ARTICLE

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Diagnostic accuracy of liver stiffness measurement for the diagnosis of veno-occlusive disease/sinusoidal obstruction syndrome after hematopoietic stem cell transplantation (HSCT), the ELASTOVOD STUDY: an investigator-initiated, prospective, multicentre diagnostic clinical trial

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Hepatic Veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) is a severe complication following hematopoietic stem cell transplantation (HSCT), traditionally diagnosed based on clinical criteria. This study aimed to evaluate the diagnostic performance of liver stiffness measurement (LSM) as a non-invasive tool for non invasive diagnosis of VOD/SOS. A multicentre clinical trial was conducted in Italy from April 2018 to December 2021, screening 1089 patients across 25 centers. VOD/SOS diagnosis followed established clinical guidelines, and patients underwent comprehensive clinical, laboratory, and imaging evaluations up to +100 days post-HSCT or until VOD/SOS diagnosis. LSM was measured pre-HSCT and on specific post-transplant days (ClinicalTrials.gov: NCT03426358). The study enrolled 774 adults and 167 children. The +100-day incidence of VOD/SOS HSCT was 5.53 and 5.26 in the overall and allo-HSCT population, higher in children (14.3%) than in adults (3.68%). The 100-day overall survival (OS) probability was 89.5% (overall) and 89.0% (allo-HSCT) while one-yr OS 79% and 78%, respectively, with outcomes varying by VOD/SOS occurrence and severity. LSM significantly differed between VOD/SOS patients and non-affected individuals at all post-HSCT time points, correlating with disease severity. A diagnostic algorithm was proposed, achieving ≥95% sensitivity and specificity, with a 6 kPa rule-out and 25 kPa rule-in cut-off, enhanced by the "three-time pre-HSCT rule." Survivors showed declining LSM over time, while non-survivors did not. Fully recovered patients had lower LSM than non-improvers. LSM also distinguished VOD/SOS from other liver complications within +100 days post-HSCT in both adults and children. In conclusion, LSM is a reliable, non-invasive diagnostic tool for VOD/SOS. LSM contribute to differential diagnosis and to treatment response as well. This study underscores the potential of LSM, combined with multidisciplinary expertise, to guide VOD/SOS diagnosis and management in HSCT patients, improving potentially the clinical outcomes.

HIGHLIGHTS

- A multicentre trial established liver stiffness measurement (LSM) as a reliable tool for diagnosing VOD/SOS after HSCT.
- LSM helps differentiating VOD/SOS from other complications and predicting treatment response.

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INTRODUCTION

Veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS), is a potentially fatal complication after hematopoietic stem cell transplantation (HSCT), high-dose chemotherapy, radiotherapy, or liver transplantation. Less frequently, it can result from ingestion of toxic alkaloids [1]. The reported incidences vary based on diagnostic criteria in HSCT, ranging from 1.8 to 14%, with some studies peaking at 40% [2–5]. These values are primarily

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based on retrospective cohorts, with a lack of prospective studies to determine the true incidence and risk factors of VOD/SOS. Diagnosis of VOD/SOS relies on criteria such as the revised Seattle, Baltimore, and EBMT criteria, predominantly encompassing clinical manifestations like weight gain, painful hepatomegaly, ascites, and elevated bilirubin [6, 7]. Despite the efforts of EBMT to differentiate these criteria in clinical settings for both adults and children, accurate differential diagnosis remains challenging due to overlapping symptoms with other HSCT complications. This can result in either underdiagnosis or treatment delays with detrimental effects on outcomes.

The EBMT grading criteria help physicians making a diagnosis and prompt intervention, particularly when full criteria are unmet, aiming to prevent progression to multi-organ dysfunction (MOD) [8]. From a pathophysiological perspective, VOD/SOS is characterized by post-sinusoidal portal hypertension (PH) resulting from toxic injury induced by the conditioning regimen. Endothelial cell damage in zone 3 of the liver acinus triggered by the conditioning regimen initiates a complex cascade leading to PH [9]. The compromised endothelial layer between sinusoids and the Disse space allows the abnormal passage of red blood cells, white blood cells, and cellular debris, disrupting the thrombo-fibrinolytic balance, which in turn causes embolisation and impediment of hepatic blood flow downstream. This deranged thrombo-fibrinolytic equilibrium ultimately leads to post-sinusoidal portal hypertension, with subsequent activation of stellate cells, fibroblasts, and collagen deposition in the extracellular matrix, culminating in perivenous and parenchymal liver fibrosis [10]. The development of overt PH can manifest clinically as ascites, hepatomegaly, and weight gain, among others. These clinical signs may also be present in conditions such as Graft-versus-Host Disease (GVHD) or infection.

Ultrasound assessment in VOD/SOS diagnosis primarily relies on the evaluation of signs of PH and has been explored extensively in the literature [9, 11–14]. While it can contribute significantly to diagnosis, its utility is often limited by delayed findings (especially Doppler parameters and patency of the paraumbilical vein) and variability due to operator dependence. Moreover, suboptimal sensitivity and specificity hinder the effective utilisation of ultrasonography for accurate and early VOD/SOS diagnosis and prognostication of clinical progression [15]. Invasive measures of PH, such as hepatic venous pressure gradient (HVPG) measurement and liver biopsy, have a narrow role due to their invasiveness, which implies the need of well trained multidisciplinary expertise to limit the harm of such procedures, emphasizing the ongoing need for precise non-invasive diagnostic tools for VOD/SOS [16]. Liver stiffness measurement (LSM) has emerged as a non-invasive technique for staging liver fibrosis in chronic liver diseases [17]. However, alterations in liver stiffness can occur in conditions beyond fibrosis, such as congestion, PH, necrosis, or cholestasis [18]. LSM is highly correlated with HVPG and is useful in measuring portal hypertension complications [19]. Notably, in the latest Consensus on Portal Hypertension (Baveno VII), LSM has been suggested to replace HVPG in clinical practice [20]. Since VOD causes PH, we aimed to prospectively investigate the diagnostic role of LSM, assessed by elastographic methods, in SOS/VOD among HSCT patients.

MATERIAL AND METHODS

Patients and study design

The ELASTOVOD/SOS study was a pragmatic, investigator-initiated, prospective diagnostic clinical trial run in 25 HSCT programs in Italy. The trial design was approved by the Central Emilia Wide Area Ethical Committee of the Emilia-Romagna Region (CE-AVEC) with protocol number **95/2017/U/Sper** and by all local ethics committees of the participating centers. All patients provided written informed consent. The study was done in accordance with the Declaration of Helsinki and Good Clinical Practice principles. The study is registered with ClinicalTrials.gov (NCT03426358).

Inclusion criteria were any haematological diseases requiring either allogeneic or autologous hematopoietic stem cell transplantation (HSCT), age between 3 and 70. Patients with grade III obesity (BMI > 40 kg/m^2), presence of either implantable cardioverter-defibrillator or pacemaker, or ascites at pre-HSCT assessment (due to its possible interference with LSM) were exclusion criteria.

Patients were screened within 30 days before HSCT and monitored until +100 days post-HSCT, with follow-up data collected up to one year for overall survival.

The VOD/SOS diagnosis was performed by each treating physician according to the local institutional policy, following defined clinical diagnostic criteria, such as the modified Seattle Criteria [21], Baltimore Criteria [22] and the EBMT diagnostic criteria, both for paediatric and adult patients [2, 5]. VOD/SOS grading was defined in accordance with EBMT criteria for severity grading [2, 5] and reported by all investigators, independently of the diagnostic criteria used. Each component of the clinical diagnostic criteria was reported in the electronic case report form (eCRF) and completed by the investigators at each time point and at the diagnosis of VOD/SOS. Abdominal ultrasound has been performed whenever clinically required, as well as for differential diagnosis between VOD/SOS and other hepatobiliary complications. During the baseline pre-HSCT assessment, a clinical evaluation including patient characteristics (demographic, hematopoietic cell transplantation-specific comorbidity index [HCT-CI Sorror], history of liver disease and blood transfusion history), transplant characteristics (transplant indication, type of HSCT, disease phase, pre-HSCT disease status, stem cell sources, conditioning drugs, GVHD and VOD/SOS prophylaxis) and the European Group for Blood and Marrow Transplantation (EBMT) risk factors assessment [2, 5]. Before HSCT, all patients underwent a gray-scale and Color-Doppler ultrasound, as well as an LSM evaluation (T0). During the follow-up period after HSCT, patients were monitored until +100 day for VOD/SOS and for other complication occurrence, thereafter overall survival data were recorded; any complications that occurred during the follow-up time were recorded, and their severity was graded based on the Common Terminology Criteria for Adverse Events (CTC AE) version 4 [23]. Study findings were reported based on the STARD Statement [24].

Liver stiffness measurement (LSM)

LSM was obtained using either vibration-controlled transient elastography (VCTE; FibroScan, Echosens, France) or point shear wave elastography (p-SWE) or two-dimensional shear wave elastography (2D-SWE). LSM was recorded in kilopascals (kPa) or meter to second (m/sec), accordingly. Generally, LSM values were measured after 4 h of fasting, as previously reported [25]. LSM was performed by expert physicians with experience in

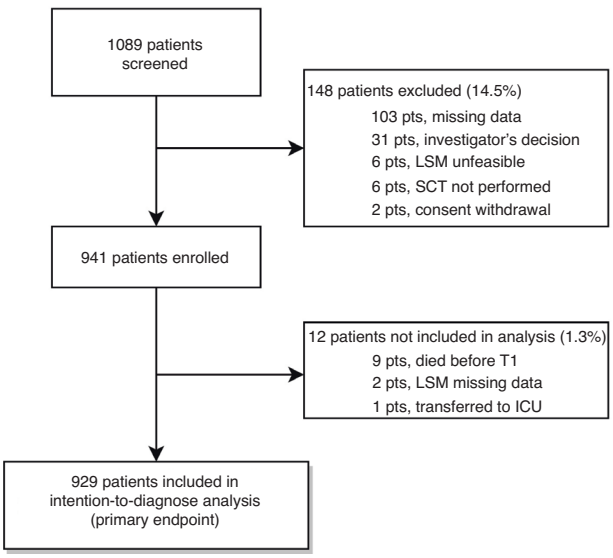


Fig. 1 CONSORT flow diagram of the ELASTOVOD study. The CONSORT diagram illustrates the number of patients assessed for eligibility, enrolled, randomized, and included in the final analysis. ICU intensive care unit, LSM liver stiffness measurement, pts patients, SCT stem cell transplantation, T1 time point 1 (+9/10 days).

Table 1. Baseline characteristics of patients enrolled.

Variables	OVERALL $n = 941$	NO SOS/VOD $n = 889$	SOS/VOD $n = 52$	Missing	*p*-value
Patients characteristics					
Age (years)	50 (27–60)	51 (29–61)	20 (12–52)	.	0.0001
Sex					
Male	571 (60.7)	539 (60.6)	32 (61.5)	.	0.896
Female	370 (39.3)	350 (39.4)	20 (38.5)	.	
BMI (kg/m2)	23.7 (20.5–26.9)	23.9 (20.7–26.9)	21.5 (18.2–24.8)	1	0.006
Ethnicity					
White	881 (93.7)	834 (93.9)	47 (90.4)	1	0.773
Asian	19 (2)	18 (2)	1 (1.8)		
Latin-American	20 (2)	18 (2)	2 (3.9)		
Black -African	19 (2)	17 (1.9)	2 (3.9)		
Others	1 (0.3)	1 (0.2)	0		
Lifestyle					
Smokers (yes)	154 (16.4)	152 (17.1)	2 (3.9)	46	0.033
Moderate alcohol (yes)	68 (7.2)	66 (7.4)	2 (3.9)	15	0.387
Regular physical activity (yes)	118 (12.5)	108 (12.2)	10 (19.2)	80	0.325
HCT-CI					
Arrhythmia	32 (3.4)	32 (3.6)	0	.	0.164
Cardiac disorder	60 (6.4)	55 (6.2)	5 (9.6)	.	0.325
Inflammatory bowel disease	9 (1)	8 (0.9)	1 (1.9)	.	0.461
Diabetes	42 (4.5)	40 (4.5)	2 (3.9)	.	0.825
Cerebrovascular disease	20 (2.1)	20 (2.3)	0	.	0.274
Psychiatric disturbance	52 (5.5)	49 (5.5)	3 (5.8)	.	0.937
Mild hepatic insufficiency	87 (9.3)	84 (9.5)	3 (5.8)	.	0.373
Obesity	50 (5.3)	47 (5.3)	3 (5.8)	.	0.880
Infection	103 (11)	96 (10.8)	7 (13.5)	.	0.550
Rheumatological disorder	16 (1.7)	15 (1.7)	1 (1.9)	.	0.898
Peptic ulcer	8 (0.9)	8 (0.9)	0	.	0.492
Moderate/severe renal insufficiency	11 (1.2)	11 (1.2)	0	.	0.420
Moderate pulmonary dysfunction	161 (17.1)	154 (17.3)	7 (13.5)	.	0.472
Prior solid tumor	78 (8.3)	76 (8.6)	2 (3.9)	.	0.232
Heart valve disease	25 (2.7)	24 (2.7)	1 (1.9)	.	0.735
Severe pulmonary dysfunction	93 (9.9)	91 (10.2)	2 (3.9)	.	0.095
Moderate/severe hepatic insufficiency	15 (1.6)	14 (1.6)	1 (1.9)	.	0.845
HCT-CI n.	1 (0-3)	1 (0-3)	0 (0-2)	.	0.042
History of liver diseases	168 (17.9)	162 (18.3)	6 (11.5)	.	0.221
HCV	7 (4.2)	7 (4.3)	0	.	0.522
HBV	55 (23.7)	53 (32.7)	2 (33.3)	.	0.465
NAFLD/NASH	34 (20.2)	33 (20.4)	1 (16.7)	.	0.598
Others	72 (42.9)	69 (42.6)	3 (50)		0.678
Blood transfusion history (yes)	803 (85.3)	759 (85.4)	44 (84.6)	.	0.880
Iron Chelation Therapy (yes)	54 (5.7)	52 (5.9)	2 (3.9)	.	0.546
Number of pre-HSCT blood transfusions					
<10	155 (19.3)	146 (19.2)	9 (20.5)	.	0.292
10–20	356 (44.3)	343 (45.2)	13 (29.6)	.	
20–40	207 (25.8)	192 (25.3)	15 (34.1)	.	
40–50	41 (5.1)	38 (5)	3 (6.8)	.	
>50	44 (5.5)	40 (5.3)	4 (9.1)	.	

Table 1. continued

Variables	OVERALL $n = 941$	NO SOS/VOD $n = 889$	SOS/VOD $n = 52$	Missing	*p*-value
Hematological characteristics					
Diagnosis					
AML	378 (40.2%)	362 (40.7%)	16 (30.8%)	.	0.155
ALL	162 (17.2%)	141 (15.9%)	21 (40.4%)	.	<0.001
Lymphoproliferative disorders°	146 (15.5%)	144 (16.2%)	2 (3.8%)		0.017
MDS	72 (7.7%)	71 (8%)	1 (1.9%)	.	0.111
MPN	69 (7.3%)	66 (7.4%)	3 (5.8%)	.	0.656
CML	20 (2.1%)	18 (2.0%)	2 (3.8%)	.	0.376
Ewing Sarcoma	18 (1.9%)	14 (1.6%)	4 (7.7%)	.	0.002
Neuroblastoma	8 (0.9%)	7 (0.8%)	1 (1.9%)	.	0.386
*Non malignant disease**	45 (4.8%)	43 (4.8%)	2 (3.8%)	.	0.745
Others	23 (2.4%)	23 (2.6%)	0 (0.0%)	.	0.241
Disease phase					
Early	550 (58.4%)	523 (58.8%)	27 (51.9%)		0.326
Advanced	391 (41.6%)	366 (41.2%)	25 (48.1%)		
Transplant characteristics					
Type of HSCT					
Allogenic	895 (95.1)	848 (95.4)	47 (90.4)	.	0.104
Autologous	46 (4.9)	41 (4.6)	5 (9.6)	.	
Stem Cells Source					
PBSC	751 (79.8)	714 (80.3)	37 (71.2)	.	0.054
BM	166 (17.6)	151 (17)	15 (28.9)	.	
CB	24 (2.6)	24 (2.7)	0	.	
Stem cell donor (limited to allogeneic HSCT only)					
Haploidentical Donor	202 (22.6%)	193 (22.8%)	9 (19.1%)		0.564
MSD	152 (17.0%)	147 (17.3%)	5 (10.6%)		0.234
MUD	464 (51.8%)	439 (51.8%)	25 (53.2%)		0.849
MMUD	77 (8.6%)	69 (8.1%)	8 (17.0%)		0.034
Conditioning Intensity					
Myeloablative	596 (63.3)	551 (62)	45 (86.5)	.	<0.0001
Reduced Intensity	345 (36.7)	338 (38)	7 (13.5)	.	
Conditioning drugs					
TBI-based	131 (13.9%)	119 (13.4%)	12 (23.1%)		0.05
TBF	350 (37.2%)	335 (37.7%)	15 (28.8%)		0.198
Bu-Flu	69 (7.3%)	68 (7.7%)	1 (1.9%)		0.123
Bu-others calculators	57 (6.1%)	40 (4.5%)	17 (32.7%)		<0.001
Cy ± Flu	22 (2.3%)	21 (2.4%)	1 (1.9%)		0.838
Treo-Flu ± TT	145 (15.4%)	143 (16.1%)	2 (3.8%)		0.017
Mel-Treo-Flu	71 (7.6%)	69 (7.8%)	2 (3.8%)		0.298
TT-Cy-Flu	35 (3.7%)	35 (3.9%)	0		0.145
Others	60 (6.4%)	58 (6.5%)	2 (3.8%)		0.441
Conditioning drugs					
Busulfan containing (yes)	479 (51%)	445 (50.1%)	34 (65.4%)		0.032
Treosulfan containing (yes)	240 (25.5%)	234 (26.4%)	6 (11.5%)		0.017
Thiotepa containing (yes)	488 (51.9%)	460 (51.8%)	28 (53.8%)		0.774
Melphan containing (yes)	138 (14.7%)	126 (14.2%)	12 (23.1)		0.078
TBI-based	131 (13.9%)	119 (13.4%)	12 (23.1%)		0.05
N. of alkylating agents					
0	40 (4.9%)	37 (4.7%)	3 (8.3%)		0.331
1	234 (28.6%)	227 (29.1%)	7 (19.4%)		
2	543 (66.5%)	517 (66.2%)	26 (72.2%)		

Table 1. continued

Variables	OVERALL $n = 941$	NO SOS/VOD $n = 889$	SOS/VOD $n = 52$	Missing	*p*-value
SOS/VOD prophylaxis					
Yes	409 (44.1)	393 (45)	15 (29.4)	14	0.030
No	518 (55.9)	482 (55)	36 (70.6)		
SOS/VOD prophylaxis - drugs (yes)					
Defibrotide	7 (0.8)	7 (0.8)	0	14	0.522
Ursodeoxycholic Acid	401 (43.3)	386 (44.1)	15 (29.4)	14	0.040
PUFA	2 (0.2)	2 (0.2)	0	14	0.733
GVHD prophylaxis (limited to allogeneic HSCT only)					
CNI + antimetabolites	60 (6.7%)	58 (6.8%)	2 (4.3%)	.	0.442
ATG + CNI + antimetabolites	425 (47.5%)	396 (46.7%)	29 (61.7%)	.	0.114
PT-CY-based	211 (23.6%)	200 (23.6%)	11 (23.4%)	.	0.821
Sirolimus-based	177 (19.8%)	172 (20.3%)	5 (10.6%)	.	0.081
Ex-vivo *T cell-depletion*	22 (2.5%)	22 (2.6%)	0 (0.0%)	.	0.251

Data are *n* (%), median (IQR), unless otherwise specified. °Lymphoprolipherative disorders (Lymphomas + Multiple myeloma); *Non malignant disease (Severe Aplastic Anemia+Thalassemia+Immunodeficency+Medullary Aplasia+Sickle cell disease+Hemophagocytic lymphohistiocytosis+Haemoglobinopathies).
ALL acute lymphoblastic leukaemia, *AML* acute myeloid leukaemia, *ATG* Anti thymocyte globulin, *BM* Bone Marrow, *BMI* Body Mass Index, *Bu-Cy* Busulfan-Cyclophosphamide, *Bu-Flu* Busulfan-Fludarabine, *Bu-Mel* Busulfan-Melphalan, *CB* Cord Blood, *CML* chronic myelogenous leukaemia, *CNI* calcineurin inhibitor, *Cy-ATG* Cyclophosphamide- Anti thymocyte/Lymphocytic globulin, *Cy-Flu* Cyclophosphamide- Fludarabine, *Cy-Mel- Flu* Cyclophosphamide- Melphalan-Fludarabine, *HBV* Hepatitis B, *HCT-CI* Hematopoietic cell transplantation-specific comorbidity index, *HCV* Hepatitis C, *kg* kilogram, *m2* meter square, *MDS* Myelodysplastic syndrome, *Mel-Flu* Melphalan-Flidarabine, *MMUD* Mismatched Unrelated Donor, *MPN* Myeloproliferative neoplasms, *MSD* Matched Sibling Donor, *MUD* Matched Unrelated Donor, *n* number, *NAFLD/NASH* Non-alcoholic-fatty-liver-disease/Non-alcoholic-steatohepatitis, *PBSC* Peripheral Blood Stem Cells, *PT-CY* post transplant-cyclophosphamide, *PUFA* polyunsaturated fatty acids, *SOS* sinusoidal obstruction syndrome, *TBF* Thiotepa-Busulfan-Fludarabine, *TBI-Cy* Total Body Irradiation-Cyclophosphamide, *TBI-Flu* Total Body Irradiation-Fludarabine, *TBI-Treo-Flu* Total Body irradiation-Treosulfan-Fludarabine, *TBI-TT-Flu* Total Body Irradiation-Thiotepa-Fludarabine, *Treo-Flu* Treosulfan-Fludarabine, *Treo-Mel-Flu* Treosulfan-Melphalan- Fludarabine, *TT-Cy-Flu* Tiotepa-Cyclophosphamide-Fludarabine, *TT-Treo-Flu* Thiotepa-Treosulfan-Fludarabine, *VOD* veno-occlusive disease.

ultrasound elastography or after appropriate training; the reliability criteria were established following the latest EFSUMB Guidelines and Recommendations on the Clinical Use of Ultrasound Elastography [26]. The Supplemental Table 1 provided a detailed report on the specific devices utilised and the operators responsible for performing LSM at each center. LSM assessments were performed pre-transplant (T0) and according to the protocol by means of a dense schedule on days +9/10 (T1), +15/17 (T2) and +22/24 (T3) after HSCT. In the presence of clinical suspicion of VOD/SOS during the time between two scheduled evaluations, additional LSM evaluations were then conducted. If VOD/SOS was diagnosed, LSM was repeated, and weekly evaluations were carried out until there was either clinical resolution or progression.

Outcomes

The study's primary endpoint was to evaluate the diagnostic role of liver stiffness measurement (LSM) in diagnosing VOD/SOS after HSCT.

Secondary endpoints included (i) determining the incidence, characteristics, treatment, and evolution of VOD/SOS in an actual real-world cohort, (ii) identifying the predictive factors associated with the occurrence of VOD/SOS, (iii) exploring the role of LSM in stratifying the severity of VOD/SOS and in managing follow-up, and (iv) investigating how LSM can be used in the differential diagnosis of VOD/SOS and other liver-related HSCT complications occurred within day +100.

Data collection and quality assessment

Study data were collected and managed using REDCap electronic data capture tools [27]. Upon the conclusion of the enrollment phase and follow-up, a data quality evaluation was conducted through the utilisation of the REDCap quality module to avoid data inconsistencies and ensure high precision and thoroughness data quality with a specific focus on LSM evaluations, patient and transplant characteristics, VOD/SOS diagnosis and characteristics, and outcomes. The selection process including the number of patients for each center and the reasons for screening failure were reported in the Supplemental Table 2. Incidence, characteristics, treatment, and evolution of VOD/SOS were assessed in the enrolled population (where baseline and follow-up data were available), while diagnostic accuracy was evaluated in the intention-to-diagnose cohort (baseline LSM and at least one LSM after HSCT) for the primary endpoint.

Statistical analysis

The study endpoints were based on a sample size calculation using Confidence Intervals for One Proportion. Assuming a 10% VOD/SOS incidence, a minimum of 595 patients was needed to achieve a 95% confidence interval with 50 VOD/SOS cases. To account for a 20% drop-out rate, the study required at least 744 participants. Upon reaching this number, we extended the enrollment period to meet the target cases. Continuous data are presented as medians with IQRs and compared using the Wilcoxon test, while categorical data were analysed with frequencies, proportions, and $\chi 2$ tests. Visual data distributions were represented via violin and box plots. Kaplan-Meier method was used to estimate +100 day and one-year overall survival. The crude prevalence of VOD was reported as the ratio between the number of cases over the population analyzed; the cumulative incidence of VOD/SOS was calculated, accounting for death for non-VOD/SOS-related causes as a competitive risk. The log-rank test and Gray's test were used to assess group differences for survival and VOD/SOS cumulative incidence. Competing-risks regressions based on Fine and Gray's proportional subhazards models were performed to evaluate the predictor factors of VOD/SOS development after HSCT. Multivariable competing-risk regression analyses were conducted on variables reaching $p < 0.1$ at univariate analysis, with results reported via subhazard ratios (SHR), Wald-chi2 tests, and AUC c-statistic ≥0.70. To assess the diagnostic impact of LSM, cut-off values were determined via ROC-optimization. We calculated Sensitivity, Specificity, NPV, and PPV for each cut-off.

Since the number of enrolled auto-HSCT patients was quite limited, likely leading to an uncontrolled selection bias across centers, we performed a sensitivity analysis exclusively in allo-HSCT patients for the regression analysis. Given that the diagnostic value is independent of the type of HSCT, we have reported the diagnostic values accordingly. Full details on methods and extended results are available in the Supplemental Material.

Data sharing

Deidentified individual participant data will be made available by contacting the corresponding author. Study proposals will need to be

Table 2. EBMT risk factors for VOD/SOS in allo-HSCT patients enrolled.

OVERALL COHORT	OVERALL	NO SOS/VOD	SOS/VOD	*p*-value	*ADULTS PATIENTS*	OVERALL	NO SOS/VOD	SOS/VOD	*p*-value	*PAEDIATRICS PATIENTS*	OVERALL	NO SOS/VOD	SOS/VOD	*p*-value
	n = 805	*n* = 848	*n* = 47			*n* = 762	*n* = 734	*n* = 28			*n* = 133	*n* = 114	*n* = 19	
General EBMT risk factors (n.)	4.0 (3.0–5.0)	4.0 (3.0–5.0)	5.0 (4.0–7.0)	<0.001	**General EBMT risk factors (n.)**	4.0 (3.0–5.0)	4.0 (3.0–5.0)	6.0 (5.0–6.5)	<0.001	**General EBMT risk factors (n.)**	4.0 (3.0–5.0)	4.0 (3.0–5.0)	5.0 (3.0–7.0)	0.040
Unrelated donor	529 (59.1%)	497 (58.6%)	32 (68.1%)	0.198	*Unrelated donor*	451 (59.2%)	435 (59.3%)	16 (57.1%)	0.823	*Unrelated donor*	78 (58.6%)	62 (54.4%)	16 (84.2%)	0.015
HLA mismatch	397 (44.4%)	375 (44.2%)	22 (46.8%)	0.728	*HLA mismatch*	341 (44.8%)	324 (44.1%)	17 (60.7%)	0.083	*HLA mismatch*	56 (42.1%)	51 (44.7%)	5 (26.3%)	0.132
Non T-Cell Depletion	569 (63.6%)	533 (62.9%)	36 (76.6%)	0.057	*Non T-Cell Depletion*	480 (63.0%)	456 (62.1%)	24 (85.7%)	0.011	*Non T-Cell Depletion*	89 (66.9%)	77 (67.5%)	12 (63.2%)	0.707
Myeloablative conditioning	558 (62.3%)	517 (61.0%)	41 (87.2%)	<0.001	*Myeloablative conditioning*	452 (59.3%)	429 (58.4%)	23 (82.1%)	0.012	*Myeloablative conditioning*	106 (79.7%)	88 (77.2%)	18 (94.7%)	0.078
Oral/high dose busulfan	357 (39.9%)	330 (38.9%)	27 (57.4%)	0.012	*Oral/high dose busulfan*	310 (40.7%)	295 (40.2%)	15 (53.6%)	0.157	*Oral/high dose busulfan*	47 (35.3%)	35 (30.7%)	12 (63.2%)	0.006
High dose TBI	101 (11.3%)	91 (10.7%)	10 (21.3%)	0.026	*High dose TBI*	60 (7.9%)	56 (7.6%)	4 (14.3%)	0.199	*High dose TBI*	41 (30.8%)	35 (30.7%)	6 (31.6%)	0.939
Second HSCT	94 (10.5%)	87 (10.3%)	7 (14.9%)	0.313	*Second HSCT*	76 (10.0%)	70 (9.5%)	6 (21.4%)	0.039	*Second HSCT*	18 (13.5%)	17 (14.9%)	1 (5.3%)	0.255
Transaminasis increase	28 (3.1%)	28 (3.3%)	0 (0.0%)	0.206	*Transaminasis increase*	20 (2.6%)	20 (2.7%)	0 (0.0%)	0.376	*Transaminasis increase*	8 (6.0%)	8 (7.0%)	0 (0.0%)	0.234
Bilirubin increase	20 (2.2%)	20 (2.4%)	0 (0.0%)	0.287	*Bilirubin increase*	18 (2.4%)	18 (2.5%)	0 (0.0%)	0.402	*Bilirubin increase*	2 (1.5%)	2 (1.8%)	0 (0.0%)	0.561
Cirrhosis	2 (0.2%)	2 (0.2%)	0 (0.0%)	0.739	*Cirrhosis*	2 (0.3%)	2 (0.3%)	0 (0.0%)	0.782	*Cirrhosis*	0	0	0	.
Viral Hepatitis	51 (5.7%)	49 (5.8%)	2 (4.3%)	0.661	*Viral Hepatitis*	49 (6.4%)	48 (6.5%)	1 (3.6%)	0.530	*Viral Hepatitis*	2 (1.5%)	1 (0.9%)	1 (5.3%)	0.146
Abdominal Irradiation	43 (4.8%)	36 (4.2%)	7 (14.9%)	<0.001	*Abdominal Irradiation*	28 (3.7%)	25 (3.4%)	3 (10.7%)	0.044	*Abdominal Irradiation*	15 (11.3%)	11 (9.6%)	4 (21.1%)	0.146
Previous Gemtuzumab or Inotuzumab	34 (3.8%)	26 (3.1%)	8 (17.0%)	<0.001	*Previous Gemtuzumab or Inotuzumab*	26 (3.4%)	20 (2.7%)	6 (21.4%)	<0.001	*Previous Gemtuzumab or Inotuzumab*	8 (6.0%)	6 (5.3%)	2 (10.5%)	0.372
Hepatotoxic Drugs	360 (40.2%)	341 (40.2%)	19 (40.4%)	0.977	*Hepatotoxic Drugs*	329 (43.2%)	318 (43.3%)	11 (39.3%)	0.672	*Hepatotoxic Drugs*	31 (23.3%)	23 (20.2%)	8 (42.1%)	0.036
Iron Overload	210 (23.5%)	196 (23.1%)	14 (29.8%)	0.293	*Iron Overload*	194 (25.5%)	184 (25.1%)	10 (35.7%)	0.204	*Iron Overload*	16 (12.0%)	12 (10.5%)	4 (21.1%)	0.192
					Specific EBMT risk factors for adult					***Specific EBMT risk factors for pediatric***				
					Advanced Age	159 (20.9%)	155 (21.1%)	4 (14.3%)	0.383	*<2 years old*	2 (1.5%)	0 (0.0%)	2 (10.5%)	<0.001
					Karnosfky score < 90%	49 (6.4%)	47 (6.4%)	2 (7.1%)	0.876	*Low Weight*	7 (5.3%)	6 (5.3%)	1 (5.3%)	1.000
					Advanced Stage Disease	247 (32.4%)	232 (31.6%)	15 (53.6%)	0.015	*Advanced Stage Disease*	33 (24.8%)	28 (24.6%)	5 (26.3%)	0.870
					Genetic Factors	30 (3.9%)	29 (4.0%)	1 (3.6%)	0.919	*Genetic Factors*	0	0	0	.
					Metabolic Syndrome	47 (6.2%)	46 (6.3%)	1 (3.6%)	0.561	*Previous Actinomycin*	0	0	0	.
					Previous Norethindrone (only females)	3 (0.4%)	3 (0.4%)	0 (0.0%)	0.735	*Metabolic Syndrome*	1 (0.8%)	1 (0.9%)	0 (0.0%)	0.682
					Thalassemia	0	0	0	.	*High Risk Disease*	10 (7.5%)	9 (7.9%)	1 (5.3%)	0.687

Data are *n* (%), median (IQR), unless otherwise specified.
EBMT European Group for Blood and Marrow Transplantation, *HLA* human leukocyte antigen, *n* numbers, *SCT* stem cells transplantation, *TBI* total body irradiation.

Table 3. Characteristics of VOD/SOS patients.

	(A) Overall enrolled HSCT				(B) Allo-HSCT			
	OVERALL $n = 52$	**ADULT** $n = 28$	**PAEDIATRICS** $n = 24$	***p*-value**	**OVERALL** $n = 47$	**ADULT** $n = 28$	**PAEDIATRICS** $n = 19$	***p*-value**
VOD/SOS prevalence	5.53%	3.62%	14.37%	<0.0001	5.25%	3.68%	14.29%	<0.0001
95% Confidence Interval	[4.13–7.25]	[2.40–5.23]	[9.21–21.38]		[3.88–6.92]	[2.46–5.27]	[8.82–21.41]	
VOD/SOS incidence	5.5%	3.6%	14.4%	<0.0001	5.26%	3.68%	14.3%	<0.0001
95% Confidence Interval	[4.2–7.1]	[2.5–5.1]	[9.5–20.2]		[3.93–6.68]	[2.51–5.2]	[8.96–20.8]	
Days post-SCT; median (IQR)	18 (11-25)	19 (11–29)	17 (11–22)	0.358	16 (10–26)	19 (11–29)	14 (9–21)	0.182
Late-onset (≥ 21 days) VOD/SOS; *n*. (%)	19 (36.5)	13 (46.4)	6 (25)	0.105	17 (36.2)	12 (42.9)	5 (26.3)	0.247
Severity grading SOS/ VOD; *n*. (%)								
Mild	4 (7.6)	2 (7.1)	2 (8.3)	0.478	4 (8.5)	2 (7.1)	2 (10.5)	0.478
Moderate	11 (21.2)	4 (14.3)	7 (29.2)		10 (21.3)	4 (14.3)	6 (31.6)	
Severe	25 (48.1)	16 (57.1)	9 (37.5)		23 (48.9)	16 (57.1)	7 (36.8)	
Very Severe	12 (23.1)	6 (21.5)	6 (25)		10 (21.3)	6 (21.5)	4 (21.1)	
SOS/VOD needing treatment*; *n*. (%)	37 (71.2)	22 (78.6)	15 (62.5)	<0.0001	33 (70.2)	22 (78.6)	11 (57.9)	<0.0001
SOS/VOD therapy; *n*. (%)								
Defibrotide	44 (84.6)	24 (85.7)	20 (80.3)	0.812	41 (87.2)	24 (85.7)	17 (89.5)	0.705
Diuretics	35 (67.3)	17 (60.7)	18 (75)	0.274	30 (63.8)	17 (60.7)	13 (68.4)	0.589
UDCA	17 (32.7)	8 (28.6)	9 (37.5)	0.494	13 (27.7)	8 (28.6)	5 (26.3)	0.865
Others°	6 (11.5)	2 (7.1)	4 (16.7)	0.284	4 (8.5)	2 (7.1)	2 (10.5)	0.683
SOS/VOD evolution; *n*. (%)								
Resolution	38 (73.1)	18 (64.3)	20 (83.3)	0.187	32 (68.1)	18 (64.3)	14 (73.7)	0.188
MOF	12 (23.1)	6 (21.4)	6 (25)	0.761	12 (25.5)	6 (21.4)	6 (31.6)	0.434
SOS/VOD-related death	14 (26.9)	11 (39.3)	3 (12.5)	0.05	13 (27.7)	11 (39.3)	2 (10.5)	0.134

*severe & very severe VOD/SOS; °others SOS/VOD therapy: $n = 2$ steroides; $n = 3$ paracentesis; $n = 2$ dopamine.
*severe & very severe VOD/SOS; °others SOS/VOD therapy: $n = 1$ steroides; $n = 3$ paracentesis; $n = 1$ dopamine.
IQR interquartile range, *MOF* multi-organ failure, *n* number, *SOS* sinusoidal obstruction syndrome, *UDCA* Ursodeoxycholic acid, *VOD* veno-occlusive disease.
Characteristics of VOD/SOS patients; 3 A overall enrolled HSCT; 3B allo-HSCT.

approved by the Scientific Committee of the ELASTOVOD/SOS Study Group and approved by the Institutional Ethical Committee of IRCCS Sant'Orsola-Malpighi University Hospital (Bologna, Italy).

RESULTS

Study cohorts

Between 12 April 2018 and 22 December 2021, a total of 1089 patients were screened in 25 HSCT programs. Out of the 1089 patients initially screened, 148 were excluded for not meeting the eligibility criteria (Fig. 1). A total of 12 patients were excluded from the study due to missing LSM after HSCT, leaving 941 patients for intention-to-diagnose analysis. Table 1 reported the baseline characteristics of patients enrolled. The study enrolled a total of 941 patients, out of which 774 (82.3%) were adults and 167 (17.7%) were paediatric patients. The Table S3 contains a comprehensive report of the baseline characteristics found in both adult, pediatric and in allo-HSCT cohorts **(**Table S4**)**. According to the EBMT guidelines, we assessed the risk factors for VOD/SOS in patients with allo-HSCT (Table 2) and in the overall population (Table S5). Allo-HSCT patients had a median of 4 (IQR 3-5) EBMT risk factors, significantly higher in the group of patients who developed VOD/SOS (p-value < 0.0001).

VOD/SOS incidence and survival

Over a period of 100 days after allo-HSCT, 5.25% (47) of patients developed VOD/SOS with an incidence rate of 5.26 [95% CI 3.93–6.86]. The incidence rate significantly differed between adult and pediatric cohorts ($p < 0.0001$). The adult cohort had 28 (3.68%) cases of VOD/SOS, with an incidence rate of 3.68 [95% CI 2.51–5.20]. The pediatric cohort had 19 (14.3297%) cases of VOD/SOS, with an incidence rate of 14.3 [95% CI 8.96–20.80]. Table 3 reports the characteristics of patients who developed VOD/SOS. The median time for the occurrence of VOD/SOS was 16 days (IQR 10–26) after allo-HSCT, with late-onset VOD/SOS accounting for 36.2% of cases. Among the VOD/SOS cases occurred after allo-HSCT, the majority (70.2%) were graded as severe or very severe, with a higher prevalence in the adult population (78.6% vs. 57.7%). In 87.2% of cases, the VOD/SOS resolved after specific treatments (mainly Defibrotide), while in 27.7% of cases, it resulted in death related to VOD/SOS. The Supplemental Tables S6, S7 we included a report on the characteristics of patients with VOD/SOS, detailing

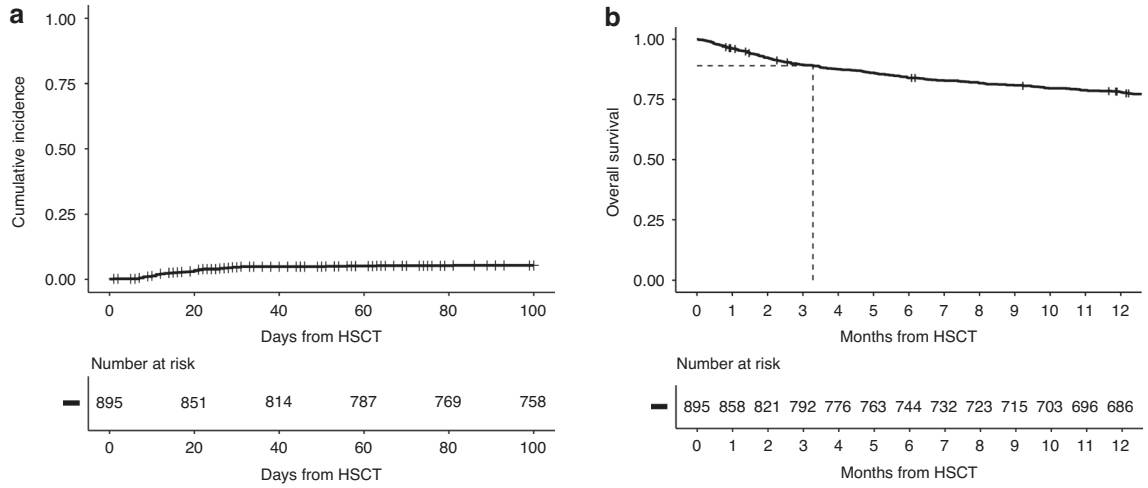


Fig. 2 Incidence of sinusoidal obstruction syndrome/veno-occlusive disease (SOS/VOD) and overall survival in the ELASTOVOD cohort. a shows the 100-day cumulative incidence of SOS/VOD after allogeneic hematopoietic stem cell transplantation (allo-HSCT). **b** presents the Kaplan–Meier estimate of overall survival in the same population. Cumulative incidence was calculated accounting for competing risks, and survival curves are shown with 95% confidence intervals. CI confidence interval, CI cumulative incidence, HSCT hematopoietic stem cell transplantation, OS overall survival, SOS sinusoidal obstruction syndrome, VOD veno-occlusive disease.

Table 4. Competing-risks Cox regression analysis of predictive factors of SOS/VOD after allo-HSCT.

UNIVARIATE - Variables	**Overall population (*n* = 895)**		
	sHR	**(95% CI)**	***p*-value**
Sex (male)	0.923	0.516–1.651	0.787
Age (years)	0.968	0.954–0.983	<0.0001
Cohort (adults vs. pediatrics)	4.143	2.313–7.420	<0.0001
BMI (kg/m2)	0.930	0.867–0.998	0.045
HCT-CI total Sorror score (n.)	0.872	0.724–1.051	0.150
Diagnosis			
AML	0.698	0.382–1.276	0.243
ALL	3.810	2.148–6.760	<0.0001
*Lymphoproliferative disorders**	0.255	0.062–1.049	0.058
MDS	0.246	0.034–1.799	0.167
Myelofibrosis (MPN)	0.810	0.252–2.605	0.724
CML	1.967	0.486–7.954	0.343
Ewing Sarcoma	.	.	.
Non malignant diseases	0.868	0.208–3.615	0.845
Disease phase			
Early	0.745	0.421–1.321	0.314
Advanced	1.342	0.757–2.378	0.314
Second HSCT	1.509	0.677–3.364	0.314
Stem cells source			
PBSC	0.646	0.342–1.219	0.178
Bone Marrow	1.851	0.981–3.492	0.057
Umbilical Cord	8.44e-20	5.16e-20–1.38e-19	<0.0001
Stem cell donor, *n* (%)			
Haploidentical Donor	0.806	0.391–1.665	0.561
MFD (Matched family related Donor)	0.573	0.227–1.446	0.238
MUD (Matched Unrelated Donor)	1.060	0.598–1.879	0.841
MMUD (HLA Miss-Matched Unrelated Donor)	2.245	1.049–4.801	0.037

Table 4. continued

UNIVARIATE - Variables	**Overall population ($n = 895$)**		
	sHR	**(95% CI)**	***p*-value**
Conditioning Intensity			
Reduced Intensity	1 (ref.)	.	.
Myeloablative	4.272	1.820–10.028	<0.001
Conditioning drugs			
Busulfan containing (yes)	2.045	1.148–3.645	0.015
Treosulfan containing (yes)	0.393	0.167–0.922	0.032
Thiotepa containing (yes)	1.223	0.683–2.188	0.498
Melphan contaiining (yes)	1.191	0.533–2.662	0.67
TBI-based	2.084	1.076–4.035	0.029
Alkylating agents (n.). *0-1*	1 (ref.)		
2	0.717	0.417–1.234	0.230
SOS/VOD prophylaxis-drugs (yes)	0.565	0.318–1.002	0.051
GVHD prophylaxis (limited to allogeneic HSCT only)			
CNI + antimetabolites	0.611	0.148–2.511	0.494
ATG + CNI + antimetabolites	1.802	1.001–3.242	0.049
PT-CY-based	0.991	0.505–1.946	0.979
Sirolimus-based	0.479	0.188–1.208	0.119
Ex-vivo T cell-depletion	8.46e-20	5.10e-20–1.40e-19	<0.0001
Viral Hepatitis	0.736	0.178–3.047	0.672
Abdominal Irradiation	3.768	1.671–8.495	0.001
Previous therapy with either Gemtuzumab or Inotuzumab	5.793	2.710–12.384	<0.0001
Hepatotoxic Drugs	1.024	0.572–1.833	0.936
Iron Overload	1.407	0.752–2.631	0.286
Genetic Factors	0.910	0.121–6.843	0.927
Metabolic Syndrome	0.562	0.077–4.088	0.569
High Risk Disease (pediatric cohort; $n = 167$)	0.661	0.903–4.829	0.683
Liver Stiffness Measurement prior HSCT			
by kPa (n.806)	1.062	0.973–1.159	0.181
by m/sec (n.70)	0.093	0.009–1.006	0.061
MULTIVARIATE-Variables	**sHR**	**(95% CI)**	***p*-value**
Cohort (adults vs. pediatrics)	3.8147	2.078–7.005	<0.0001
Diagnosis-ALL	2.291	1.246–4.211	0.008
Conditioning drugs-Busulfan containing (yes)	2.870	1.537–5.359	0.001
GVHD prophylaxis-Ex-vivo T cell-depletion	5.26e-07	1.75e-07–1.58e-06	<0.0001
Abdominal Irradiation	4.699	1.939–11.391	0.001
Previous therapy with Gemtuzumab or Inotuzumab	5.337	2.324–12.257	<0.0001
MMUD (HLA Miss-Matched Unrelated Donor)	3.165	1.425–7.013	0.005
Stem Cells Source-Umbilical Cord	1.36e-06	3.34e-07–5.52e-06	<0.0001
Model accuracy parameters			
Discrimination (AUROC)	0.7610		
Goodness of fit (AIC)	582,124		
Goodness of fit (BIC)	620,498		

AIC Akaike Information Criterion, *ALL* acute lymphoblastic leukaemia, *AML* acute myeloid leukaemia, *ATG* Anti thymocyte globulin, *AUROC* Area Under the Receiver Operating characteristic Curve, *BIC* Bayesian Information Criterion, *BM* Bone Marrow, *BMI* Body Mass Index, *Bu-Cy* Busulfan-Cyclophosphamide, *Bu-Flu* Busulfan-Fludarabine, *Bu-Mel* Busulfan-Melphalan, *CB* Cord Blood, *CML* chronic myelogenous leukaemia, *CNI* calcineurin inhibitor, *Cy-ATG* Cyclophosphamide- Anti thymocyte/Lymphocytic globulin, *Cy-Flu* Cyclophosphamide- Fludarabine, *Cy-Mel- Flu* Cyclophosphamide- Melphalan- Fludarabine, *HBV* Hepatitis B, *HCT-CI* Hematopoietic cell transplantation-specific comorbidity index, *HCV* Hepatitis C, *kg* kilogram, *m2* meter square, *MDS* Myelodysplastic syndrome, *Mel-Flu* Melphalan-Flidarabine, *MMUD* Mismatched Unrelated Donor, *MPN* Myeloproliferative neoplasms, *MSD* Matched Sibling Donor, *MUD* Matched Unrelated Donor, *n* number, *NAFLD/NASH* Non-alcoholic-fatty-liver-disease/Non-alcoholic-steatohepatitis, *PBSC* Peripheral Blood Stem Cells, *PT-CY* post transplant-cyclophosphamide, *PUFA* polyunsaturated fats, *SOS* sinusoidal obstruction syndrome, *TBF* Thiotepa-Busulfan-Fludarabine, *TBI-Cy* Total Body Irradiation-Cyclophosphamide, *TBI-Flu* Total Body Irradiation-Fludarabine, *TBI-Treo-Flu* Total Body irradiation-Treosulfan-Fludarabine, *TBI-TT-Flu* Total Body Irradiation-Thiotepa-Fludarabine, *Treo-Flu* Treosulfan-Fludarabine, *Treo-Mel-Flu* Treosulfan-Melphalan- Fludarabine, *TT-Cy-Flu* Tiotepa-Cyclophosphamide-Fludarabine, *TT-Treo-Flu* Thiotepa-Treosulfan-Fludarabine, *VOD* veno-occlusive disease.
*Lymphoprolipherative disorders (Lymphomas + Multiple myeloma).

the time of diagnosis, clinical features, diagnostic criteria, and ultrasound findings on the day of diagnosis.

Figure 2 displays the overall survival curve (2 A) and the cumulative incidence of VOD/SOS (2B) after allo-HSCT. Overall survival probability at +100 days and one year was 89.0% [95% CI 87.0–91.1] and 78.0% [95% CI 75.4–80.8], respectively. The overall survival probability significantly differed (p-value < 0.01) between patients who developed VOD/SOS (68.1 [95% CI 56.0–82.8] at 100 days) compared to others (90.2 [95% CI 88.2–92.2] at 100 days) and across VOD/SOS severity grading (p-value < 0.01). The overall survival probability for mild-moderate and severe-very severe VOD/SOS were 76.9% (95% CI 57.1–100) and 64.7% (95% CI 50.5–82.9), respectively. The same analyses for the entire enrolled population was reported in the Supplementary Figs. S1–S3.

Prediction of VOD/SOS

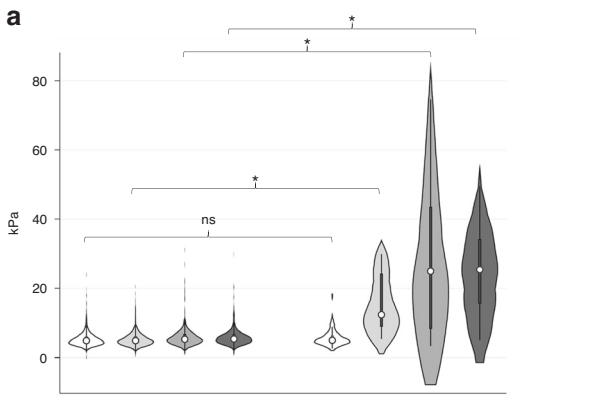
Table 4 reported the univariate competing risk regression analysis of the predictive factors associated with VOD/SOS after allo-HSCT. Across these variables, only the type of cohort (adults vs. paediatrics patients), the acute lymphoblastic leukaemia, conditioning regimens based on busulphan, GvHD prophylaxis based on ex-vivo T cell depletion, previous abdominal irradiation, stem cell from HLA mismatched unrelated donor, stem cells source from umbilical cord and previous therapy with either Gemtuzumab or Inotuzumab were independently associated to VOD/SOD in the multivariable model. The related analysis of the overall population is reported in Supplementary Table S8.

Liver stiffness measurement can diagnose VOD/SOS

Among the 929 patients analysed, LSM was predominantly performed using the TE technique, accounting for 76.4% of the cases. The remaining patients underwent LSM by p-SWE (13.6%) and 2D-SWE (10%). Specifically, LSM was recorded by kPa in 835 patients who had 46 VOD/SOS, while LSM was recorded by m/sec in 94 patients who had 4 VOD/SOS. Prior to HSCT, both the LSM measured in kPa and m/sec did not differ in patients with (5 kPa [IQR 4.3–6.4 kPa]; 1.02 m/s [IQR 0.8–1.15 m/s]) and without (4.9 kPa [IQR 3.9–6.1 kPa]; 1.19 m/s [IQR 1.01–1.43 m/s]) occurrence of VOD/SOS.

Figure 3 showed that LSM differed significantly at each time point after HSCT in patients with VOD/SOS (**3 A**) and across the severity grades of VOD/SOS (**3B**). At the diagnosis of VOD/SOS, LSM was significantly associated with the severity of the disease (mild to moderate VOD/SOS vs. severe/very severe VOD/SOS; $p = 0.017$): the values increased from 13.8 kPa [7.4–26.2], 19.4 kPa [14.6–32 kPa], 26.3 [12.4–39.7 kPa], and 27.4 [22–28.4 kPa] in mild, moderate, severe, and very severe forms respectively. We found the high diagnostic performance of LSM for the diagnosis of VOD/SOS with an area under ROC of 0.9747 [95% CI 0.9477–1.000] using kPa and of 0.9542 [95% CI 0.8975–1.000] using m/sec (Supplementary Fig. S4). Using ROC optimization, we identified the optimal cut-off values: 6 kPa to rule out VOD/SOS (Sensitivity ≥95%) and 25 kPa to confirm VOD/SOS (Specificity ≥95%), based on the Youden index at 9.5 kPa. In Table 5, we presented the patient's classification based on all the operating characteristics of the LSM cut-offs and assessed by VOD/SOS's adults and paediatrics prevalence. The results revealed that by the LSM rule-out cut-off of 6 kPa, 502 out of 835 patients were correctly classified, and none of the patients with LSM ≤ 6 kPa had VOD/SOS. On the other hand, by the LSM rule-in cut-off of 25 kPa, 26 patients with VOD/SOS were correctly identified, and only one patient was wrongly classified. We have identified that 306 patients fall into an area of uncertainty between these two cut-offs, called the "gray zone". To address this uncertainty, we suggest using a stepwise approach by calculating the difference between the LSM on the day of the diagnosis and before HSCT (using the formula provided in the Supplementary Table S9). If the delta (Δ)LSM value is greater than or equal to 2 (which is equal to three times the baseline LSM value), VOD/SOS diagnosis can be confirmed by LSM. This stepwise algorithm showed good accuracy with an AUROC of 0.898 and good positive (84.1% [69.9-93.4]) and negative (98.9% [97.9–99.5]) predictive values. In the Supplementary Tables S10, we have included the cut-off values and operating characteristics for patients whose LSM was assessed in m/sec **(**Fig. S5**)**; however, a stepwise approach cannot be developed and proposed due to this group's limited numbers of VOD/SOS. Sensitivity analyses were also performed in allo-HSCT patients, yielding comparable results (Supplementary Tables S10b–11**)**.

When VOD/SOS occurs, appropriate treatment is given, and the patient is closely monitored until their condition improves or they die. Patients who responded positively to therapy and were still alive at the +100-day mark showed a significant reduction in their liver stiffness measurement (LSM) week after week (p-value = 0.0074). In contrast, those who died during the follow-up period did not experience a significant decrease in LSM **(**Fig. 4**)**. Furthermore,



Time	NO VOD/SOS (n=789)	VOD/SOS (n=46)	P-values (Kruskal-Wallis)
T0	4.9 kPa (3.9 – 6.1 kPa)	5 kPa (4.3 – 6.4 kPa)	0.350
T1(+9 [8 – 10.])	4.9 kPa (4 –6.1 kPa)	12.4 kPa (8.9 –24.3 kPa)	<0.0001
T2+16 [15 – 17])	5.3 (4.3 – 6.8 kPa)	25 kPa (8.3 – 43.6 kPa)	<0.0001
T3 (+23 [22 – 25])	5.4 kPa (4.4 – 6.7 kPa)	25.4 kPa (15.6–34.3 kPa)	<0.0001

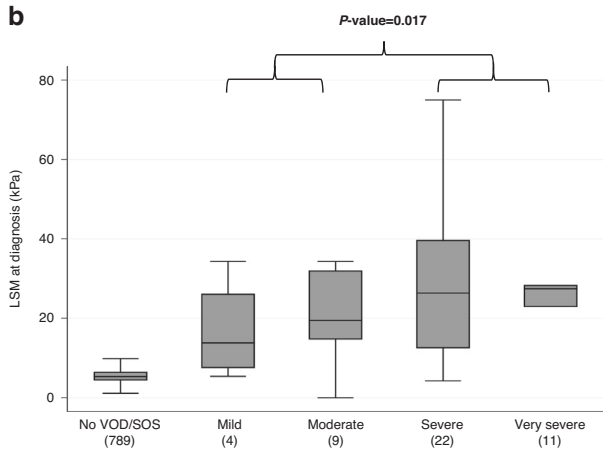
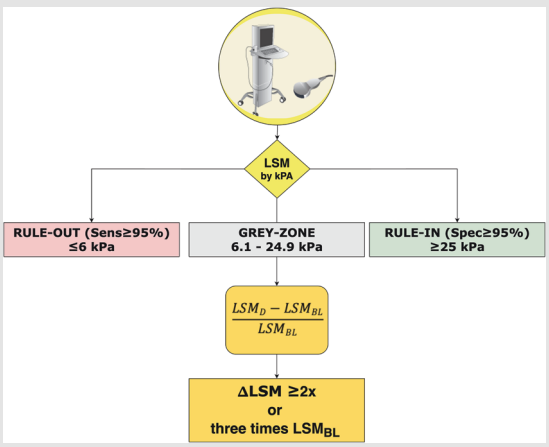


Fig. 3 Distribution of liver stiffness measurements (LSM) by SOS/VOD diagnosis and severity. a shows violin plots of LSM values (kPa) at different time points post-allo-HSCT, stratified by the presence or absence of SOS/VO. **b** displays LSM values according to SOS/VOD severity grades. Each violin plot illustrates the kernel density of the data, with medians and interquartile ranges indicated. Statistically significant differences between groups are marked (*p < 0.0001). ns not significant, kPa kilopascal, T time, SOS sinusoidal obstruction syndrome, VOD veno-occlusive disease.

Table 5. Diagnostic accuracy of LSM for SOS/VOD diagnosis post-HSCT (by kPa).

LSM by kPa ($n = 835$ pts; 46 VOD)	Rule - out (Sens ≥ 95%) ≤6 kPa ($n = 502$)	Best cut-off (Youden) 9.5 kPa	Rule-in (Spec ≥ 95%) ≥25 kPa ($n = 27$)
Diagnostic test results			
True Positive (TP)	46	42	26
False Positive (FP)	287	41	1
True Negative (TN)	502	748	788
False Negative (FN)	0	4	20
Operating characteristics (study incidence = 5.5% [95% CI 4.2–7.1%])			
Sensitivity (95% CI)	100 [92.3 - 100]	91.3 [79.2–97.6]	56.5 [41.2–71.1]
Specificity (95% CI)	63.6 [60.2–67]	94.8 [93–96.2]	99.9 [99.3–100]
PPV (95% CI)	13.8 [10.3–18]	50.6 [39.4–61.8]	96.3 [81.0–99.9]
NPV (95% CI)	100 [99.3–100]	99.5 [98.6–99.9]	97.5 [96.2–98.5]
LR-positive (95% CI)	2.75 [2.51–3.01]	17.6 [12.9–24]	445.96 [61.9–3214]
LR-negative (95% CI)	0 [0–0]	0.092 [0.036–0.234]	0.44 [0.31–0.61]
AUROC (95% CI)	0.820 [0.80–0.830]	0.931 [0.889–0.872]	0.780 [0.710–0.850]
Operating characteristics (pediatrics incidence = 14.4% [95% CI 9.5–20.2%])			
PPV (95% CI)	31.6 [29.7–33.7]	74.7 [68.4–80.1]	98.7 [91.2–99.8]
NPV (95% CI)	100 [100–100]	98.5 [96.2–99.4]	93.2 [90.8–95]
Operating characteristics (adults incidence = 3.6% [95% CI 2.5–5.1%])			
PPV (95% CI)	9.3 [8.6–10.1]	40 [32.5–47.2]	94.3 [69.8–99.2]
NPV (95% CI)	100 [100–100]	99.7 [99.1. 99.9]	98.4 [97.8–98.8]



Diagnostic test results	
True Positive (TP)	37
False Positive (FP)	7
True Negative (TN)	782
False Negative (FN)	9
Operating characteristics (study incidence = 5.5% [95% CI 4.2–7.1%])	
Sensitivity (95% CI)	80.4 [66.1–90.6]
Specificity (95% CI)	99.1 [98.2–99.6]
PPV (95% CI)	84.1 [69.9–93.4]
NPV (95% CI)	98.9 [97.9–99.5]
LR-positive (95% CI)	90.7 [42.8–192]
LR-negative (95% CI)	0.197 [0.110–0.355]
AUROC (95% CI)	0.898 [0.840–0.956]
Operating characteristics (pediatrics incidence = 14.4% [95% CI 9.5–20.2%])	
PPV (95% CI)	93.8 [87.8–97]
NPV (95% CI)	96.8 [94.4–98.2]
Operating characteristics (adults incidence = 3.6% [95% CI 2.5–5.1%])	
PPV (95% CI)	77.2 [61.5–87.8]
NPV (95% CI)	99.3 [98.7–99.6]

AUROC the area under ROC curve, *CI* confidence interval, *LR* likelihood ratio, *n* numbers, *NPV* negative predictive value, *PPV* positive predictive value, *SOS* sinusoidal obstruction syndrome, *VOD* veno-occlusive disease.

patients who fully recovered from VOD/SOS exhibited significantly lower LSM values one week after starting the treatment (11.6 kPa vs. 23.7 kPa; p-value = 0.039) and had a much greater difference in LSM compared to those who did not improve and ultimately died (−12.2% vs. −6.2%; p-value < 0.05).

Differential diagnosis

During the study, in addition to VOD/SOS, most patients (95.96%) experienced other complications and were classified as CTC 4-5 in 63.1% of cases (Table 6). Among these complications, 27 (2.9%), 35 (3.7%), 67 (7.1%), 5 (0.5%), and 11 (1.2%) were diagnosed as liver GvHD, DILI, isolated hyperbilirubinemia, hepatitis, and cholecystitis/cholangitis, respectively. In 9 cases, liver biopsies (5 by transjugular approach) were performed. Out of these, 4 confirmed the diagnosis of VOD/SOS, 3 diagnosed hepatic GVHD, 1 case diagnosed hepatic/bowel GVHD, and 1 case diagnosed with DILI. In Supplementary Table S12 we reported the non-SOS/VOD hepatic complications frequency by age cohort and in allo-HSCT

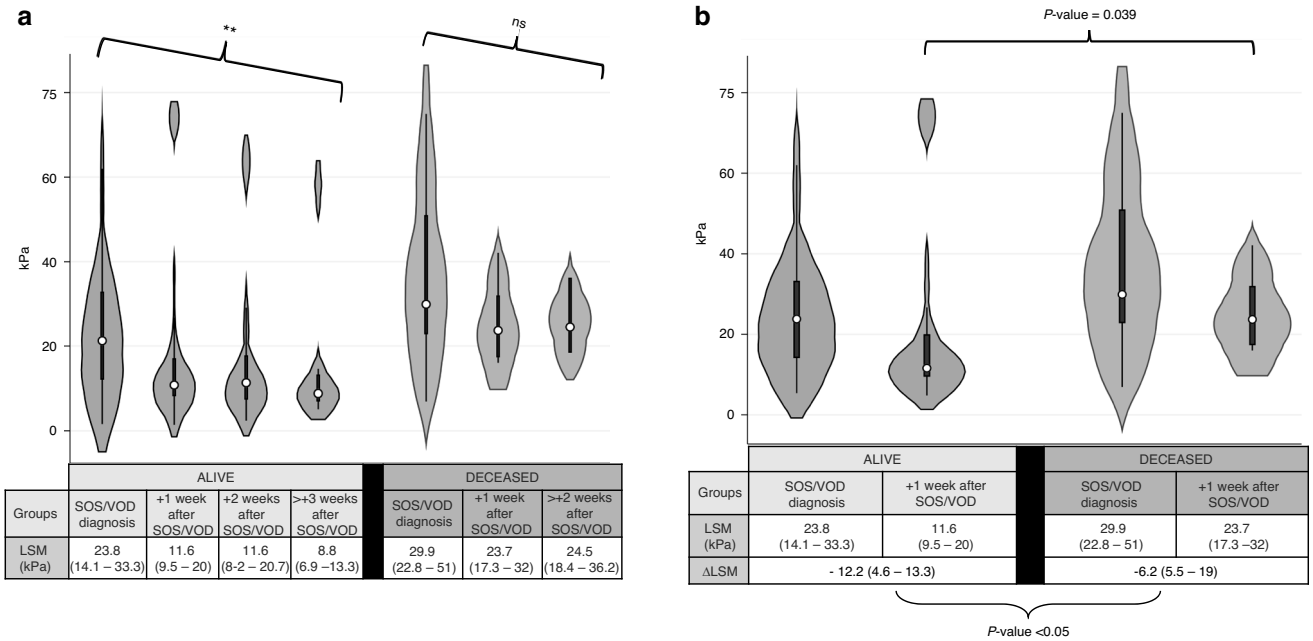


Fig. 4 Modification of liver stiffness measurement (LSM) following SOS/VOD diagnosis and treatment. a shows the distribution of liver stiffness measurement (LSM) values (kPa) over time in patients who survived, at the time of SOS/VOD diagnosis and at successive time points (+1 week, +2 weeks, and >+3 weeks post-diagnosis). **b** displays corresponding LSM values in patients who died. Violin plots represent the distribution of values, with the median indicated by a white dot and interquartile ranges by a black bar. Kernel density outlines reflect the shape of the distribution. LSM liver stiffness measurement, kPa kilopascal, SOS sinusoidal obstruction syndrome, VOD veno-occlusive disease, ns not significant. *p value < 0.05; **p value < 0.005.

Table 6. Non-SOS/VOD hepatic complications on day + 100.

Variables	Overall population (n.941)
Overall + 100 days complications	903
	95.96
	[95% CI: 94.7–96.9]
CTC 0-3	347 (36.9)
CTC 4-5	594 (63.1)
Liver GvHD	27 (2.9)
CTC 0-3	27 (100)
CTC 4-5	0
DILI	35 (3.7)
CTC 0-3	35 (100)
CTC 4-5	0
Isolated Hyperbilirubinemia	67 (7.1)
CTC 0-3	65 (97)
CTC 4-5	2 (3)
Hepatitis	5 (0.53)
CTC 0-3	4 (80)
CTC 4-5	1 (20)
Cholecystitis and/or cholangitis	11 (1.2)
CTC 0-3	11 (100)
CTC 4-5	0
Data are n (%), unless otherwise specified	

CTC common terminology criteria, *DILI* drug induced liver injury, *GVHD* graft versus host disease, *n* number, *SOS* sinusoidal obstruction syndrome, *VOD* veno-occlusive disease.

population. Figure 5 showed that LSM at the day of diagnosis differed significantly between VOD/SOS and other liver-related complications classified as either CTC 4-5 or CTC 0-3, whether LSM was measured in kPa (5 A) or m/sec (5B). In the Supplementary Figs. S6, S7, significant differences in LSM values between patients with VOD/SOS and those experiencing other HSCT complications within +100 days, according to CTC classification are reported as well as the sensitive analysis for differential diagnosis among allo-HSCT patients (Supplementary Fig. S8**)**.

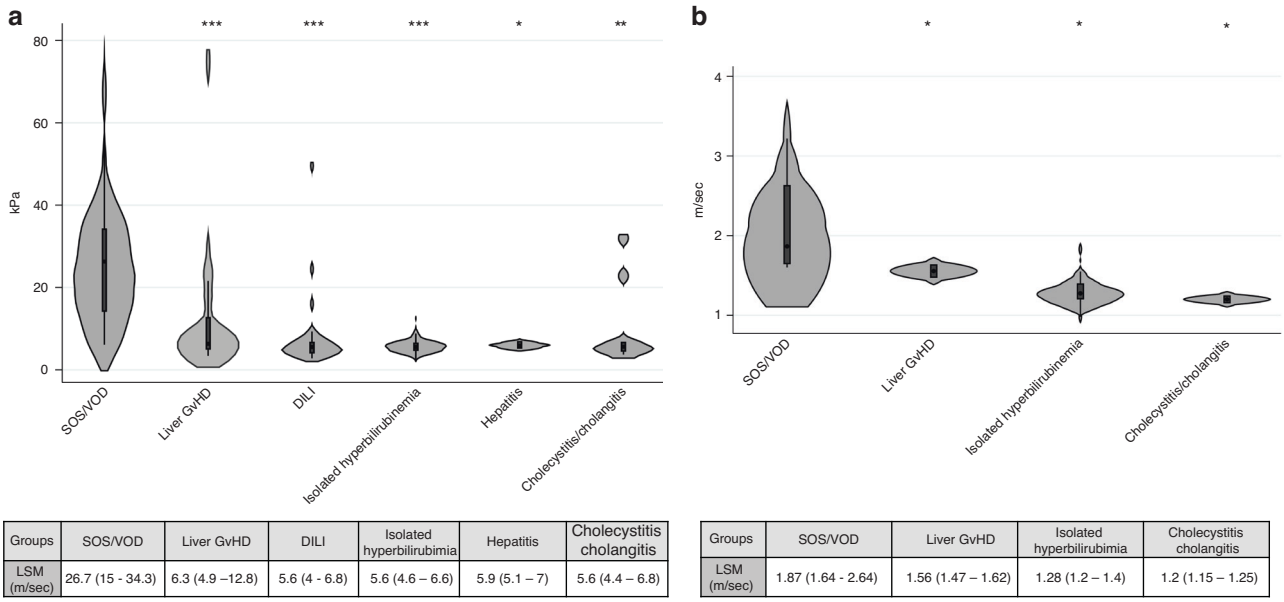
DISCUSSION

The diagnosis of VOD still poses a significant challenge [28]. This stems from the mortality risk when diagnosis is delayed [29] and the complexity of the differential diagnosis [9]. While clinical criteria are the primary diagnostic tool [2, 5], their limited performance accuracy further complicates the process, especially in the case of frail patients where invasive procedures pose a considerable risk [16]. Therefore, a noninvasive approach shows promise in improving diagnostic accuracy, given high sensitivity and specificity [15].

Liver elastography is an established, validated, noninvasive procedure for assessing portal hypertension in patients with advanced chronic liver diseases. Given portal hypertension's pivotal role in the pathophysiology of VOD/SOS, elastography emerges as a potential noninvasive diagnostic tool within clinical contexts [17].

Retrospective and prospective studies conducted within single-institution settings have provided evidence supporting elastography in practice [30–38]. These findings prompted its inclusion in the revised European Society for Blood and Marrow Transplantation (EBMT) criteria [2], though without extensive multicentric validation.

Our study successfully met the primary endpoint and established, for the first time, the diagnostic ability of LSM to non-invasively diagnose VOD/SOS after HSCT. LSM below 6 kPa excludes VOD/SOS with 100% sensitivity, while a value above 25 kPa confirms it with



Groups	SOS/VOD	Liver GvHD	DILI	Isolated hyperbilirubimia	Hepatitis	Cholecystitis cholangitis
LSM (m/sec)	26.7 (15 - 34.3)	6.3 (4.9 –12.8)	5.6 (4 - 6.8)	5.6 (4.6 – 6.6)	5.9 (5.1 – 7)	5.6 (4.4 – 6.8)

Groups	SOS/VOD	Liver GvHD	Isolated hyperbilirubimia	Cholecystitis cholangitis
LSM (m/sec)	1.87 (1.64 - 2.64)	1.56 (1.47 – 1.62)	1.28 (1.2 – 1.4)	1.2 (1.15 – 1.25)

Fig. 5 Differential diagnosis between SOS/VOD and other liver-related complications after allogeneic stem cell transplantation. a shows liver stiffness measurement (LSM) values expressed in kilopascals (kPa), and **b** shows LSM values expressed in meters per second (m/s), in patients diagnosed with SOS/VOD compared to those with other liver-related complications within +100 days post-stem cell transplantation (SCT). Violin plots display the distribution of values, with medians (white dots) and interquartile ranges (black bars). These data highlight the potential of LSM to support differential diagnosis in the context of post-transplant hepatic complications. CTC common terminology criteria, DILI drug-induced liver injury, GvHD graft-versus-host disease, m/s meter per second, ns not significant, LSM liver stiffness measurement, kPa kilopascal, SOS sinusoidal obstruction syndrome, VOD veno-occlusive disease. *p value < 0.05; **p value < 0.005; ***p value < 0.0001.

99.9% specificity and 96.3% PPV. Values between these thresholds are evaluated using a step-wise algorithm applying the "three-time pre-HSCT rule," enhancing diagnostic accuracy.

LSM diagnostic cut-off values were observed exclusively in patients who developed VOD/SOS, distinguishing it from other complications such as GVHD, drug-induced liver injury (DILI), and other liver/biliary diseases. This highlights the potential of LSM in facilitating an accurate differential diagnosis process in clinical practice, in addition to its diagnostic capabilities. Finally, LSM was significantly associated with treatment response and patient outcomes in those specifically managed for VOD/SOS, offering also a valuable measure of response to therapy.

LSM's merits for VOD/SOS diagnosis and management are notable, especially given VOD/SOS's high mortality and dependence on early intervention. Despite the mortality rate being somewhat mitigated by specific medications such as defibrotide, which effectively reduces it to roughly 30% [3], as even confirmed in this cohort, a prompt and accurate diagnosis of VOD/SOS can lead to a life-saving treatment that can significantly improve the patient's prognosis [29, 39].

Our study, which was conducted in Italy between 2018 and 2022, is one of the largest prospective cohorts that has been conducted on HSCT population. Beyond diagnostics and monitoring, it provides insights into real-world incidence and risk factors for VOD/SOS, serving as a benchmark for incidence, treatment, and outcomes. Notably, we found an incidence of VOD/SOS of approximately 5.5%, with higher rates observed in pediatric patients compared to adults (14.4% vs. 3.6%); relevant literature reported highly variable incidence of VOD/SOS after HSCT across the last decades [28] and our study showed lower incidence than the rates recently reported by the DEFIFrance Registry Study [40] and in line with a real-world UK experience [41]. This study stands out for its significant contribution in prospectively defining the true incidence of this complication in both pediatric and adult settings. It is crucial to understand that the diagnostic test's effectiveness, measured by high PPV and NPV, is not inherent to the test itself but varies depending on the prevalence of the condition being tested for. Although the incidence of the condition may be low, our LSM stepwise algorithm has been shown to have significant diagnostic accuracy even in subgroups of the population.

Conducting a prospective, large-scale study, our results also identified the current cumulative incidence and risk factors of VOD/SOS in the real-world clinical practice. Our findings confirmed in a prospective trial, some of the risk factors already identified by the EBMT, often derived from retrospective studies and/or expert opinion [2, 5]. However, our findings also indicate that some previously identified risk factors may no longer be as relevant or strongly associated with VOD/SOS in the context of modern HSCT epidemiology and management. Our investigation showed that traditional hepatological risk factors, such as viral hepatitis, may lack statistical significance. Furthermore, our multivariable analysis unveiled hitherto unrecognised risk factors, such as a diagnosis of ALL, which underscore the necessity for external validation due to their potential clinical implications. This comprehensive approach enhances our understanding of the disease landscape and facilitates the development of targeted interventions.

While our study provides valuable insights, it's essential to acknowledge potential limitations. Criticisms may question the relationship among incidence, risk factors, and elastometry, as diagnostic measures can be influenced by disease prevalence. However, our study addressed this concern by leaving VOD/SOS diagnosis to clinical investigators, ensuring diagnostic accuracy and minimising bias. It is important to note that the results obtained by the operators were not blinded to the VOD/SOS diagnosis; additionally, even though 82% of the patients presented with ascites (mild to moderate; mainly lower quadrant) at the time of diagnosis, the LSM assessment was not affected, and valid results were obtained. Despite these factors, it reflects each center's real-world, multidisciplinary approach with successful collaboration.

Furthermore, our study was not designed to assess the role of preclinical diagnosis since we evaluated LSM by preplanned fixed schedule. Although we considered LSM on the day of clinical

diagnosis, it would be possible that earlier assessments or a day-by-day assessment could provide further insights into disease development and progression [9]. In fact, applying the stepwise algorithm to the LSM taken before the diagnostic one would have allowed a preclinical diagnosis in 21% of VOD/SOS patient. LSM predicts the onset of VOD/SOS diagnosis by a median of +7 days (ranging from +1 to +11 days), and only 6% of patients without VOD/SOS were incorrectly classified. LSM can increase before the onset of clinical symptoms due to the presence of VOD/SOS. During the initial phase of VOD/SOS development, only a few areas near the centrolobular vein (zone 3) are affected by progressive sinusoidal damage, leading to initial necrosis and congestion. Recent studies have shown that these conditions can induce an increase in LSM, even in the absence of clinically significant portal hypertension (CSPH) [18]. An additional limitation is the small proportion of patients undergoing auto-HSCT included in our study (< 5% of the cohort). Given the underrepresentation of auto-HSCT cases relative to real-world transplantation activity, their inclusion may introduce a potential selection bias. To address this, we performed a sensitivity analysis focused exclusively on allo-HSCT patients, which confirmed the robustness of our findings showing no significant differences in diagnostic analysis. Notably, since auto-HSCT does not play a role in key aspects such as the differential diagnosis with GVHD, its exclusion allows for a clearer assessment of risk factors and diagnostic accuracy in the allogeneic setting. The updated analyses are reported in the Supplementary Materials.

Finally, the relatively low number of cases assessed by m/sec could result in less reliable outcomes when modelling, although the findings are concordant with those obtained with kPa measures.

In conclusion, our study highlights the significant potential of LSM as a non-invasive diagnostic tool for VOD/SOS following HSCT. The ability of LSM to expedite diagnosis, aid in differential diagnosis, and predict treatment response represents a major advancement in improving patient outcomes. LSM, particularly when measured in kPa via TE, is emerging as a valuable addition to the diagnostic and therapeutic arsenal for hematologists.

From a broader perspective, we strongly believe that in the current era of hepatology, LSM assessment should be considered the hepatologist's 'stethoscope' and routinely performed in all patients undergoing HSCT to assess liver health. While we acknowledge that its immediate global implementation may face challenges, we are confident that increasing awareness of VOD/SOS will facilitate the integration of LSM assessment, alongside liver ultrasound, into routine screening protocols for HSCT patients.

Several attributes make LSM particularly valuable in clinical practice. Its non-invasive nature, ease of bedside application, and high patient tolerability enhance its practicality and patient-centered approach. Moreover, its reproducibility, standardized quantitative assessment, and elimination of risks associated with radiation, contrast agents, and invasive procedures make it a preferable alternative to HVPG measurement [15]. LSM has demonstrated high accuracy in distinguishing VOD/SOS from other hepatobiliary complications post-HSCT, providing reliable diagnostic insights even for operators with limited ultrasound proficiency.

Looking foreard, the role of LSM in VOD/SOS diagnosis and management remains highly promising, with ongoing efforts focused on validation and optimization. Despite the need for further research, its current achievements mark a substantial step forward in improving VOD/SOS diagnosis, fostering enhanced patient care and clinical outcomes.

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AUTHOR CONTRIBUTIONS

Federico Ravaioli, Antonio Colecchia, Andrea Pession, Davide Festi, and Francesca Bonifazi were responsible for the study concept and design, literature search, and data collection from participating centers. Federico Ravaioli, Antonio Colecchia, Francesco Barbato and Francesca Bonifazi were responsible for data review, verification and analysis, data interpretation, manuscript drafting, and statistical analysis. Jacopo Peccatori, Daria Pagliara, Anna Grassi, Riccardo Masetti, Barbara Sarina, Simona Sica, Simone Cesaro, Chiara Nozzoli, Giovanni Manfredi Assanto, Lucia Prezioso, Stella Santarone, Francesco Saglio, Ester Vanni, Attilio Olivieri, Mario Delia, Edoardo Benedetti, Francesco Zallio, Fabrizio Pane, Cristina Skert, Mariacristina Menconi, Fabio Benedetti, Francesco De Felice, Luigi Colecchia, Tamara Belotti, Luigina Vanessa Alemanni, Margherita Ursi, Giovanni Marasco, Marcello Roberto, Amanda Vestito, Elton Dajti, Matteo Garcovich, Stefania Bramanti, Daniela Taurino, Francesco Quagliarella, Fabio Ciceri, and Arcangelo Prete were responsible for obtaining original data, coding and providing data, interpreting data, and critically revising the manuscript. All authors critically revised the manuscript and approved the final version. All authors were responsible for data and submission decisions.

COMPETING INTERESTS

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