Article:
Clark, A., Kenyon, M., Pagliuca, A. et al. (3 more authors) (2025) Results from a UK consensus via Delphi on practical considerations surrounding risk assessment and patient monitoring for a prompt diagnosis of severe veno-occlusive disease (VOD) in adults post-HSCT. eJHaem, 6 (5). e70143. ISSN: 2688-6146

https://doi.org/10.1002/jha2.70143

eJHaem

eJHaem | British Society for Haematology

RESEARCH ARTICLE OPEN ACCESS

Results From a UK Consensus via Delphi on Practical Considerations Surrounding Risk Assessment and Patient Monitoring for a Prompt Diagnosis of Severe Veno-Occlusive Disease (VOD) in Adults Post-HSCT

A. Clark[1] | M. Kenyon[2] | A. Pagliuca[2] | R. Shah[3] | E. Tholouli[4] | J. A. Snowden[5]

[1]Queen Elizabeth University Hospital, Glasgow, UK | [2]Kings College Hospital NHS Foundation Trust, London, UK | [3]University College London Hospitals NHS Trust, London, UK | [4]Manchester Royal Infirmary, Manchester University NHS Foundation Trust, Manchester, UK | [5]Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK

Correspondence: A. Clark (andrew.clark12@nhs.scot)

Received: 19 March 2025 | **Accepted:** 26 August 2025

Funding: The study was initiated and funded by Jazz Pharmaceuticals.

Keywords: Delphi consensus | patient monitoring | risk assessment | stem cell transplantation | sinusoidal obstruction syndrome | veno-occlusive disease

ABSTRACT

Introduction: Veno-occlusive disease (VOD) is a life-threatening complication of haematopoietic stem cell transplantation (HSCT). The diagnosis remains challenging, with under recognition of the initial signs and symptoms potentially resulting in delayed diagnoses. The aim of this Delphi study is to establish a consensus regarding the optimal risk assessment and onward care of patients with VOD.

Methods: The process employed a modified Delphi methodology. A steering group of six VOD experts working in the United Kingdom attended a virtual meeting in September 2023, developed 44 statements for testing. Respondents were offered a four-point Likert scale to indicate their level of agreement with each statement.

Results: A total of 70 responses were received from healthcare providers working in the area of haematology and oncology in the United Kingdom. All statements achieved consensus. Overall, 82% of statements achieved ≥ 90% ($n = 36/44$), and 18% achieved ≥ 75% agreement ($n = 8/44$).

Conclusion: This modified Delphi process achieved consensus across all statements, allowing for a set of recommendations to be developed to support a consistent approach across the United Kingdom for the risk assessment and patient monitoring procedures for VOD post-HSCT.

Trial Registration: The authors have confirmed clinical trial registration is not needed for this submission.

1 | Introduction

Veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS), is a life-threatening complication of haematopoietic stem cell transplantation (HSCT) [1, 2]. The prevalence of the condition varies from 3% to 5% in adults aged > 25 years [1, 2].

There are several risk factors associated with VOD, and the presence of two is considered an indication of increased risk of VOD

development which requires vigilance and prompt management [2, 3]. Yoon et al. found that amongst 203 patients, very severe VOD was associated with a significantly lower overall survival (OS) than lower severity cases (58.6% vs. 89.3%, $p < 0.0001$) and a higher Day +100 transplant-related mortality (36.7% vs. 8.3% in mild, 8.0% in moderate and 2.7% in severe) ($p < 0.0001$) [4]. An analysis of the European Society for Blood and Marrow Transplantation (EBMT) database suggests that mortality rates due to VOD are underreported, and around 30% of post-transplant deaths attributed to multi-organ failure (MOF) of unknown origin may be due to VOD [5].

The development of VOD involves activation of sinusoidal endothelial cells and damage to hepatocytes [1, 2]. Sinusoidal endothelial cells swell, resulting in damage to the sinusoidal barrier. Blood cells are then able to infiltrate gaps formed in the sinusoidal barrier, leading to further damage of the endothelial lining [2]. Progressive narrowing of the venous lumen leads to a reduction of sinusoidal venous outflow and subsequent post-sinusoidal portal hypertension. As a consequence, ascites, weight gain, painful hepatomegaly and jaundice may be observed [1, 2].

Prior to HSCT, patients undergo a conditioning regimen to maximise disease control and assist engraftment, but some regimens may be limited by associated toxicity [6]. In some patients, the use of chemotherapy +/− total body radiation can lead to severe VOD [7]. Severe VOD can lead to multi-organ failure, resulting in increased length of hospitalisation, transfer to intensive care units (ICUs) and is characterised by mortality rate of greater than 80% [1, 2, 7].

Symptoms of VOD typically develop within 3 weeks post-HSCT. However, this varies, and a significant number of cases are considered late-onset, occurring > 21 days post-HSCT [1, 8, 9]. In the United Kingdom, approximately 30% of cases are late onset [8].

Daily monitoring is essential for the prompt identification of VOD from the start of conditioning to at least 21 days post-HSCT [2, 10, 11]. The role of the multidisciplinary team (MDT) in early identification and prompt management is key, although awareness of patients and caregivers also has a significant role to play—particularly in cases of late-onset VOD which may occur after discharge from inpatient care [3, 12].

In practice, the Baltimore or modified Seattle criteria are widely used for the purposes of diagnosis [2, 9]. However, in 2016 the EBMT proposed a set of criteria for diagnosis and grading of the severity of VOD [13]. The limitations of the EBMT criteria have been demonstrated in real-world studies, indicating that patients often did not meet EBMT criteria for VOD and may subsequently remain undiagnosed. In 2023 the EBMT criteria were updated to address the limitations of the 2016 version [2, 5, 8].

Despite these validated criteria, VOD diagnosis remains challenging. In the earlier stages, the disease can manifest subtly, and the presence of other clinical problems, such as sepsis or drug-induced liver injury, can confound early diagnosis. The heterogeneity of clinical manifestations, particularly in late-onset cases, can also complicate diagnosis [5, 8].

A standard approach to risk assessment and monitoring for signs and symptoms of VOD is needed to ensure best-practice care for patients, and a focus on raising the profile of VOD to improve suspicion and early detection amongst both HCPs and patients is needed. To achieve this, the Delphi method was chosen to establish consensus amongst the UK VOD experts regarding current best practice in risk assessment and onward care of patients with VOD, and avoid unwarranted variation in practice.

2 | Methods

The process followed a modified Delphi methodology (Figure 1). In June 2023, a literature review on the topic of VOD was conducted on PubMed and Google Scholar identifying 452 records. After removal of duplicates and screening for relevance to the study objectives, 25 full-text articles were included in the literature review. The findings from this review were used to inform a steering group expert meeting.

The expert steering group composed of four Consultant Haematologists, a Haematology Consultant Nurse and a Lead Haematology Specialist Pharmacist convened in September 2023. The steering group was selected based on location, role, previous publications in the relevant area and clinical experience. The information gathered from the literature review was used to inform the meeting discussion. As part of the discussion, the group agreed on six main domains of focus:

A. Pre-transplant risk assessment of VOD
B. Assessing and diagnosing VOD
C. Monitoring VOD patient
D. Escalation of care
E. Care delivery considerations
F. Other considerations

All domains were discussed in detail, and statements were developed by the steering group working collaboratively. The statements were then independently rated by the group members as either 'accept', 'remove' or 'reword with suggested changes', with acceptance based on a simple majority. This constituted the initial round of consensus.

A four-point Likert survey ('*strongly agree*', '*agree*', '*disagree*' and '*strongly disagree*') was developed and distributed by a third party, M3 Global, to a wider panel for Round 2 of the process. Selection for the survey panel was according to:

- Current role of haematology/oncology consultant, nurse specialist or clinical pharmacist
- Experience in VOD

Panel selection ($N = 70$) was based on the rarity of the condition [7], resource availability, location within the United Kingdom and therapeutic area. Demographic data collected included practicing nation, role, experience with VOD, proportion of the role concerned with autologous versus allogeneic HSCT and the esti-

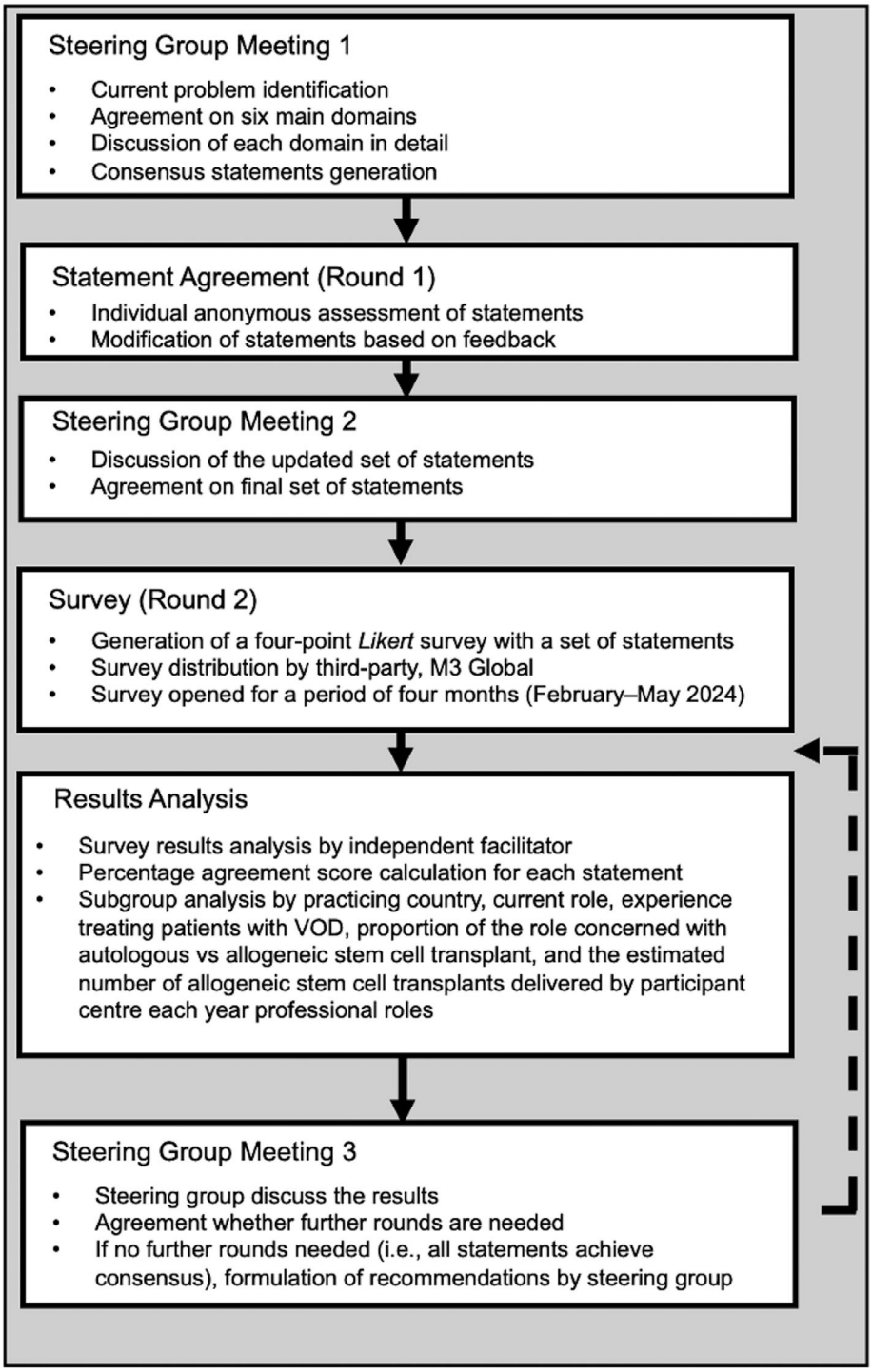

FIGURE 1 | Modified Delphi study design.

mated number of allogeneic HSCT delivered by the participants centre each year.

Stopping criteria were established as 70 responses, 90% of statements achieving consensus and a threshold for consensus set at 75% [14]. A statement of consent was included at the start of the survey. Completed surveys were analysed and responses were aggregated to provide an overall agreement level for each statement.

3 | Results

After review, one statement was removed for duplication, resulting in a final set of 44 statements for testing during Round 2. Completed surveys were received from clinical nurse specialists in haematology/oncology ($n = 30$), clinical pharmacists in haematology/oncology ($n = 20$) and consultant haemato-oncologists ($n = 20$) (Figure S1). Further demographic information can be found in Figures S2–S4.

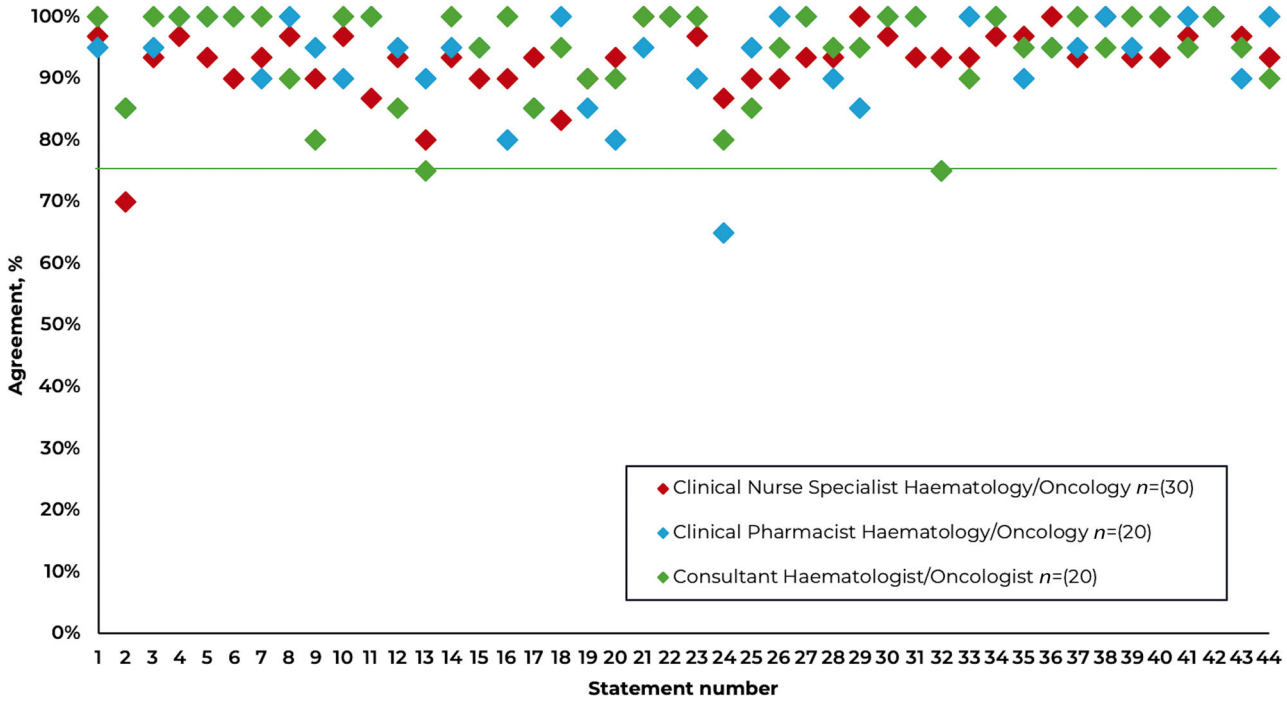

FIGURE 2 | Agreement level according to specialist roles.

At the end of Round 2, all statements achieved consensus, with 36/44 achieving ≥ 90% agreement (Table 1, Figure S4). Figure 2 shows agreement levels by responder role, which indicates that agreement was largely role-agnostic. The steering group agreed upon a set of recommendations based on the achieved consensus.

4 | Discussion

Outside of paediatric medicine, allogeneic transplants are carried out less frequently than autologous transplants. According to British Society of Blood and Marrow Transplantation and Cellular Therapy (BSBMT) data, 1535 allogeneic and 2913 autologous transplants were performed in the United Kingdom in 2022 [15]. The majority of respondents (n = 52) reported working in a centre that delivers more than 50 allogeneic transplants annually, suggesting many respondents were based at larger centres.

A high agreement level for all statements suggests good understanding of the issues covered, which is more likely to be gained at larger centres. In addition, a significant level of experience has been established with severe VOD treatment since defibrotide became available for use in the NHS [7, 16]. However, there are currently no definitive diagnostic tests for VOD, and diagnosis relies on clinical judgement. Therefore, where knowledge and experience of VOD is limited, there is potential for missed diagnosis, resulting in a significant number of patients remaining undiagnosed [5].

4.1 | Pre-HSCT

Prior to HSCT, the level of VOD risk should be established for each patient (S3, 95.7%) to inform the ongoing care plan. To assist the risk-assessment process, a locally agreed standard operating procedure (SOP) should be in place with specific criteria used to determine VOD risk (S6, 95.7%), and should use a validated score such as the Centre for International Blood and Marrow Transplant Research (CIBMTR) Risk Calculator or the Endothelial Activation and Stress Index (EASIX) score (S8, 95.7%; S9, 88.6%). Both are valid, but the EASIX risk score provides an indication of mortality risk and survival outcomes which CIBMTR does not [17, 18]. There was a strong agreement (S10, 95.7%) that local risk-assessment protocols should also be based on the most recent 2023 EBMT risk factor classification [2].

There are some specific risk factors that indicate an elevated risk of VOD, and HCPs need to be aware of these [2, 19]:

- Prior exposure to gemtuzumab ozogamicin, inotuzumab ozogamicin, busulfan or total body irradiation (TBI)
- Existing liver disease
- Previous HSCT transplantation

If a patient is deemed at elevated increased risk of VOD, the transplant team should consider how the protocol might be adapted to mitigate this risk. Although not specifically included in the Delphi consensus statements (and therefore not tested with the wider expert group), the authors suggest that this may primarily include the use of reduced intensity conditioning (RIC), but may also include strict fluid management and prophylactic use of heparin and/or ursodeoxycholic acid, but these decisions should be made by the HSCT team according to individual patient factors. Compared with RIC, patients who undergo myeloablative conditioning (MAC) prior to allogeneic HSCT tend to develop VOD earlier and more often in allogeneic transplant patients (S16,

TABLE 1 | Defined consensus statements and corresponding levels of agreement (all numbers rounded to 1 decimal place).

No.	Statement	Strongly agree	Tend to agree	Tend to disagree	Strongly disagree	Agreement
Domain A: Pre-transplant risk assessment of VOD						
1	VOD is a potentially life-threatening complication of HSCT	61.4%	35.7%	2.9%	0.0%	**97.1%**
2	Once established, VOD is difficult to manage in practice	21.4%	57.1%	21.4%	0.0%	**78.6%**
3	All HSCT patients should be assessed for VOD risk factors	70.0%	25.7%	2.9%	1.4%	**95.7%**
4	The clinical transplant team must be aware of the transplant protocol and the outcome of patient risk assessment	68.6%	30.0%	1.4%	0.0%	**98.6%**
5	During ward rounds, the patient records should be updated with any change in clinical presentation relevant to emergent VOD (weight, poor fluid balance, etc.)	77.1%	20.0%	2.9%	0.0%	**97.1%**
6	Patients deemed to be at increased risk of VOD should receive more frequent monitoring for emergent signs and symptoms	67.1%	28.6%	4.3%	0.0%	**95.7%**
7	A locally agreed standard operating procedure (SOP) should include defined risk score thresholds for use in VOD risk assessment	57.1%	37.1%	5.7%	0.0%	**94.3%**
8	VOD risk assessment should include the use of the online Center for International Blood and Marrow Transplant Research (CIBMTR) Risk Calculator	44.3%	51.4%	4.3%	0.0%	**95.7%**
9	VOD risk assessment should include the use of the Endothelial Activation and Stress Index (EASIX) score	38.6%	50.0%	11.4%	0.0%	**88.6%**
10	VOD risk assessment should be based on EBMT risk factor classification (2023)	54.3%	41.4%	4.3%	0.0%	**95.7%**
11	Patients with specific factors (prior gemtuzumab ozogamicin, inotuzumab ozogamicin, busulfan, treosulfan, liver disease and previous transplantation) should be carefully assessed for VOD risk, including autologous BMT or CAR-T patients	61.4%	32.9%	5.7%	0.0%	**94.3%**
Domain B: Assessing and diagnosing VOD						
12	Fibroscan may be a useful tool but requires all patients to receive a baseline assessment and further assessments at agreed intervals according to risk	42.9%	48.6%	7.1%	1.4%	**91.4%**
13	Trans-jugular liver biopsy is the definitive method for diagnosing VOD	32.9%	48.6%	17.1%	1.4%	**81.4%**
14	Access to ultrasound services, with training in the identification of VOD (using HokUS-10 Scoring as per EBMT 2023), would be beneficial to diagnose VOD	45.7%	50.0%	2.9%	1.4%	**95.7%**
15	Thrombocytopaenia is often found in patients with VOD and treatment of VOD can cause an increase in bleeding risk, subsequently more frequent platelet administration at higher doses than normally expected may be required	41.4%	51.4%	5.7%	1.4%	**92.9%**
16	Myeloablative conditioning (MAC) patients tend to develop VOD earlier than reduced intensity conditioning (RIC) patients	40.0%	50.0%	10.0%	0.0%	**90.0%**
17	Patients being treated via ambulatory care should be continually screened for VOD in the same way as inpatients	37.1%	51.4%	11.4%	0.0%	**88.6%**
18	Patients should be monitored up to Day 21 for classical VOD	45.7%	45.7%	7.1%	1.4%	**91.4%**
19	Patients should be monitored beyond Day 21 for late-onset VOD	31.4%	57.1%	11.4%	0.0%	**88.6%**
20	The absence of elevated bilirubin does not exclude a diagnosis of (anicteric) VOD	30.0%	58.6%	11.4%	0.0%	**88.6%**
21	Patient management protocols should be audited regularly and updated as necessary to optimise patient outcome	35.7%	62.9%	1.4%	0.0%	**98.6%**

(Continues)

TABLE 1 | (Continued)

No.	Statement	Strongly agree	Tend to agree	Tend to disagree	Strongly disagree	Agreement
22	Transplant protocols should be adapted for high-risk patients	48.6%	51.4%	0.0%	0.0%	**100.0%**
Domain C: Monitoring VOD patient						
23	Patients with severe VOD should remain as an inpatient until sufficient resolution of signs and symptoms permits careful individualised discharge planning and close monitoring as an outpatient	55.7%	40.0%	4.3%	0.0%	**95.7%**
24	Ambulatory care is not recommended in patients at high-risk of VOD	32.9%	45.7%	17.1%	4.3%	**78.6%**
25	Patients who are being treated via ambulatory care (e.g., once discharged, as an outpatient, and not at high risk) should continually be screened for VOD	34.3%	55.7%	7.1%	2.9%	**90.0%**
26	Patients suspected/diagnosed with VOD should be admitted to hospital, if not already inpatients	58.6%	35.7%	4.3%	1.4%	**94.3%**
27	Proformas should be used to standardise how (and what is) assessed for VOD risk, agnostic of care setting	44.3%	52.9%	2.9%	0.0%	**97.1%**
28	Proformas should be used to standardise how (and what is) monitored once VOD is diagnosed, agnostic of care setting	47.1%	45.7%	7.1%	0.0%	**92.9%**
29	Critical care support is often required to address the complications of VOD in collaboration with the appropriate specialist care team	51.4%	42.9%	5.7%	0.0%	**94.3%**
Domain D: Escalation of care						
30	Weight gain, ascites, right upper quadrant pain, elevated liver enzymes, elevated bilirubin, platelet refractoriness, are all indicators of VOD and the presence of more than one of these may require an escalation of care for VOD	57.1%	41.4%	1.4%	0.0%	**98.6%**
31	Timings of presentation of signs and symptoms should also be recorded and assessed	64.3%	32.9%	2.9%	0.0%	**97.1%**
32	National Early Warning Score (NEWS) is useful for VOD detection and escalation of care	35.7%	47.1%	15.7%	1.4%	**82.9%**
33	Patients should be educated about their risk of VOD and how to take their own measurements	58.6%	35.7%	5.7%	0.0%	**94.3%**
34	Patients educated about their risk of VOD should liaise with their dedicated nurse specialist to discuss concerns	61.4%	37.1%	1.4%	0.0%	**98.6%**
Domain E: Care delivery considerations						
35	Close collaboration with ICU teams is often required to deliver effective care for severe VOD	58.6%	35.7%	5.7%	0.0%	**94.3%**
36	Close collaboration with hepatology, renal medicine and other teams is required to deliver effective care for VOD	57.1%	40.0%	2.9%	0.0%	**97.1%**
37	Pharmacy should be advised at the earliest opportunity when VOD is suspected or diagnosed	52.9%	42.9%	4.3%	0.0%	**95.7%**
38	Assessing risk, diagnosis and managing VOD patients should be considered at relevant clinical transplant team meetings in the planning phases of transplant and following commencement of the transplant procedure	64.3%	34.3%	1.4%	0.0%	**98.6%**
39	Assessing the risk of and managing diagnosed VOD patients should be considered daily (to ensure earliest recognition)	58.6%	37.1%	2.9%	1.4%	**95.7%**
Domain F: Other considerations						
40	Radiology liaison colleagues with expertise in VOD would be beneficial	42.9%	54.3%	1.4%	1.4%	**97.1%**

(Continues)

TABLE 1 | (Continued)

No.	Statement	Strongly agree	Tend to agree	Tend to disagree	Strongly disagree	Agreement
41	Training should be provided to the extended staff team (nurses, pharmacy) about the risk of VOD	65.7%	31.4%	2.9%	0.0%	**97.1%**
42	Improving awareness and education of assessing, stratifying and managing VOD with the wider-care team would be beneficial	60.0%	40.0%	0.0%	0.0%	**100.0%**
43	A VOD registry would be useful in quality improvement and research to optimise management of VOD	64.3%	30.0%	5.7%	0.0%	**94.3%**
44	The role of clinical biomarkers in VOD risk assessment, diagnosis and response to treatment should be further evaluated	55.7%	38.6%	4.3%	1.4%	**94.3%**

90.0%). Therefore, pre-transplant conditioning regimen should be considered in risk management [20].

4.2 | Post-Transplant Monitoring and Subsequent VOD Diagnosis

The overarching principle for early diagnosis is one of vigilance by the entire MDT, and all professionals working with HSCT patients require education to recognise the early signs of VOD and escalate care accordingly (S30, 98.6%). A dedicated nursing monitoring protocol has been previously recommended [10].

Post-HSCT, regular monitoring of patients (and subsequent update of patient records) should be standard practice to facilitate continuity of care and detection of emergent VOD. Patient weight, fluid balance/ascites and tender hepatomegaly are classic signs of VOD which should be clearly specified in monitoring protocols (S5, 97.1%) [2, 10, 11].

Although invasive, trans-jugular liver biopsy and haemodynamic studies are definitive diagnostic methods (S13, 81.4%). However, standard ultrasound imaging might be helpful in identifying abnormalities in blood flow [21, 22]. Liver stiffness measurements through two-dimensional shear wave elastography and transient elastography may be useful (S12, 91.4%). Both are non-invasive and accurate but may not be suitable for those with ascites, or who are morbidly obese or who have large amounts of chest wall fat [22]. The Hokkaido US-based scoring system (HokUS-10) defines 10 parameters which can be assessed during ultrasound examination, and it's use can be important in predicting patient outcomes post-HSCT (S14, 95.7%) [21].

In the absence of elevated bilirubin (anicteric VOD), diagnosis can be made using EBMT or modified Seattle criteria. Whilst anicteric VOD is characterised by better patient outcomes, it is more likely to remain undiagnosed and consequently progress to severe VOD, it is important that HSCT care teams are educated regarding anicteric VOD [23]. In addition, patients should be continuously monitored regardless of care setting for > 21 days to detect potential late onset VOD (S17, 88.6%; S18, 91.4%; S19, 88.6%) [24].

4.3 | Post-Diagnosis Monitoring of VOD Patients

Once VOD has been confirmed, patients should be managed via MDT to enable implementation of comprehensive patient management protocols [25] which should be audited and updated regularly to ensure that best practice is reflected (S21, 98.6%) [2, 10, 11].

In many cases, mild VOD can resolve with supportive care only, but progression to more severe forms of the disease require immediate initiation of treatment, and potential provision of intensive care protocols (S26, 94.3%) [26, 27]. As the only licensed agent, defibrotide should be initiated upon diagnosis of severe VOD. In addition, results from the treatment-IND study showed higher Day +100 overall survival rates associated with early initiation of defibrotide, supporting immediate administration upon diagnosis of severe disease [28]. Severe VOD patients should be treated in an in-hospital setting until sufficient resolution of signs and symptoms. Where VOD is non-severe, supportive care should be implemented which includes not only daily assessment of symptoms and risk factors but also therapeutic interventions to manage pain and discomfort [27].

When combined into a comprehensive service, elements of care such as access to intensive care, a multidisciplinary approach to patient care, diligent risk assessment and earlier initiation of treatment can help to minimise VOD-associated mortality [27].

4.4 | Escalation of Care

Both patients and HCPs should understand the major signs and symptoms associated with VOD and that the presence of more than one may require an escalation of care (S30, 98.6%; S31, 97.1%; S33, 94.3%) [1, 2]. In addition, patients and caregivers should receive personalised education on VOD prior to HSCT and provided with a named dedicated nurse specialist to discuss any concerns (S34, 98.6%). Botti et al. suggests use of a traffic light monitoring guide to assist identification of possible symptoms of VOD [12]. As the HCP role most often in contact with the patient, nurses should regularly check fluid

intake, weight and be alert for incidence of abdominal discomfort and pain [29].

The National Early Warning Score (NEWS) is used to identify and respond to patients at risk of deteriorating [30]. In retrospect, S32 may have been better worded, NEWS is intended for detection of deterioration in individuals which may be due to VOD, but cannot be used to detect/diagnose VOD. Additional parameters should supplement NEWS, such as weight-gain, ascites and abdominal circumference to support differential diagnosis of VOD [27].

4.5 | Delivery of Care and Other Considerations

Statements 35–39 (94.3%–98.6%) align with Joint Accreditation Committee International Society for Cell & Gene Therapy (ISCT)-Europe & EBMT (JACIE) accredited services. In the United Kingdom, all interventions involved in HSCT must conform to Human Tissue Authority requirements and meet JACIE standards. The NHS recommends each centre has a local SOP in place, and principles of collaborative working should be formally included [7].

A named radiology liaison colleague with expertise in VOD would be beneficial for delivery and reporting of imaging findings (S40, 97.1%). Chan et al. [31], provides a comprehensive review of the use of imaging in VOD, with parameters for common grading criteria.

Agreement for statements 41 and 42 (S41,97.1%; S42,100.0%, respectively) emphasises the perceived need for increased awareness and training on patient assessment, stratification and management among the wider care team, to promote vigilance and early intervention when VOD is suspected [3, 10, 12, 13, 32].

A national VOD registry would support quality improvement and research to optimise management of VOD, this should include relevant biomarkers (S43, 94.3%). On this point, the role of clinical biomarkers in VOD requires further research (S44, 94.3%), as currently none are validated [27]. Identification of biomarkers would help to improve detection and diagnosis of VOD [13].

5 | Strengths and Limitations

The strength of this study is the high level of agreement demonstrated by healthcare professionals of different roles across all statements. Respondents clearly recognise and agree with the steering group proposed statements, however, high agreement may indicate a lack of challenge or a bias towards agreeability. Given the recognised low levels of general awareness surrounding VOD, the steering group wished to establish the key principles and agree a set of statements that can be used to inform practice.

According to the BSBMT data, there were two centres that performed over 100 allogeneic HSCTs in 2022, and three centres reported performing ≥ 80. The number of responders reporting this level of activity may indicate the inclusion of groups of responders from larger centres, which might introduce a bias towards practices in these centres. Equally, responder reported activity levels (Figure S3) may be inaccurate. Therefore, the uneven distribution of specialists poses a potential limitation for the interpretation of results. In addition, the Round 2 survey did not assess whether the centres have access to some of the resources suggested as best practice (e.g., monitoring tools, HOKUS-10 trained radiographers). In retrospect, this could have been applied as part of the respondents inclusion criteria, however, given that most respondents appeared to be based at larger centres, it is reasonable to assume they had access to such resource.

6 | Recommendations

Based on the survey results and subsequent discussions within the steering group, the authors propose the following recommendations for achieving rapid diagnosis of severe VOD post-HSCT.

1. Pre-transplant
   i. A locally agreed standard operating procedure (SOP) should be in place for VOD risk assessment, diagnosis and management
   ii. All patients should be assessed for VOD risk factors prior to HSCT, risk assessment should be based on the latest EBMT criteria and include a validated score such as CIBMTR or EASIX as locally agreed
   iii. Patients with specific factors (including autologous BMT or CAR-T patients) require careful assessment of VOD risk such as prior gemtuzumab ozogamicin, inotuzumab ozogamicin, busulfan, total body irradiation, liver disease and previous transplantation
   iv. Patients identified at being at an elevated risk of VOD should be flagged for appropriate close monitoring post-transplant
   v. Transplant protocols should be adapted for high-risk patients according to clinical risk
   vi. All HSCT patients should receive education on VOD prior to transplant, this should be tailored to the individual's level of risk
2. Post-transplant monitoring for VOD
   i. All allogeneic HSCT patients should be formally monitored up to Day +21 (for classical VOD) and beyond Day +21 (for late-onset VOD) post-HSCT, regardless of care setting
   ii. A minimum dataset for clinical parameters and biochemical data should be agreed locally and a common proforma/template developed for use by the care team
   iii. Precise timing of presentation of any signs or symptoms of VOD is critical, and should be included in the monitoring proforma/template
   iv. Ambulatory patients should be empowered to recognise and report any signs or symptoms indicative of late-onset VOD
   v. All care staff should maintain a high-suspicion of VOD, with particular attention to weight gain, hyperbilirubinemia, hepatomegaly or ascites
3. Diagnosis of VOD

i. If there is a clinical suspicion of VOD, supportive care to manage symptoms should be implemented immediately while diagnosis is confirmed
ii. The Seattle, Baltimore and EBMT (where possible, EBMT criteria should be used primarily) diagnostic criteria should be applied in combination and according to locally agreed protocol when considering a diagnosis of VOD
iii. Radiology liaison colleagues with experience of VOD should be in place to support the diagnostic process
iv. Access to ultrasound services, with training in the identification of VOD (using HokUS-10 Scoring as per EBMT 2023) is recommended
v. The absence of elevated bilirubin does not exclude the potential presence of anicteric VOD

4. Escalation of care
   i. Ambulatory patients with suspicion of or confirmed VOD should be admitted to the hospital for escalation of care and monitoring
   ii. Weight gain, ascites, right upper quadrant pain, elevated liver enzymes, elevated bilirubin and platelet refractoriness are all indicators of VOD, and the presence of more than one of these requires immediate diagnostic investigation and implementation of supportive care for VOD
   iii. National Early Warning Score is useful for determining patients who are deteriorating
   iv. Access to critical or intensive care support may be required for severe VOD, the appropriate specialist team should be consulted at the earliest opportunity to ensure measures are in place to provide required levels of care

This modified Delphi exercise was able to achieve consensus from a panel of 70 HCPs currently involved in management of patients with VOD for all statements. This allowed for the formulation of a set of recommendations, the implementation of which in practice could support a consistent approach across the United Kingdom for risk assessment and patient monitoring in post-HSCT VOD.

Author Contributions

A. Clark, M. Kenyon, A. Pagliuca, R. Shah, E. Tholouli and J. Snowden acted as the steering group for this study, developed and reviewed initial statements, contributed to the analysis and discussion of results equally and reviewed, edited and approved the final manuscript. All authors developed the initial statements, contributed to the analysis and discussion of results equally, and read and approved the final manuscript.

Acknowledgements

The authors wish to thank Tim Warren and Ian Walker from Triducive Partners Limited (funded by Jazz Pharmaceuticals) for their support in collating the data, analysing the results, writing the manuscript and reviewing the final draft. All steering group members received honoraria from Jazz Pharmaceuticals for their input during the steering group meetings. Triducive Partners Limited facilitated the project and analysed the responses to the consensus statements in line with the Delphi methodology; these activities were funded by Jazz Pharmaceuticals. Jazz Pharmaceuticals had no input into the design or development of the study or draft manuscript. Jazz Pharmaceuticals were allowed a courtesy review of the manuscript; the final manuscript content and decision to submit for publication was controlled independently by the authors.

Ethics Statement

The authors have nothing to report.

Consent

The authors have nothing to report.

Conflicts of Interest

E. Tholouli declares advisory board and speaker fees from Astellas, Autolus, Janssen, Jazz Pharmaceuticals, Kite/Gilead, Pfizer, SOBI, Takeda and Vertex. R. Shah declares advisory board and speaker fees Abbvie Pharmaceuticals, Janssen, Jazz Pharmaceuticals Kite/Gilead, Medac, Novartis Pharmaceuticals, Pfizer, Roche and SERB. M. Kenyon declares honoraria and consultancy/speaker fees for Jazz Pharmaceuticals, Mallinckrodt, Pfizer, Sanofi, Roche and Vertex. A.P. declares advisory board and speaker fees from Jazz Pharmaceuticals. J. A. Snowden declares honoraria for scientific advisory boards for BMS, Medac, Vertex and remunerated membership of an Independent Drug Monitoring Committee for a Kiadis Pharma Clinical Trial in the last 3 years. This work is not linked to EBMT, BSBMTCT or NHS England. All authors received honoraria from Jazz Pharmaceuticals while undertaking this study. Jazz Pharmaceuticals commissioned Triducive Partners Limited to facilitate the project and analyse the responses to the consensus statements in line with the Delphi methodology.

Data Availability Statement

Data are available upon written request from Triducive Partners Ltd.

References

1. C. Marcoux, R. M. Saliba, W. Wallis, et al., "Incidence and Risk Factors of Early Onset VOD/SOS Differ in Younger vs Older Adults After Stem Cell Transplantation," *Blood Advances* 8 (2024): 1128–1136.

2. M. Mohty, F. Malard, A. S. Alaskar, 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 Transplantation* 58, no. 7 (2023): 749–754, https://doi.org/10.1038/s41409-023-01992-8.

3. E. Wallhult, M. Kenyon, S. Liptrott, et al., "Management of Veno-Occlusive Disease: The Multidisciplinary Approach to Care," *European Journal of Haematology* 98, no. 4 (2017): 322–329, https://doi.org/10.1111/ejh.12840.

4. J.-H. Yoon, K. H. Yoo, K. W. Sung, et al., "Validation of Treatment Outcomes According to Revised Severity Criteria From European Society for Blood and Marrow Transplantation (EBMT) for Sinusoidal Obstruction Syndrome/Veno-Occlusive Disease (SOS/VOD)," *Bone Marrow Transplantation* 54 (2019): 1361–1368.

5. A. H. Bazarbachi, R. Al Hamed, M. Labopin, et al., "Underdiagnosed Veno-Occlusive Disease/Sinusoidal Obstruction Syndrome (VOD/SOS) as a Major Cause of Multi-Organ Failure in Acute Leukemia Transplant Patients: An Analysis From the EBMT Acute Leukemia Working Party," *Blood* 134 (2019): 4483–4483.

6. M. Gooptu, H. T. Kim, V. T. Ho, et al., "A Comparison of the Myeloablative Conditioning Regimen Fludarabine/Busulfan With Cyclophosphamide/Total Body Irradiation, for Allogeneic Stem Cell Transplantation in the Modern Era: A Cohort Analysis," *Biology of Blood and Marrow Transplantation* 24 (2018): 1733–1740.

7. "Clinical Commissioning Policy (Revised) Use of Defibrotide in Severe Veno-Occlusive Disease Following Stem Cell Transplant (All Ages) [210401P]," NHS England, https://www.england.nhs.uk/wp-

content/uploads/2020/11/Use-of-defibrotide-in-severe-veno-occlusive-disease-following-stem-cell-transplant-all-ages.pdf.

8. V. Mehra, S. Tetlow, A. Choy, et al., "Early and Late-Onset Veno-Occlusive Disease/Sinusoidal Syndrome Post Allogeneic Stem Cell Transplantation—A Real-World UK Experience," *American Journal of Transplantation* 21, no. 2 (2020): 864–869, https://doi.org/10.1111/ajt.16345.

9. S. Corbacioglu, E. J. Jabbour, and M. Mohty, "Risk Factors for Development of and Progression of Hepatic Veno-Occlusive Disease/Sinusoidal Obstruction Syndrome," *Biology of Blood and Marrow Transplantation* 25 (2019): 1271–1280.

10. F. Bonifazi, S. Sica, A. Angeletti, et al., "Veno-Occlusive Disease in HSCT Patients: Consensus-Based Recommendations for Risk Assessment, Diagnosis, and Management by the GITMO Group," *Transplantation* 105 (2021): 686–694.

11. E. Carreras, C. Dufour, M. Mohty, and N. Kröger, The EBMT Handbook*: Hematopoietic Stem Cell Transplantation and Cellular Therapies* (Springer Nature, 2020).

12. S. Botti, I. Agreiter, L. Orlando, et al., "Nursing Role in the Assessment and Care of Hepatic Sinusoidal Obstruction Syndrome Patients: A Consensus Paper by the "Gruppo Italiano Trapianto di Midollo Osseo"," *Supportive Care in Cancer* 28 (2020): 5125–5137.

13. M. Mohty, F. Malard, M. Abecassis, 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 Transplantation* 51 (2016): 906–912.

14. I. R. Diamond, R. C. Grant, B. M. Feldman, et al., "Defining Consensus: A Systematic Review Recommends Methodologic Criteria for Reporting of Delphi Studies," *Journal of Clinical Epidemiology* 67 (2014): 401–409.

15. "2022 UK & ROI Transplant Activity Table By Disease," British Society of Blood and Marrow Transplantation and Cellular Therapy, accessed June 24, 2024, https://bsbmtct.org/activity/2022/.

16. F. L. Dignan, R. F. Wynn, N. Hadzic, et al., "BCSH / BSBMT Guideline: Diagnosis and Management of Veno-Occlusive Disease (Sinusoidal Obstruction Syndrome) Following Haematopoietic Stem Cell Transplantation," *British Journal of Haematology* 163 (2013): 444–457.

17. C. Strouse, Y. Zhang, M.-J. Zhang, et al., "Risk Score for the Development of Veno-Occlusive Disease After Allogeneic Hematopoietic Cell Transplant," *Biology of Blood and Marrow Transplantation* 24 (2018): 2072–2080.

18. S. Jiang, O. Penack, T. Terzer, et al., "Predicting Sinusoidal Obstruction Syndrome After Allogeneic Stem Cell Transplantation With the EASIX Biomarker Panel," *Haematologica* 106 (2020): 446.

19. J. Kloehn, G. Brodt, J. Ernst, and B. Gruhn, "Analysis of Risk Factors for Hepatic Sinusoidal Obstruction Syndrome Following Allogeneic Hematopoietic Stem Cell Transplantation in Pediatric Patients," *Journal of Cancer Research and Clinical Oncology* 148 (2022): 1447–1455.

20. S. Corbacioglu, E. Carreras, M. Ansari, 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 Transplantation* 53 (2018): 138–145.

21. S. Shiratori, K. Okada, J. Sugita, et al., "HokUS-10 Scoring System Predicts the Treatment Outcome for Sinusoidal Obstruction Syndrome After Allogeneic Hematopoietic Stem Cell Transplantation," *Scientific Reports* 13, no. 1 (2023): 17374, https://doi.org/10.1038/s41598-023-43806-3.

22. L. Lazzari, P. Marra, R. Greco, et al., "Ultrasound Elastography Techniques for Diagnosis and Follow-Up of Hepatic Veno-Occlusive Disease," *Bone Marrow Transplantation* 54 (2019): 1145–1147, https://doi.org/10.1038/s41409-019-0432-5.

23. J. Naples, M. Skeens, and R. Bajwa, "Anicteric Hepatic Veno-Occlusive Disease After Hematopoietic Stem Cell Transplantation in Children," *Blood* 124 (2014): 5849.

24. M. Mohty, F. Malard, M. Abecasis, et al., "Prophylactic, Preemptive, and Curative Treatment for Sinusoidal Obstruction Syndrome/Veno-Occlusive Disease in Adult Patients: A Position Statement From an International Expert Group," *Bone Marrow Transplantation* 55 (2020): 485–495.

25. K. L. Mangada, J. Moffet, M. Nishitani, S. Albuquerque, and C. N. Duncan, "Interprofessional Team-Based Care of the Hematopoietic Cell Transplantation Patient With Hepatic Veno-Occlusive Disease/Sinusoidal Obstruction Syndrome," *Journal of Pediatric Hematology/Oncology* 45 (2023): 12–17.

26. P. Tewari, W. Wallis, and P. Kebriaei, "Manifestations and Management of Veno-Occlusive Disease/Sinusoidal Obstruction Syndrome in the Era of Contemporary Therapies," *Clinical Advances in Hematology & Oncology* 15, no. 2 (2017): 130–139.

27. F. Bonifazi, F. Barbato, F. Ravaioli, et al., "Diagnosis and Treatment of VOD/SOS After Allogeneic Hematopoietic Stem Cell Transplantation," *Frontiers in Immunology* 11 (2020): 489, https://doi.org/10.3389/fimmu.2020.00489.

28. N. A. Kernan, S. Grupp, A. R. Smith, et al., "Final Results From a Defibrotide Treatment-IND Study for Patients With Hepatic Veno-Occlusive Disease/Sinusoidal Obstruction Syndrome," *British Journal of Haematology* 181 (2018): 816–827.

29. M. Mohty, F. Malard, M. Abecassis, 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 Transplantation* 50, no. 6 (2015): 781–789, https://doi.org/10.1038/bmt.2015.52.

30. "Resources to Support the Adoption of the National Early Warning Score," Royal College of Physicians, 2019, https://www.england.nhs.uk/wp-content/uploads/2019/12/Resources_to_support_the_adoption_of_NEWSFINAL.pdf.

31. S. S. Chan, A. Colecchia, R. F. Duarte, F. Bonifazi, F. Ravaioli, and J. H. Bourhis, "Imaging in Hepatic Veno-Occlusive Disease/Sinusoidal Obstruction Syndrome," *Biology of Blood and Marrow Transplantation* 26, no. 10 (2020): 1770–1779, https://doi.org/10.1016/j.bbmt.2020.06.016.

32. E. C. Sosa, "Veno-Occlusive Disease in Hematopoietic Stem Cell Transplantation Recipients," *Clinical Journal of Oncology Nursing* 16 (2012): 507–513.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Figure S1: Respondent roles. **Supporting Figure S2:** Proportion of autologous vs allogeneic stem cells transplant carried out. **Supporting Figure S3:** Estimated number of allogeneic stem cell transplants delivered by centre each year. **Supporting Figure S4:** Consensus agreement levels by statement. The threshold for consensus is depicted by the green line (75%). **Supporting Figure S5:** Percentages of agreement level by statement.