -                          | -                         | -               | -                         | -                          |

*SIB* matched sibling donor, *MUD* matched unrelated donor, *MMUD* mismatched unrelated donor, *UCB* umbilical cord blood, *Haplo* haploidentical donor, *BM* bone marrow, *PBSC* peripheral blood stem cells, *TBI* total body irradiation, *BU* busulfan, *CY* cyclophosphamide, *MEL* melphalan, *FLU* fludarabin, *Treo* treosulfan, *VP16* etoposide, *THIO* thiota, *PVOD* pulmonary veno-occlusive disease, *ALL* acute lymphoblastic anemia
No difference was observed in risk of acute (\( p = 0.31 \)) or chronic (\( p = 0.99 \)) GvHD between patients fulfilling and not fulfilling EBMT SOS criteria (results not shown).

**Mortality**

Seven out of 87 patients (8.0%) died within the first year following HSCT. One of the patients transplanted for non-malignant disorders died due to the progression of neurologic manifestations of metachromatic leukodystrophy post-HSCT. Six patients transplanted for malignant diseases relapsed, four of these with a fatal outcome.

Two patients died in remission of treatment-related complications, both selectively fulfilling the pediatric EBMT criteria for very severe SOS, but neither fulfilling the classical criteria. One of these patients died in multiorgan failure day +111, initially dominated by liver failure, propagating to kidney failure, and respiratory insufficiency. The second patient developed progressing liver failure and respiratory insufficiency with signs of pulmonary hypertension 4.5 months after HSCT and passed away in a condition of multiorgan failure. A post-mortem lung-biopsy showed changes indicating pulmonary VOD (Fig. 3).

This limited frequency of mortality did not allow further statistical assessment in relation to fulfillment of EBMT SOS criteria.

**Discussion**

The new diagnostic EBMT criteria for pediatric SOS were developed in an attempt to create a more dynamic diagnostic tool adapted to the pediatric characteristics of SOS. Since these criteria, like Seattle and Baltimore criteria, were developed based on expert opinion rather than clinical data, they warrant assessment and validation in clinical cohorts. Although retrospective in design, the overall results of this study indicate that these new criteria could be useful in the clinic and may help to identify patients with severe SOS and a poor outcome that do not fulfill Seattle or Baltimore criteria. Accordingly, the EBMT criteria appear to compensate for the shortcomings of Seattle and Baltimore criteria in the pediatric setting.

The modification to more dynamic assessment of weight gain and hyperbilirubinemia as well as the addition of the consumptive RT criterion was the primary cause that a larger proportion of patients in our cohort were diagnosed with SOS using the pediatric EBMT criteria. Although most children still developed hyperbilirubinemia during SOS, the alteration of the essential requirement of rising bilirubin in the EBMT criteria allowed for diagnoses of SOS in six patients with moderate/severe SOS despite the absence of hyperbilirubinemia.

The classical criteria restrict disease onset to 21 days post-HSCT, despite the fact that late occurring symptoms of SOS are frequent in children. The absence of this time restriction in the EBMT criteria played a minor role, being critical for only 3 patients, and fulfillment of hepatomegaly and ascites criteria was not critical for any patient in this study.

Potential advantages of the new pediatric EBMT criteria are related to minimization of imprecise and partly subjective clinical assessment of parameters such as pain, ascites, and hepatomegaly. This is done with the Fig. 2 a Duration of primary admission after hematopoietic stem cell transplantation according to the severity grading of SOS based on pediatric EBMT criteria. Kaplan–Meier estimates with log-rank test for grade 0, grade I–II, and grade III–IV SOS are shown. The \( p \)-value indicates a significant difference between the three groups. Patients fulfilling grade III–IV SOS had a longer duration of their primary (\( p = 0.001 \)) than patients without SOS. There was no significant difference between patients with milder degrees of SOS and patients with no SOS. b Number of days on diuretics within the first 3 months after HSCT for patients fulfilling grade 0, grade I–II, and grade III–IV SOS.

The \( p \)-values indicate the difference between the groups of SOS patients and patients without SOS (using the Mann–Whitney-\( U \)-test). c Time to stable platelet counts >50 × 10^9/L for patients fulfilling grade 0, grade I–II, and grade III–IV SOS shown as Kaplan–Meier estimates with log-rank test. The \( p \)-value indicates a significant difference between the three groups. Stable platelet counts >50 × 10^9/L were achieved later in patients with grade III–IV SOS compared to patients without SOS (\( p = 0.003 \)), while no significant difference was seen for patients with milder SOS.
implementation of imaging, potentially increasing the reliability of the diagnosis. By applying baseline values, the new criteria also correct for shortcomings related to individual variations caused by pre-existing clinical conditions, which may be more frequent in the pediatric setting (e.g., immunodeficiencies).

However, there remain some challenges in the clinical implementation of the new EBMT criteria. Rising bilirubin from a baseline value on 3 consecutive days and otherwise unexplained weight gain on 3 consecutive days despite the use of diuretics are not fully defined regarding magnitude of the deviation from the normal. Further, guidelines as to whether thrombocytopenia should be interpreted as mainly consumptive or transfusion refractory could be more closely defined, although the EBMT severity grading criteria indicate that persistent RT >3 days is representative of moderate SOS. In this study, we have investigated different interpretations and chosen the most consistent assessment based on our patient data. We hope this can help give perspective and further optimize the criteria.

Application of the pediatric EBMT criteria in this study defined a broader group of patients diagnosed with SOS than the group defined by the Seattle criteria, though most of these patients are still included when using the pediatric EBMT criteria. The comparatively large number of patients fulfilling the pediatric EBMT criteria indicates a risk of over-diagnosis. There is, for instance, a risk that slight increases in bilirubin may be caused by hepatotoxic side effects of medication frequently used in the clinic, such as antibiotics, antiviral drugs and antifungals (in particular voriconazole [33] and carbapenems [34]). As we are the first to assess these proposed criteria, we have only our own numbers to consider regarding the risk of over-diagnosis.

However, when considering treatment of SOS based on the new EBMT criteria, we find that application of the severity grading criteria could possibly limit the group of patients where treatment is indicated. Overall, patients meeting the EBMT criteria for SOS had a longer duration of the primary admission, later occurrence of stable platelet counts, and received diuretics for a longer period, indicating higher morbidity. This was also the case for patients with grade III–IV SOS, but generally not for patients with grade I–II SOS. Importantly, application of the EBMT criteria also identified two patients among the very severe SOS group not identified by the Seattle criteria, who developed
liver insufficiency progressing to fatal multiorgan failure. This indicates that patients fulfilling severe–very severe SOS have significantly higher morbidity and could benefit from earlier recognition of SOS and initiation of treatment, while mild–moderate SOS diagnosed by the EBMT criteria might not require treatment. The median time of diagnosis was rather early for our patients compared to the previously reported debut at around 2 weeks post-HSCT [7–9], however, this may be explained by our retrospective study design allowing for strict daily assessment compared to clinical observations.

Defibrotide was not implemented in our clinic in the beginning of the study period. Accordingly, only a few patients were treated with defibrotide on suspicion of SOS, and all these retrospectively fulfilled grade III–IV SOS by EBMT criteria. Thus, this study suggests an increased clinical awareness of patients fulfilling severe–very severe EBMT SOS criteria. Further optimization and adjustment of the pediatric EBMT SOS criteria should be based on prospective studies.

The main limitation of this study is the retrospective use of the EBMT criteria. The lack of patients fulfilling Baltimore criteria can partly be explained by improper clinical assessment and registration of hepatomegaly and ascites throughout this period, as well as the inaccuracy of this clinical investigation, especially in children. In general, there was an absence of baseline ultrasound for most of our patients as this has not been the practice in our clinic previously. However, none of our SOS diagnoses by the pediatric EBMT criteria were dependent on hepatomegaly/ascites alone and thus our results should not be altered. Further limitations are that competing conditions may be difficult to assess retrospectively as well as clinically, especially those that mimic SOS such as thrombotic microangiopathy and engraftment syndrome. In addition, the high survival rates in this study did not allow any conclusive analysis of mortality, indicating that the proposed EBMT criteria should be assessed in larger pediatric cohorts. The low frequency of high-risk patients in our study compared to others, as well as the limited use of TBI, could partly account for the generally excellent outcomes [9, 35]. However, this is difficult to assess due to variation and inconsistency in risk assessment of SOS in the literature as well as the specific inclusion of high-risk patients in many studies of pediatric SOS.

In conclusion, our findings suggest that application of the pediatric EBMT diagnostic and severity grading criteria for SOS may be helpful in identifying patients at increased risk of severe treatment-related complications and mortality. However, further assessment of the EBMT criteria based on larger prospective studies with the potential for clinical intervention is needed.

Acknowledgements The financial support was obtained from The Research Council at Rigshospitalet.

Compliance with ethical standards

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

Publisher’s note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this license, visit http://creativecommons.org/licenses/by/4.0/.

References

1. Fan CQ, Crawford JM. Sinusoidal obstruction syndrome (hepatic veno-occlusive disease). J Clin Exp Hepatol. 2014;4:332–46. https://doi.org/10.1016/j.jceh.2014.10.002
2. Carreras E, Diaz-Ricart M. The role of the endothelium in the short-term complications of hematopoietic SCT. Bone Marrow Transplant. 2011;46:1495–502. https://doi.org/10.1038/bmt.2011.65
3. Coppel JA, Richardson PG, Soiffer R, Martin PL, Kernan NA, Chen A, et al. Hepatic veno-occlusive disease following stem cell transplantation: incidence, clinical course, and outcome. Biol Blood Marrow Transplant. 2010;16:157–68. https://doi.org/10.1016/j.bbmt.2009.08.024
4. Mohy M, Malard F, Abeassios M, Aerts A, Alaskar AS, Aljurf M, et al. Sinusoidal obstruction syndrome/veno-occlusive disease: current situation and perspectives-a position statement from the European Society for Blood and Marrow Transplantation (EBMT). Bone Marrow Transplant. 2015;50:781–9. https://doi.org/10.1038/bmt.2015.52
5. Corbacioglu S, Cesaro S, Faraci M, Valteau-Couanet D, Gruhn B, Novelli A, 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;379:1301–9. https://doi.org/10.1016/S0140-6736(11)61938-7
6. Richardson PG, Riches ML, Kernan NA, Brochstein JA, Mineishi S, Termuhlen AM, et al. Phase 3 trial of defibrotide for the treatment of severe veno-occlusive disease and multi-organ failure. Blood. 2016;127:1656–66. https://doi.org/10.1182/blood-2015-10-676924
7. Corbacioglu S, Carreras E, Ansari M, Balduzzi A, Cesaro S, Dalle JH, 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;53:138–45. https://doi.org/10.1038/bmt.2017.161
8. Barker CC, Butzner JD, Anderson RA, Brant R, Sauve RS. Post-transplant complications incidence, survival and risk factors for
the development of veno-occlusive disease in pediatric hematopoietic stem cell transplant recipients. Bone Marrow Transplant. 2003;32:79–87. https://doi.org/10.1038/sj.bmt.1704069

9. Cesaro S, Pillon M, Talenti E, Toffolotti T, Calore E, Tridello G, 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;90:1396–404.

10. Cheuk D, Wang P, Lee TL, Chiang AK, Ha SY, Lau YL, et al. Risk factors and mortality predictors of hepatic veno-occlusive disease after pediatric hematopoietic stem cell transplantation. Bone Marrow Transplant. 2007;40:935–44. https://doi.org/10.1038/sj.bmt.1705835

11. Carreras E, Berti H, Arcese V, Vernant JP, Tomás JF, Hagglund H, et al. Incidence and outcome of hepatic veno-occlusive disease after blood or marrow transplantation: a prospective cohort study of the European Group for Blood and Marrow Transplantation. Blood. 1998;92:3599–605.

12. Dignan FL, Wynn RF, Hadzic N, Karani J, Quagliia A, Pagliuca A, et al. BCSH/BSBMT guideline: diagnosis and management of veno-occlusive disease (sinusoidal obstruction syndrome) following haematopoietic stem cell transplantation. Br J Haematol. 2013;163:444–57. https://doi.org/10.1111/bjh.12558

13. Corbacioglu S, Hönig M, Lahr G, Stöhr S, Berry G, Friedrich W, et al. Stem cell transplantation in children with infantile osteopetrosis is associated with a high incidence of VOD, which could be prevented with defibrotide. Bone Marrow Transplant. 2006;38:547–53. https://doi.org/10.1038/sj.bmt.1705485

14. McDonald GB, Sharma P, Matthews DE, Shulman HM, Thomas ED. Venoocclusive disease of the liver after bone marrow transplantation: diagnosis, incidence, and predisposing factors. Hepatology. 1984;4:116–22.

15. Jones RJ, Lee KS, Beschorner WE, Vogel VG, Grochow LB, Braine HG, et al. Venoocclusive disease of the liver following bone marrow transplantation. Transplantation. 1987;44:778–83.

16. Toh HC, Mcafee SL, Sackstein R, Cox BF, Colby C, Spitzer TR. Late onset veno-occlusive disease following high-dose chemotherapy and stem cell transplantation. Bone Marrow Transplant. 1999;24:891–5.

17. Bearman SI, Anderson GL, Mori M, Hinds MS, Shulman HM, McDonald GB. Venoocclusive disease of the liver: development of a model for predicting fatal outcome after marrow transplantation. J Clin Oncol. 1993;11:1729–36.

18. Naples JC, Skeens MA, Auletta J, Rangarajan H, Abu-Arja R, Horowitz E, et al. Anicteric veno-occlusive disease after hematopoietic stem cell transplantation in children. Bone Marrow Transplant. 2015;51:135–7. https://doi.org/10.1038/bmt.2015.208

19. Mcdonald G, Hinds M, Fisher L, Schoch H, Wolford J, Banaji M, et al. Veno-occlusive disease of the liver and multiorgan failure after bone marrow transplantation: a cohort study of 355 patients. Ann Intern Med. 1993;118:255–67.

20. Hod E, Schwartz J. Platelet transfusion refractoriness. Br J Haematol. 2008;142:348–60. https://doi.org/10.1111/j.1365-2457.2008.07189.x

21. Rio B, Andreu G, Nicod A, Arrago J, Dutrillaux F, Samama M, et al. Thrombocytopenia in venoocclusive disease after bone marrow transplantation or chemotherapy. Blood. 1986;6:1773–6.

22. Richardson PG, Murakami C, Jin Z, Warren D, Montaz P, Hoppensteadt D, et al. Multi-institutional use of defibrotide in 88 patients after stem cell transplantation with severe veno-occlusive disease and multisystem organ failure: response without significant toxicity in a high-risk population and factors predictive of outcome. Blood. 2002;100:4337–43. https://doi.org/10.1182/blood-2002-04-1216

23. Corbacioglu S, Carreras E, Mohty M, Pagliuca A, Boeens JJ, Damaj G, et al. Defibrotide for the treatment of hepatic veno-occlusive disease: final results from the International Compassionate-Use Program. Biol Blood Marrow Transplant. 2016;22:1874–82. https://doi.org/10.1016/j.bbmt.2016.07.001

24. Corbacioglu S, Greil J, Peters C, Wulffraat N, Laws HJ, Dilloo D, et al. Defibrotide in the treatment of children with veno-occlusive disease (VOD): a retrospective multicentre study demonstrates therapeutic efficacy upon early intervention. Bone Marrow Transplant. 2004;33:189–95. https://doi.org/10.1038/sj.bmt.1704329

25. Richardson PG, Smith AR, Tripllett BM, Kerman NA, Grupp SA, Antin JH, 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;178:112–8. https://doi.org/10.1111/bjh.14727

26. Carreras E, Grafena A, Navasa M, Bruguera M, Marco V, Sierra J, et al. On the reliability of clinical criteria for the diagnosis of hepatic veno-occlusive disease. Ann Hematol. 1993;13:77–80.

27. Kielsen K, Jordan KK, Uhling HH, Pontoppidan PL, Shamim Z, Ifversen M, et al. T cell reconstitution in allogeneic hematopoietic stem cell transplantation: prognostic significance of plasma interleukin-7. Scand J Immunol. 2015;81:72–80. https://doi.org/10.1111/sji.12244

28. Kielsen K, Ryder LP, Lennox-hvenekilde D, Gad M, Nielsen CH, Heilmann C, et al. Immunobiology reconstitution of Th17, Tc17 and Treg cells after paediatric haematopoietic stem cell transplantation: Impact of interleukin-7. Immunobiology. 2018;223:220–6. https://doi.org/10.1016/j.imbio.2017.10.023

29. Jordan K, Pontoppidan P, Uhling HH, Kielsen K, Burritt DG, Weischendorf S, et al. Biology of blood and marrow transplantation gastrointestinal toxicity, systemic inflammation, and liver biochemistry in allogeneic hematopoietic stem cell transplantation. Biol Blood Marrow Transplant. 2017;23:1170–6. https://doi.org/10.1016/j.bbmt.2017.03.021

30. Pontoppidan PL, Jordan K, Carlsen AL, Uhling H, Kielsen K, Christensen M, et al. International Immunopharmacology Associations between gastrointestinal toxicity, micro RNA and cytokine production in patients undergoing myeloablative allogeneic stem cell transplantation. Int Immunopharmacol. 2015;25:180–8. https://doi.org/10.1016/j.intimp.2014.12.038

31. Schwartz GJ, Schneider MF, Maier PS, Moxey-Mims M, Dhar Damaj G, et al. Deferasirox initiation post-diagnosis of veno-occlusive disease/sinusoidal obstruction syndrome improves Day +100 survival following haematopoietic stem cell transplantation. Compassionate-Use Program. Biol Blood Marrow Transplant. 2014;99:766–72. https://doi.org/10.1016/j.bbmt.2014.03.028

32. Schwartz GJ, Reindollar RH, Moxey-Mims M, Dhar Damaj G, et al. Improved equations estimating GFR in children with chronic kidney disease using an immunonephelometric determination of cystatin C. Kidney Int. 2012;82:445–53. https://doi.org/10.1038/ki.2012.169

33. Schwartz GJ, Mun A, Schneider MF, Mak RH, Kaskel F, Warady BA, et al. New equations to estimate GFR in children with CKD. J Am Soc Nephrol. 2009;20:629–37. https://doi.org/10.1681/ASN.2008030287.

34. Xing Y, Chen L, Feng Y, Zhou Y, Zhai Y, Lu J. Meta-analysis of the safety of voriconazole in definitive, empirical, and prophylactic therapies for invasive fungal infections. BMC Infect Dis. 2017;17:798. https://doi.org/10.1186/s12879-017-2913-8

35. Vardakas KZ, Kalimeris GD, Triarides NA, Falagas ME. An update on adverse drug reactions related to β-lactam antibiotics. Expert Opin Drug Saf. 2018;17:499–508. https://doi.org/10.1080/14740338.2018.1462334

36. Maximova N, Ferrara G, Minute M, Pizzol A, Kiren V, Montico M, et al. Experience from a single paediatric transplant centre with identification of some protective and risk factors concerning the development of hepatic veno-occlusive disease in children after allogeneic hematopoietic stem cell transplantation. Int J Hematol. 2014;99:766–72. https://doi.org/10.1007/s12185-014-1578-y