ARTICLE

An international survey to better understand the current incidence, severity, and management of VOD/SOS

Marion Larue[1✉], Myriam Labopin[1], Eolia Brissot[1], Ahmed S. Alaskar[2], Mahmoud Aljurf[3], Mutlu Arat[4], Frederic Baron[5], Ali Bazarbachi[6], Fabio Ciceri[7], Selim Corbacioglu[8], Fiona L. Dignan[9], Michelle Kenyon[10], Florent Malard[1], Arnon Nagler[11], Antonio Pagliuca[10], Annalisa Ruggeri[7], Ibrahim Yakoub-Agha[12], Yishan Ye[13], Rafael F. Duarte[14], Tapani Ruutu[15], Enric Carreras[16], Zinaida Peric[17] and Mohamad Mohty[1,18]

This international questionnaire survey aimed to explore the current incidence, diagnostic policies, management, and outcomes of veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) among healthcare providers involved in the management of these patients. A questionnaire was e-mailed to practitioners with an interest in allogeneic hematopoietic cell transplantation (allo-HCT). Of the respondents, 144 of 215 (67.0%) felt that early detection or diagnosis of VOD/SOS was difficult. Regarding diagnostic criteria, 142 (66.1%) already declared using the 2023 EBMT refined criteria. Most respondents (163/215, 75.8%) found these recent refined EBMT criteria useful for diagnosis, and 193 (89.8%) found the severity criteria easy to use. The major risk factors identified for VOD/SOS were a second allo-HCT (41.4%), pre-existing liver disease (54.9%), and prior use of antibody-drug conjugates (49.8%). Preferences for starting VOD/SOS treatment varied, with 61 (28.4%) preferring initiating therapy at a mild stage, and 122 (56.7%) preferring the moderate stage. In summary, this survey provided valuable insight into the challenges and opportunities of the identification and management of VOD/SOS. By improving current knowledge and increasing collaboration among healthcare professionals, early detection, management, and clinical outcomes for patients with this potentially serious complication can also be improved.

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INTRODUCTION

Veno-occlusive disease (VOD) or sinusoidal obstruction syndrome (SOS) is a serious and potentially fatal complication of the liver. It is characterized by endothelial dysfunction leading to occlusion of the small veins in the liver, resulting in post-sinusoidal hypertension with hepato-renal syndrome and, in extreme cases, multi-organ dysfunction (MOD) [1]. It often occurs after allogeneic hematopoietic cell transplantation (allo-HCT) or liver transplantation, but can also occur in other contexts, such as after the administration of high-dose chemotherapies. The use of immunotherapy for the treatment of acute leukemia, such as gemtuzumab ozogamicin and inotuzumab ozogamicin, has also been associated with the development of VOD/SOS [2, 3]. The incidence of VOD/SOS after HCT in children is approximately 20%, rising to 60% in patients considered at high risk [4]. In adults, the incidence is approximately 10% [5]. Typical symptoms of VOD/SOS include rapid weight gain due to fluid retention, abdominal pain, hepatomegaly, rapid onset of ascites, jaundice, refractory thrombocytopenia and liver dysfunction [3]. Diagnosis is usually based on a combination of clinical symptoms, liver function tests, and medical imaging, such as liver ultrasound or computed tomography (CT) scan. However, it is now well established that VOD/SOS differs considerably between age groups in terms of incidence, genetic predisposition, clinical presentation, prevention, treatment and outcome, calling into question the use of the Baltimore and modified Seattle criteria for diagnosis [6]. In 2023, the refined diagnostic and severity criteria for adults, of the European Society of Blood and Marrow Transplantation (EBMT 2023 refined criteria) were endorsed [7]. The revision introduced new diagnostic categories, namely VOD/SOS probable, clinical, and proven. Elastography has been included in the new criteria for the probable diagnosis of VOD/SOS. In addition, the Sequential

[1]Sorbonne Université, Centre de Recherche Saint-Antoine INSERM UMRs938, Service d'Hématologie Clinique et de Thérapie Cellulaire, Hôpital Saint Antoine, AP-HP, Paris, France. [2]King Abdullah International Medical Research Center, Ministry of National Guard Health Affairs, Riyadh, Saudi Arabia. [3]King Faisal Specialist Hospital and Research Center Riyadh, Riyadh, Saudi Arabia. [4]F Sisli Florence Nightingale Hospital, HSCT Unit, Istanbul, Turkey. [5]CHU and University of Liège, Liège, Belgium. [6]BMT program, department of internal medicine, American University of Beirut, Beirut, Lebanon. [7]San Raffaele Scientific Institute, Hematology and Bone marrow Transplantation Unit, Milan, Italy. [8]Department of Pediatric Hematology, Oncology and Stem Cell Transplantation, University of Regensburg, Regensburg, Germany. [9]Department of clinical haematology, Manchester University NHS Foundation Trust, Manchester, UK. [10]Department of Haematology, King's College Hospital, London, UK. [11]Hematology and Bone Marrow Transplantation, Chaim Sheba Medical center, Tel-Hashomer, Israel. [12]CHU de Lille, université de Lille, Infinite, Inserm U1286, 59000 Lille, France. [13]Bone Marrow Transplantation Center, Zhejiang University School of Medicine, Hangzhou, China. [14]Department of Hematology, Hospital Universitario Puerta de Hierro Majadahonda, Madrid, Spain. [15]Clinical Research Institute and Comprehensive Cancer Center, Helsinki University Hospital, Helsinki, Finland. [16]Josep Carreras Foundation & Leukemia Research Institute, Barcelona, Spain. [17]Department of Hematology, University Hospital Centre Zagreb and School of Medicine, University of Zagreb, Zagreb, Croatia. [18]EBMT ALWP office, Hôpital Saint-Antoine, Paris, France.
✉email: marion.larue@hotmail.fr

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Organ Failure Assessment (SOFA) score was incorporated into the VOD/SOS severity classification [4, 7, 8]. In most cases, VOD/SOS disease resolves within a few weeks; however, severe VOD/SOS disease results in MOD with a mortality rate of >80% [4, 9].

Treatment of VOD/SOS may include a variety of approaches, including supportive care to manage symptoms and specific treatments to reduce inflammation and improve liver function [10]. Defibrotide is the only drug approved for the curative treatment of severe sinusoidal obstructive disease following HCT [11, 12]. This treatment has been shown to have better results in children than in adults [5]. Recent observations suggest that early initiation of treatment could significantly improve the prognosis of patients [4]. In addition, defibrotide has demonstrated its effectiveness in preventing VOD/SOS [5, 12]. However, defibrotide is not currently approved for prophylactic use in Europe. With this background, we conducted an international questionnaire survey to explore the current incidence, diagnostic policies, management, and outcomes of VOD/SOS among healthcare providers involved in the management of these patients.

MATERIALS AND METHODS

All members of the International Academy for Clinical Hematology (IACH www.clinical-hematology.org) with an interest in allo-HCT were invited to participate in this survey in November 2023 ($N = 5000$ approximately). A questionnaire was distributed, followed by two reminders. The questionnaire included the following sections: members' demographics, qualification or job title, role, specialty/interests, memberships/affiliations, opinion on VOD/SOS diagnosis and criteria, modifiable and unmodifiable risk factors, severity classification, and VOD/SOS therapy. A total of 215 responses were received (4.3% approximately). The countries most represented were Spain with 19 practitioners, followed by France with 14, Germany with 13, Italy with 12, India with 10, the United States and Turkey each with 8, and Canada, Malaysia, Poland, Portugal, and the UK with 6 practitioners each (Data S1).

RESULTS

Of the respondents, 66 declared being clinical hematologists (30.7%), while 93 were physicians mainly specializing in adult HCT (43.3%). Sixteen specialized in pediatric HCT (7.4%). Twelve (5.6%) were interns/residents/trainees/students. Seven (3.3%) were nurses, 2 (0.9%) were in the HCT Research and Development field (MD and PharmD) and 19 (8.8%) indicated another category. Fifteen (7.0%) respondents were under the age of 30 years. The age groups 31 to 40, 41 to 50, 51 to 60, and 61 years or older were represented by 61 (28.4%), 77 (35.8%), 41 (19.1%), and 21 (9.8%) practitioners, respectively. Three (1.4%) had been practicing for less than a year, 18 (8.4%) for 1 to 2 years, 35 (16.3%) for 3 to 5 years, 45 (20.9%) for 6 to 10 years, and 114 (53.0%) for more than 10 years. Fifty-one (23.7%) were members of the American Society of Hematology (ASH), 66 (30.7%) of the European Hematology Association (EHA), 24 (11.2%) of the American Society of Clinical Oncology (ASCO), 76 (35.4%) of the EBMT, 79 (36.7%) of their National Transplant Society, and 84 (39.1%) indicated other medical societies or organizations.

Of the 215 responding practitioners, 112 (52.1%) had a special interest in conditioning regimens, 108 (50.2%) in graft-versus-host disease (GVHD) prophylaxis, 99 (46.1%) in infectious complications in general, 107 (49.8%) in early transplant complications (e.g., VOD/SOS, thrombotic microangiopathy [TMA], etc.), 105 (48.8%) in acute GVHD, 96 (44.7%) in chronic GVHD, 50 (23.3%) in post-transplant therapies, 59 (27.4%) in long-term treatment side effects, 49 (22.8%) in quality of life and rehabilitation, and 13 (6.1%) in other topics.

Of the respondents, 144 (67.0%) found it difficult to detect or make an early diagnosis of VOD/SOS, while 71 (33.0%) did not find this difficult. In their practice, 34 respondents (15.8%) reported an incidence of VOD/SOS of less than 1%, 96 (44.7%) reported 1 to 5%, 57 (26.5%) reported 6 to 10%, 3 (1.4%) reported 11 to 15%, and 25 (11.6%) said they didn't know the exact incidence because the diagnosis was often missed. No one reported an incidence higher than 15%. Eighty-three respondents (38.6%) did not see VOD/SOS outside of allo-HCT. Sixty-three (29.3%) observed VOD/SOS in the context of autologous HCT (AHCT), 29 (13.5%) when using high-dose chemotherapy alone, and 108 (50.2%) when using specific drugs (e.g. gemtuzumab ozogamicin, inotuzumab ozogamicin, etc.). Five respondents (2.3%) reported other circumstances of onset.

Twenty-six respondents (12.1%) used only the Baltimore criteria [6], 40 (18.6%) used only the Seattle and modified Seattle criteria [13], 110 (51.2%) used the original 2016 EBMT criteria [14], and 142 (66.1%) had started using the 2023 EBMT refined criteria [7]. In addition, 10 (4.7%) respondents reported using other various criteria to diagnose VOD/SOS.

Of the respondents, 163 (75.8%) felt that the introduction of the refined EBMT criteria (with the concepts of probable, clinical, and proven VOD/SOS) was useful in their practice to improve the diagnostic process for VOD/SOS. Eleven respondents (5.1%) felt that it had not been useful, while 35 (16.3%) didn't know or were unsure. Six (2.8%) people had other opinions about the usefulness of these criteria in their practice. When asked about the usefulness of the diagnostic category of probable hepatic VOD, only 13 respondents (6.1%), did not find it useful in their clinical practice, 104 (48.4%) found it useful, while 73 (34.0%) found it very useful. Twenty-five (11.6%) did not know or were unsure of its usefulness.

The three unmodifiable VOD/SOS risk factors that respondents considered most important in their practice were (Fig. 1):

1. Second HCT - 89 votes (41.4%)
2. History of pre-existing liver disease: hepatic fibrosis, cirrhosis, active viral hepatitis - 118 votes (54.9%)
3. Previous use of gemtuzumab ozogamicin or inotuzumab ozogamicin - 107 votes (49.8%)

The following risk factors received fewer votes but were well represented:

4. Iron overload (>1000 ng/mL) - 67 votes (31.2%)
5. Advanced patient age - 36 votes (16.7%)
6. Advanced disease (beyond second complete remission or relapse) - 54 votes (25.1%)

The top three modifiable VOD/SOS risk factors according to respondents were (Fig. 2):

1. High-dose (myeloablative) regimens - 157 votes (73.0%)
2. Oral or high-dose busulfan - 127 votes (59.1%)
3. High-dose treosulfan - 40 votes (18.6%)

Among the respondents, 193 (89.8%) found the VOD/SOS severity criteria described in the refined EBMT criteria easy to use and useful in their practice to improve patient prognosis. Seventeen respondents (7.9%) felt this was not the case, while five (2.3%) respondents had other opinions regarding the usefulness and ease of use of these criteria in improving prognosis in their practice.

One hundred and forty-one respondents (65.6%) currently assess the severity of hepatic VOD/SOS when it is suspected, while 46 (21.4%) do so once the diagnostic criteria are met. Fifteen (6.9%) people assessed severity after differential diagnosis (when other complications were ruled out), and 10 (4.7%) never did so.

Sixty-one respondents (28.4%) preferred to start VOD/SOS therapy when diagnosed at a mild stage, while 122 (56.7%) were in favor of starting treatment at a moderate stage. Fifty-seven (26.5%) participants preferred to start treatment at a severe stage and 25 (11.6%) at a very severe stage. In addition, 15 (7.0%) respondents preferred to decide when to start therapy on a case-by-case basis, with no preference for a particular severity level.

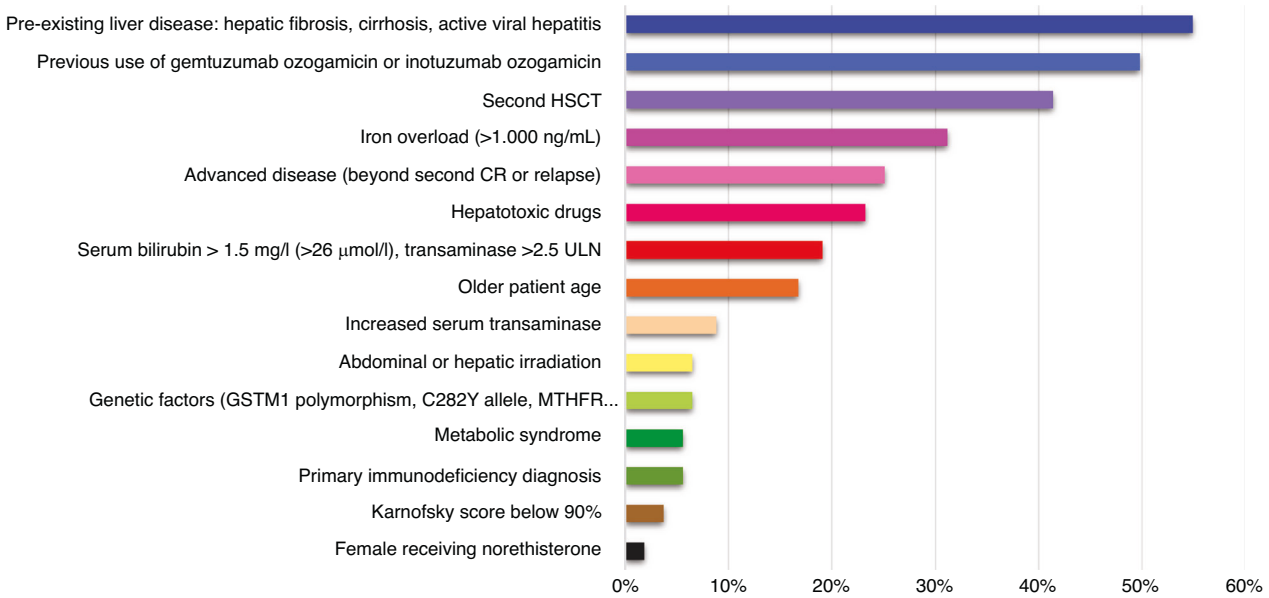

Fig. 1 The unmodifiable VOD/SOS risk factors for adults from the refined EBMT criteria: percentage of participants who consider them important. HSCT hematopoietic stem cell transplantation, CR complete response, VOD/SOS veno-occlusive disease/sinusoidal obstruction syndrome, EBMT European Society for Blood and Marrow Transplantation.

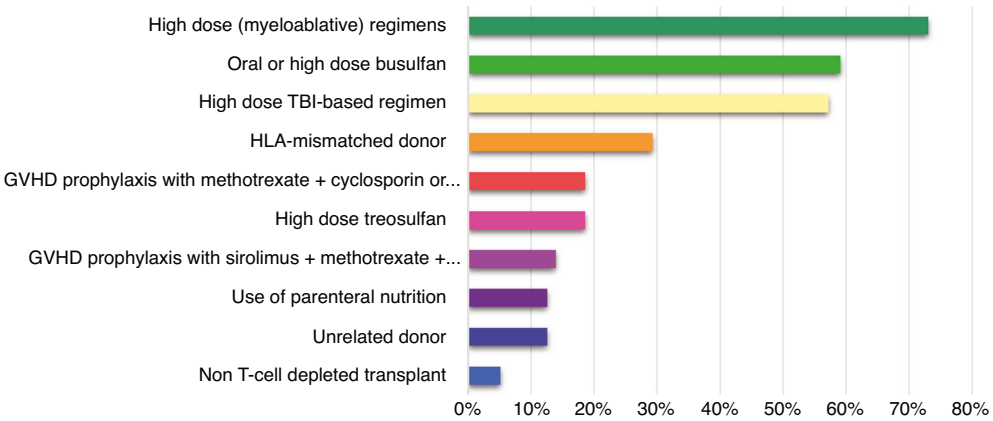

Fig. 2 The modifiable VOD/SOS risk factors for adults from the refined EBMT criteria: Percentage of participants who consider them important. TBI total body irradiation, HLA human leucocyte antigen, GVHD graft-versus-host disease, VOD/SOS veno-occlusive disease/sinusoidal obstruction syndrome, EBMT European Society for Blood and Marrow Transplantation.

According to respondents, the additional members of the multidisciplinary team who should be trained in the management of hepatic VOD were nurses (143 votes, 66.5%), radiologists (127 votes, 59.1%), intensivists (108 votes, 50.2%), and hepatologists (107 votes, 49.8%).

DISCUSSION

The results of this study highlight several critical aspects of the detection, diagnosis, and management of VOD/SOS. A thorough understanding of these elements is essential to improve clinical outcomes for patients suffering from this serious complication of HCT.

First, the low response rate of the survey is a significant limitation. The results may not fully represent the majority of practitioners, which could impact the generalizability of the findings. In addition, the survey did not explicitly ask respondents to indicate whether their data related to adult or pediatric patients. This lack of distinction is a valid concern, as it makes it difficult to draw conclusions about reported incidences without knowing patient characteristics. Future surveys must distinguish between these populations to ensure more accurate and meaningful conclusions.

Early detection of VOD/SOS appears to be an important prognostic criterion for management [15]. However, the results indicate that almost two-thirds of respondents find it difficult to detect or diagnose this complication early and 12% continue to use the historical Baltimore criteria. This underscores the importance of increased awareness and ongoing training of healthcare professionals to recognize early signs of the disease followed by prompt intervention, particularly in settings where the diagnosis may easily be missed.

The introduction of new diagnostic criteria, such as those proposed by the EBMT [7, 8, 15], seems to play an important role in improving the diagnosis of VOD/SOS. The concepts of probable, clinical, and proven VOD/SOS were considered useful by the majority of respondents. This approach may allow for more accurate identification and earlier intervention, potentially leading to improved clinical outcomes. However, we acknowledge that we did not collect specific feedback from those who did not find the

EBMT 2023 criteria useful. We emphasize the need for future research to further explore this issue in order to refine and develop the criteria.

In terms of risk factors, the results demonstrate the importance of considering both modifiable and non-modifiable factors in the management of VOD/SOS. A history of pre-existing liver disease, high-dose chemotherapy, and the use of certain medications were identified as significant risk factors, which is consistent with the literature [3]. These factors need to be considered when planning prevention and treatment strategies to reduce the incidence and severity of the disease.

Regarding the management of VOD/SOS severity, it is encouraging that the majority of respondents found the EBMT severity criteria easy to use and useful (both for diagnosis and prognosis) in their clinical practice [7, 15]. However, more than one-third of respondents reported starting treatment at an advanced or very advanced stage. This suggests that there are still differences in approaches to assessing and managing disease severity. The development of algorithms to help clinicians make informed decisions about the optimal timing and type of intervention is critical.

Finally, interdisciplinary collaboration is essential for effective management of VOD/SOS [16]. Our findings highlight the need to educate various members of the care team, including nurses, radiologists, intensivists, and hepatologists, in the recognition and management of this complication. A well-coordinated multidisciplinary approach can provide comprehensive and personalized patient management, thereby improving clinical outcomes.

In conclusion, this study provides valuable insights into the challenges and opportunities in the detection and management of VOD/SOS. By addressing the limitations, improving current knowledge and increasing collaboration among healthcare professionals, we can improve early detection, management, and clinical outcomes for patients with this potentially serious complication.

DATA AVAILABILITY

Data sharing is available through the IACH office (info@clinical-hematology.org) and Dr Myriam Labopin (myriam.labopin@upmc.fr).

REFERENCES

1. Vythoulkas D, Tsirigotis P, Griniezaki M, Konstantellos I, Lazana I. Endothelial dysfunction syndromes after allogeneic stem cell transplantation. Cancers (Basel). 2023;15:680.
2. Corbacioglu S, Jabbour EJ, Mohty M. Risk factors for development of and progression of hepatic veno-occlusive disease/sinusoidal obstruction syndrome. Biol Blood Marrow Transplant. 2019;25:1271–80.
3. Marcoux C, Saliba RM, Wallis W, Khazal S, Ragoonanan D, Rondon G, et al. Incidence and risk factors of early onset VOD/SOS differ in younger vs older adults after stem cell transplantation. Blood Adv. 2024;8:1128–36.
4. 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.
5. Corbacioglu S, Topaloglu O, Aggarwal S. A systematic review and meta-analysis of studies of defibrotide prophylaxis for veno-occlusive disease/sinusoidal obstruction syndrome. Clin Drug Investig. 2022;42:465–76.
6. 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.
7. Mohty M, Malard F, Alaskar AS, Aljurf M, Arat M, Bader P, et al. Diagnosis and severity criteria for sinusoidal obstruction syndrome/veno-occlusive disease in adult patients: a refined classification from the European society for blood and marrow transplantation (EBMT). Bone Marrow Transplant. 2023;58:749–54.
8. Ichikawa H, Yakushijin K, Kurata K, Tsuji T, Takemoto N, Joyce M, et al. Utility of the refined EBMT diagnostic and severity criteria 2023 for sinusoidal obstruction syndrome/veno-occlusive disease. Bone Marrow Transplant. 2024;59:518–25.
9. Cairo MS, Cooke KR, Lazarus HM, Chao N. Modified diagnostic criteria, grading classification and newly elucidated pathophysiology of hepatic SOS/VOD after haematopoietic cell transplantation. Br J Haematol. 2020;190:822–36.
10. Dignan FL, Wynn RF, Hadzic N, Karani J, Quaglia 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.
11. 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;127:1656–65.
12. Nauffal M, Kim HT, Richardson PG, Soiffer RJ, Antin JH, Cutler C, et al. Defibrotide: real-world management of veno-occlusive disease/sinusoidal obstructive syndrome after stem cell transplant. Blood Adv. 2022;6:181–8.
13. 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.
14. Mohty M, Malard F, Abecassis M, Aerts E, Alaskar AS, Aljurf M, et al. Revised diagnosis and severity criteria for sinusoidal obstruction syndrome/veno-occlusive disease in adult patients: a new classification from the European Society for Blood and Marrow Transplantation. Bone Marrow Transplant. 2016;51:906–12.
15. Bonifazi F, Barbato F, Ravaioli F, Sessa M, Defrancesco I, Arpinati M, et al. Diagnosis and treatment of VOD/SOS after allogeneic hematopoietic stem cell transplantation. Front Immunol. 2020;11:489.
16. Wallhult E, Kenyon M, Liptrott S, Mank A, Ní Chonghaile M, Babic A, et al. Management of veno-occlusive disease: the multidisciplinary approach to care. Eur J Haematol. 2017;98:322–9.

AUTHOR CONTRIBUTIONS

MM and ML conceived and designed the study. All authors collected the data. MM and ML analyzed the data. MM and ML wrote the manuscript. All authors critically revised and approved the final manuscript. MM is the guarantors of the study, had full access to all the data, and took responsibility for the integrity of the data and the accuracy of the data analysis.

COMPETING INTERESTS

Ahmed Alaskar: Received honoraria/consultancy fees: Novartis, Abbvie, Janssen, Takeda, Kyowa Kirin, Gilead, Roche, Sanofi. Participated in company sponsored speakers bureau: Janssen, Kyowa Kirin, Sanofi. Michelle Kenyon: Received honoraria/consultancy fees: Jazz Pharmaceuticals, Sanofi, Roche, Mallinkrodt, Vertex. Speakers bureau: Jazz Pharmaceuticals, Sanofi, Pfizer.

ETHICS APPROVAL

The IACH steering committee (www.iach.org) approved the conduct of this survey according to standard professional practices.

ADDITIONAL INFORMATION

Supplementary information The online version contains Supplementary Material available at https://doi.org/10.1038/s41409-024-02434-9.

Correspondence and requests for materials should be addressed to Marion Larue.

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