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ARTICLE

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

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Abstract

Allogeneic hematopoietic cell transplantation (alloHCT) is a complex, potentially fatal therapy featuring a myriad of complications. Triggering event(s) of such complications vary significantly, but often a so-called "multi-organ failure" (MOF) is reported as the leading cause of death. The identification of the exact trigger of MOF is critical towards early and disease-specific intervention to improve outcome. We examined data from 202 alloHCT patients reported to have died of MOF from the EBMT registry aiming to determine their exact cause of death focusing on veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) due to its life-threatening, often difficult to capture yet preventable nature. We identified a total of 70 patients (35%) for whom VOD/SOS could be considered as trigger for MOF and leading cause of death, among which 48 (69%) were previously undiagnosed. Multivariate analysis highlighted history of hepatic comorbidity or gentuzumab use and disease status beyond CR1 as the only significant factors predictive of VOD/SOS incidence (OR = 6.6; $p = 0.001$ and OR = 3.3; $p = 0.004$ respectively). VOD/SOS-related MOF was widely under-reported, accounting for 27% of deaths attributed to MOF of unknown origin without a previous VOD/SOS diagnosis. Our results suggest most missed cases developed late VOD/SOS beyond 21 days post-alloHCT, highlighting the importance of the newly revised EBMT criteria.

Introduction

Sinusoidal obstruction syndrome (SOS), previously known as veno-occlusive disease (VOD) is a life-threatening complication observed after hematopoietic cell transplantation (HCT) [1]. It is believed to occur following endothelial injury due to toxic metabolites generated from conditioning regimens [2], and its diagnosis is mostly clinical based on criterion scoring systems [3–5]. VOD/SOS can develop anytime post-transplant classically within 3 weeks but up to months later with a peak incidence of around 15% in high risk adult patients [1, 3]. While VOD/SOS can present as a mild self-resolving disease, around 46% of cases present with aggressive disease leading to multiorgan failure (MOF) with a mortality exceeding 80% [6]. Severe VOD/SOS has a very rapid clinical course and hence a very narrow therapeutic window for intervention [7], with significant survival advantage associated with early treatment with defibrotide [8]. Furthermore, prophylactic defibrotide benefits have been established in the pediatric population but is still under investigation in adults

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[9, 10]. The established criteria, in particular according to Baltimore carry the risk of underdiagnosing VOD/SOS due to the 21-day limitation and the obligatory hyperbilirubinemia, not present at diagnosis in 29 and 15% of pediatric and adult patients, respectively [11]. Accordingly it is believed by expert opinion that there is a true urgency for the awareness of VOD/SOS being widely underdiagnosed, leading to the vague diagnosis of MOF [12].

Transplant patients often have concomitant comorbidities and their deterioration is usually multifactorial encompassing their original disease, infections, graft-versus-host disease (GVHD), VOD/SOS, and drug toxicities among other factors [13]. Some studies have retrospectively reviewed transplant patients' labelled cause of death and found major discrepancies raising concerns about the accuracy of reported disease burdens [13]. No retrospective studies however, investigated the incidence of VOD/SOS as an initiating factor in patients succumbing to MOF to determine the hidden burden of this disease. The aim of this study was to quantify the proportion of adult acute leukemia patients that succumbed to MOF following alloHCT and who fit the VOD/SOS criteria prior to their deterioration. For that purpose, we studied a large sample from the European Society for Blood and Marrow Transplantation (EBMT) registry.

Materials and methods

Study design and data collection

This was a retrospective, registry-based, multicenter analysis [14]. Data were provided and approved by the EBMT Acute Leukemia Working Party. The EBMT is a voluntary collaborating working group of more than 600 transplant centers that are required to report all consecutive stem cell transplantations and follow-up once a year, with regularly performed audits to determine the accuracy of the data. Since the 1st of January 2003, all transplantation centers have been required to obtain written informed consent prior to data registration with the EBMT, as per the Declaration of Helsinki of 1975.

Eligibility criteria for this analysis included adult patients (aged >18 years) with acute leukemia who received an alloHCT between 2010 and 2018 with reported cause of death being MOF (Supplementary Table 1) anytime post-transplant.

Patient-related variables collected included recipient and donor age and gender, patient blood group, history of hepatic comorbidities and obesity, date of diagnosis, the chronologic number of the transplant, disease status, Karnofsky performance score (KPS) and HCT specific comorbidity index (HCTI) at time of transplant. Transplant-related factors included date, conditioning regimen, source of stem cells, donor type and degree of mismatch, and ex-vivo/in-vivo manipulation. GVHD-related factors included prophylaxis and treatment, with onset and grade of GVHD development.

A questionnaire was sent to participating centers for missing variables in the registry and study-specific variables. These included the use of gemtuzumab prior to transplant, VOD prophylaxis use, VOD diagnosis and date of diagnosis when applicable, weight, bilirubin, creatinine and liver enzyme levels at transplant and last month before death, the presence of iron overload, hepatomegaly, and ascites before death, and results of investigational liver ultrasounds/biopsies done prior to death when applicable. These criteria were then used for a posteriori VOD diagnosis within the last month before death which has been reported as MOF.

Definitions

Myeloablative conditioning (MAC) was defined as a regimen containing either total body conditioning (TBI) with a dose equal or greater than 8 Gy, a total dose of oral busulfan (Bu) greater than 8 mg/kg, or a total dose of intravenous Bu greater than 6.4 mg/kg. All other regimens were defined as reduced intensity conditioning (RIC) [15]. Diagnosis and grading of acute [16] and chronic GVHD [17] were performed by transplant centers using standard criteria. High-resolution HLA allele typing at loci A, B, C, DRB1, and DQ was retrieved from the EBMT registry for both the patient and the donor. Hepatic comorbidity was defined according to the HCTI definition by Sorror et al. [18].

Endpoints

Endpoints included determining the proportion of patients that fit at least one VOD/SOS diagnosis scoring system, including the Baltimore criteria [4], modified Seattle criteria [5], and classic and late EBMT criteria [3], and how many were not previously diagnosed with VOD/SOS; along with identifying risk factors for VOD/SOS development.

Statistical analysis

Patient, disease, and transplant-related characteristics were compared by using χ^2 statistics for categorical variables and the Mann-Whitney test for continuous variables. Comparison of the outcomes was performed using a logistic model and results expressed as an odds ratio (OR) with 95% confidence interval (CI). All tests were two sided. All analyses were performed using SPSS 24.0 (SPSS Inc, Chicago, IL, USA)) and R version 3.6.2 (R Core Team. R:

a language for statistical computing. 2014. R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient and transplantation characteristics

For the purpose of this analysis, we identified 253 adult patients, 51 (20%) of which were excluded due to lack of appropriate data to make or rule out a VOD/SOS diagnosis. Median age was 50.5 years, ranging from 20 to 73.4 years, and 58% of patients were males. Patients had acute leukemia (73% acute myeloid leukemia (AML), 24% acute lymphoblastic leukemia (ALL) & 3% mixed phenotype) and were reported to the EBMT registry to have died from MOF. Forty-nine percent of patients underwent transplantation in first complete remission (CR1), 23% in CR2 and 28% had advanced disease. In total, Twelve patients had a history of hepatic comorbidity, and 8 patients received gemtuzumab before transplant (Table 1).

Patients were allografted between 2010 and 2018 (median 2015) from a matched sibling (24%), unrelated (58%), haploidentical (11%), or cord blood (CB) (7%) donor. Conditioning was MAC in 57% of patients and 28% underwent TBI. Finally, approximately one-third of the study population received VOD/SOS prophylaxis, mainly consisting of ursodiol alone (49%), heparin alone (25%), or a combination of both (16%). The remaining 10% received other drugs and combinations (Table 2).

VOD/SOS as primary cause of death

Fourteen patients were initially diagnosed with VOD/SOS, and an additional 8 were reported by centers after questionnaires were sent. All remaining patients were reported as never having VOD. Applying the most common VOD/SOS scoring systems using data collected from the last month before MOF-induced death, we identified a total of 70 (35%) patients that fit a VOD/SOS diagnosis, 48 (69%) of whom were previously undiagnosed (Fig. 1). VOD/SOS could therefore be considered as a trigger of MOF progression ultimately leading to death. Twenty-four patients were diagnosed using the modified Seattle criteria, 11 also fit the classic EBMT/Baltimore criteria, and 41 patients were diagnosed using the late EBMT criteria. Five remaining patients were labeled as VOD/SOS by their centers but did not meet the criteria for any of these systems. No post-mortem pathology was available to confirm the diagnosis.

Univariate analysis comparing patients who died of VOD/SOS related MOF with non-VOD/SOS related MOF identified disease status at transplant, donor type and graft cell source, KPS, the presence of hepatic comorbidity, and the use of gemtuzumab before transplant or mycophenolate mofetil (MMF) for GVHD prophylaxis as well as acute GVHD incidence as significantly different across the two groups (Tables 1 and 2). In fact, patients with VOD/SOS related MOF were less likely to be in CR1 or have a KPS >= 90 compared to non-VOD/SOS related MOF, with rates of 35% vs 56% ($p = 0.022$) and 58% vs 72% ($p = 0.045$) respectively; but were more frequently associated with haploidentical or CB transplants, history of hepatic comorbidities, and gemtuzumab or MMF use with rates of 27% vs 13% ($p = 0.013$), 16% vs 3% ($p = 0.007$), 21% vs 4% ($p = 0.003$), 9% vs 2% ($p = 0.022$), and 46% vs 29% ($p = 0.02$) respectively. Importantly, there was a strong correlation between MMF use for GVHD prophylaxis and haploidentical or CB transplantation ($p < 0.0001$), which were associated with increased VOD/SOS incidence acting as possible confounders between the graft type and the choice of GVHD prophylaxis. Interestingly, although there were no differences in overall acute GVHD grades II-IV & III-IV rates, GVHD grades I-III were significantly increased in patients with non-VOD/SOS related MOF (43.1% vs 19.4%) while grade IV GVHD was more common in the VOD/SOS group (21% vs 10%). This disproportionate increase in grade IV GVHD in the VOD/SOS group could be explained by a possible misdiagnosis in these patients due to the overlap in MOF presentation, whereas patients were wrongly labeled as having severe GVHD and not VOD/SOS. The significantly lower median survival after transplant in the VOD/SOS group at 61 days compared to 128 days in the non-VOD/SOS related MOF ($p = 0.0005$) could explain the increased incidence of grades I-III GVHD in the non-VOD/SOS group. In a multivariate analysis using a stepwise selection of significant and clinically relevant variables (Table 3), CR1 and the presence of hepatic comorbidity or gemtuzumab use were the only two significant factors associated with VOD/SOS incidence with an OR of 0.29 ($p = 0.004$) and 6.6 ($p = 0.001$) respectively. Finally, among patients that fit VOD/SOS diagnosis criteria, 87% had high bilirubin levels before death, 51% presented with ascites, 36% with hepatomegaly, and 43 and 29% had weight gain of at least 2 and 5% of body weight respectively, from transplant day 0 to death (Supplementary Table 2).

Discussion

VOD/SOS is a life-threatening complication post-alloHCT, widely believed to be a sequela of treatment induced endothelial injury [1, 2], with mortality exceeding 80% in severe cases and a very narrow therapeutic window for intervention [6, 7]. VOD/SOS diagnosis is mostly clinical using one of many available diagnostic scoring systems [3–5], which makes it easy to overlook and requires very

Table 1 Patient characteristics comparison between VOD-related and non-VOD-related MOF.

	no VOD ($n = 132$)	VOD ($n = 70$)	P value	Population ($n = 202$)
Patient age at transplant (years)				
median (min-max) [IQR]	51.4 (20–73.4) [40.8–61.1]	50.5 (20.9–69.5) [37.4–59.9]	0.39	50.5 (20–73.4) [38.6–60.8]
Gender				
Male	76 (57.6%)	40 (57.1%)	0.95	116 (57.7%)
ABO blood group				
A	53 (40.2%)	31 (44.3%)	0.6	83 (41.6%)
B	21 (15.9%)	6 (8.6%)		27 (13.4%)
AB	8 (6.1%)	5 (7.1%)		13 (6.4%)
O	50 (37.9%)	28 (40.0%)		78 (38.6%)
Diagnosis				
AML	93 (70.5%)	54 (77.1%)	0.5	147 (72.8%)
ALL	34 (25.8%)	15 (21.4%)		49 (24.3%)
Mixed Phenotype	5 (3.8%)	1 (1.4%)		6 (3%)
AML				
de novo	71 (76.3%)	43 (79.6%)	0.65	114 (77.6%)
Secondary AML	22 (23.7%)	11 (20.4%)		33 (22.4%)
Myelodysplasia related changes				
Good	12 (15.8%)	7 (15.9%)	0.44	19 (15.8%)
Interm	46 (60.5%)	22 (50.0%)		68 (56.7%)
Poor	18 (23.7%)	15 (34.1%)		33 (27.5%)
Missing	17	10		27
ALL				
Ph- B ALL	13 (48.1%)	7 (58.3%)	0.27	20 (51.3%)
Ph+ B ALL	3 (11.1%)	3 (25%)		6 (15.4%)
T ALL	11 (40.7%)	2 (16.7%)		13 (33.3%)
Missing	7	3		10
Status at transplant				
CR1	73 (55.7%)	24 (35.3%)	0.022	97 (48.7%)
CR2+	27 (20.6%)	19 (27.9%)		46 (23.1%)
Advanced	31 (23.7%)	25 (36.8%)		56 (28.1%)
Missing	1	2		3
Status details				
Primary Refractory	13 (9.9%)	12 (17.6%)	0.089	25 (12.6%)
CR1	73 (55.7%)	24 (35.3%)		97 (48.7%)
CR2	24 (18.3%)	15 (22.1%)		39 (19.6%)
CR3 +	3 (2.3%)	4 (5.9%)		7 (3.5%)
First relapse	15 (11.5%)	11 (16.2%)		26 (13.1%)
Second relapse or more	3 (2.3%)	2 (2.9%)		5 (2.5%)
Missing	1	2		3
Karnofsky score				
<80	14 (10.9%)	9 (13.6%)	0.58	23 (11.9%)
>=80	114 (89.1%)	57 (86.4%)		171 (88.1%)
Missing	4	4		8
Karnofsky score				
<90	36 (28.1%)	28 (42.4%)	0.045	64 (33%)

Table 1 (continued)

	no VOD ($n = 132$)	VOD ($n = 70$)	P value	Population ($n = 202$)
>=90	92 (71.9%)	38 (57.6%)		130 (67%)
Missing	4	4		8
Comorbidity Index				
0	66 (69.5%)	31 (58.5%)	0.12	97 (65.5%)
1 or 2	11 (11.6%)	13 (24.5%)		24 (16.2%)
>= 3	18 (18.9%)	9 (17%)		27 (18.2%)
Missing	37	17		54
Hepatic comorbidity				
No	81 (96.4%)	34 (79.1%)	0.003	115 (91%)
Yes	3 (3.6%)	9 (20.9%)		12 (9%)
Missing	48	27		75
Obesity				
No	110 (93.2%)	53 (89.8%)	0.43	163 (92.1%)
Yes	8 (6.8%)	6 (10.2%)		14 (7.9%)
Missing	14	11		
Gentuzumab before transplant				
No	130 (98.5%)	64 (91.4%)	0.022	194 (96%)
Yes	2 (1.5%)	6 (8.6%)		8 (4%)
Hepatic comorbidity or Gentuzumab before transplant				
No	79 (94%)	32 (68.1%)	< 0.0001	111 (85%)
Yes	5 (6%)	15 (31.9%)		20 (15%)
Missing	48	23		71

VOD veno-occlusive disease, *Ph* Philadelphia, *CR* complete remission.

close attention. Expert opinion suspects that it is widely underdiagnosed [12], and our results strongly suggest that to be the case, with up to 27% of deaths from MOF of unknown origin being attributable to previously undiagnosed VOD/SOS. Furthermore, we do not believe this to be a sequelae of underreporting, as our data show that most cases were not reported by centers even after explicitly asked through questionnaires while also considering the fact that both VOD/SOS and MOF are available in the registry under secondary causes of death (Supplementary Table 1). This is extremely relevant considering the fact that appropriate treatment with defibrotide is readily available [8], and makes a stronger case for its use as prophylaxis for high-risk patients [9, 10]. In fact, pooled data from 17 defibrotide studies ($n = 2598$) have shown estimated Day+100 survival rates around 55% in patients treated with defibrotide [8]. Significant difference in survival however is noted between patients developing MOF (44%) and those without MOF (71%), highlighting the importance of prompt treatment before progression of the disease and increased mortality [8]. In addition, clinicians should recognize the existence of late onset and anicteric VOD/SOS, and the need for its prompt treatment with defibrotide and other measures beyond the immediate post-transplant period.

Known risk factors for VOD/SOS such as advanced disease beyond CR1, low performance status at transplant, and the presence of pre-existing hepatic comorbidity or use of hepatoxic drugs were significantly more common in patients with VOD/SOS. Also, importantly, the use of haploidentical and CB grafts which were possibly confounded by the consistent use of the highly hepatotoxic MMF for GVHD prophylaxis in these settings were significantly associated with increased VOD/SOS risk. The use of other GVHD prophylactic drugs might therefore be more appropriate to limit the incidence of VOD/SOS in extremely high-risk patients [19, 20]. It is interesting to note that although MAC conditioning and the use of TBI are usually associated with increased VOD/SOS incidence [21], we did not observe any significant effect. The use of FLAMSA conditioning was more prevalent in the VOD/SOS group however (20% vs 5%), which could have masked the expected advantage of RIC conditioning.

VOD/SOS can develop at any time post-transplant, but it is classically considered an early complication observed within 3 weeks of alloHCT [1, 3]. While the median VOD/SOS related MOF survival was dramatically lower than that of non-VOD/SOS related MOF (61 days vs 128 days), it is important to note that the majority of missed cases occurred

Table 2 Transplant characteristics & outcome comparison between VOD-related and non-VOD-related MOF.

	no VOD ($n = 132$)	VOD ($n = 70$)	P value	Population ($n = 202$)
Year of transplant				
median (min-max)	2015 (2010–2018)	2015 (2010–2018)	0.56	2015 (2010–2018)
Total number of alloHCTs per center				
median (range)	368 (50–1469)	446 (50–1469)	0.77	
Number of this transplant				
First	117	61	0.75	178 (88.1%)
Second	15 (11.4%)	9 (12.9%)		24 (11.9%)
Donor				
MSD	33 (25.2%)	16 (22.9%)		49 (24.4%)
UD 10/10	54 (41.2%)	19 (27.1%)		73 (36.3%)
UD 9/10	20 (15.3%)	10 (14.3%)		30 (14.9%)
UD 8/10	2 (1.5%)	2 (2.9%)		4 (2%)
UD uk	5 (3.8%)	4 (5.7%)		9 (4.5%)
Haploidentical	14 (10.7%)	9 (12.9%)		23 (11.4%)
Cord blood	3 (2.3%)	10 (14.3%)		13 (6.5%)
missing	1	0		1
MSD/UD	114 (87%)	51 (72.9%)	0.013	165 (82%)
Haplo/CB	17 (13%)	19 (27.1%)		36 (18%)
Cell source				
BM	11 (8.3%)	5 (7.1%)	0.007	16 (7.9%)
PB	115 (87.1%)	54 (77.1%)		169 (83.7%)
BM + PB	2 (1.5%)	0 (0%)		2 (1%)
CB	0 (0%)	4 (5.7%)		4 (2%)
Double CB	3 (2.3%)	6 (8.6%)		9 (4.5%)
BM + CB	1 (0.8%)	0 (0%)		1 (0.5%)
PB + CB	0 (0%)	1 (1.4%)		1 (0.5%)
ex-vivo T-cell depletion				
No	116 (89.9%)	63 (91.3%)	0.75	179 (90.4%)
Yes	13 (10.1%)	6 (8.7%)		19 (9.6%)
missing	3	1		4
In-vivo T-cell depletion				
No	56 (43.1%)	37 (52.9%)	0.19	93 (46.5%)
Yes	74 (56.9%)	33 (47.1%)		107 (53.5%)
missing	2	0		2
No	56 (43.1%)	37 (52.9%)	0.37	93 (46.5%)
ATG	69 (53.1%)	32 (45.7%)		101 (50.5%)
Campath	5 (3.8%)	1 (1.4%)		6 (3%)
missing	2	0		2
Conditioning				
MAC	75 (56.8%)	40 (57.1%)	0.96	115 (56.9%)
RIC	57 (43.2%)	30 (42.9%)		87 (43.1%)
BuCy	16 (12.3%)	9 (12.9%)		25 (12.5%)
BuFlu	34 (26.2%)	7 (10%)		41 (20.5%)
TBF	9 (6.9%)	6 (8.6%)		15 (7.5%)
FluMel	13 (10%)	6 (8.6%)		19 (9.5%)
TreoFlu	2 (1.5%)	3 (4.3%)		5 (2.5%)

Table 2 (continued)

	no VOD ($n = 132$)	VOD ($n = 70$)	P value	Population ($n = 202$)
FLAMSA	7 (5.4%)	14 (20%)		21 (10.5%)
TBI	35 (26.9%)	21 (30%)		56 (28%)
Other	14 (10.8%)	4 (5.7%)		18 (9%)
missing	2	0		2
GVHD prevention				
CSA	28 (21.5%)	13 (18.6%)	0.22	41 (20.5%)
CSA + MTX + MMF	56 (43.1%)	22 (31.4%)		78 (39%)
MTX + Tacrolimus	4 (3.1%)	1 (1.4%)		5 (2.5%)
csa+mmf+tacro	27 (20.8%)	23 (32.9%)		50 (25%)
CSA + Tacrolimus	0 (0%)	1 (1.4%)		1 (0.5%)
CSA + MTX + MMF	2 (1.5%)	4 (5.7%)		6 (3%)
MMF + Tacrolimus	6 (4.6%)	5 (7.1%)		11 (5.5%)
MMF + Sirolimus	1 (0.8%)	0 (0%)		1 (0.5%)
CSA + MMF + Tacrolimus	1 (0.8%)	0 (0%)		1 (0.5%)
Tacrolimus+Sirolimus	2 (1.5%)	1 (1.4%)		3 (1.5%)
Other	3 (2.3%)	0 (0%)		3 (1.5%)
missing	2	0		2
MMF for GVHD prevention				
No	92 (70.8%)	38 (54.3%)	0.02	130 (65%)
Yes	38 (29.2%)	32 (45.7%)		70 (35%)
missing	2	0		2
MTX for GVHD prevention				
No	68 (52.3%)	42 (60%)	0.3	110 (55%)
Yes	62 (47.7%)	28 (40%)		90 (45%)
missing	2	0		2
acute GVHD				
Grade I	8 (6.5%)	3 (4.5%)	0.009	11 (5.8%)
Grade II	24 (19.5%)	7 (10.4%)		31 (16.3%)
Grade III	21 (17.1%)	3 (4.5%)		24 (12.6%)
Grade IV	12 (9.8%)	14 (20.9%)		26 (13.7%)
Present, grade unknown	2 (1.6%)	0 (0%)		2 (1.1%)
No aGvHD	56 (45.5%)	40 (59.7%)		96 (50.5%)
missing	9	3		12
acute GVHD II-IV				
No	64 (52.9%)	43 (64.2%)	0.13	107 (56.9%)
Yes	57 (47.1%)	24 (35.8%)		81 (43.1%)
missing	11	3		14
acute GVHD III-IV				
No	88 (72.7%)	50 (74.6%)	0.78	138 (73.4%)
Yes	33 (27.3%)	17 (25.4%)		50 (26.6%)
missing	11	3		14
chronic GVHD				
No	100 (78.1%)	58 (82.9%)	0.43	158 (79.8%)
Yes	28 (21.9%)	12 (17.1%)		40 (20.2%)
missing	4	0		4

Table 2 (continued)

	no VOD ($n = 132$)	VOD ($n = 70$)	P value	Population ($n = 202$)
GVHD (acute ± chronic)				
No	61 (46.2%)	37 (52.9%)	0.37	98 (48.5%)
Yes	71 (53.8%)	33 (47.1%)		104 (51.5%)
VOD prophylaxis				
No	93 (71.0%)	43 (61.4%)	0.17	136 (67.7%)
Yes	38 (29.0%)	27 (38.6%)		65 (32.3%)
missing	1	0		1
Defibrotide	0	1 (3.8%)		1 (1.8%)
Ursodiol	11 (35.5%)	17 (65.4%)		28 (49.1%)
Heparin	11 (35.5%)	3 (11.5%)		14 (24.6%)
Other	1 (3.2%)	1 (3.8%)		2 (3.5%)
Defibrotide+Ursodiol	1 (3.2%)	0		1 (1.8%)
Heparin+Ursodiol	6 (19.4%)	3 (11.5%)		9 (15.8%)
Heparin+Ursodiol+ Other	1 (3.2%)	1 (3.8%)		2 (3.5%)
missing	7	1		8
Relapse				
No	97 (73.5%)	59 (84.3%)	0.082	156 (77%)
Yes	35 (26.5%)	11 (15.7%)		46 (23%)
Survival time (days)				
median (min-max) [IQR]	127.5 (1–2573) [54.5–324.5]	60.5 (2–620) [27.2–153.8]	0.0005	106 (1–2573) [42–265]

VOD veno-occlusive disease, *MSD* matched sibling donor, *UD* unrelated donor, *BM* bone marrow, *PB* peripheral blood, *CB* cord blood, *MAC* myeloablative conditioning, *RIC* reduced intensity conditioning, *TBI* total body irradiation, *CSA* cyclosporine, *MTX* methotrexate, *MMF* mycophenolate mofetil.

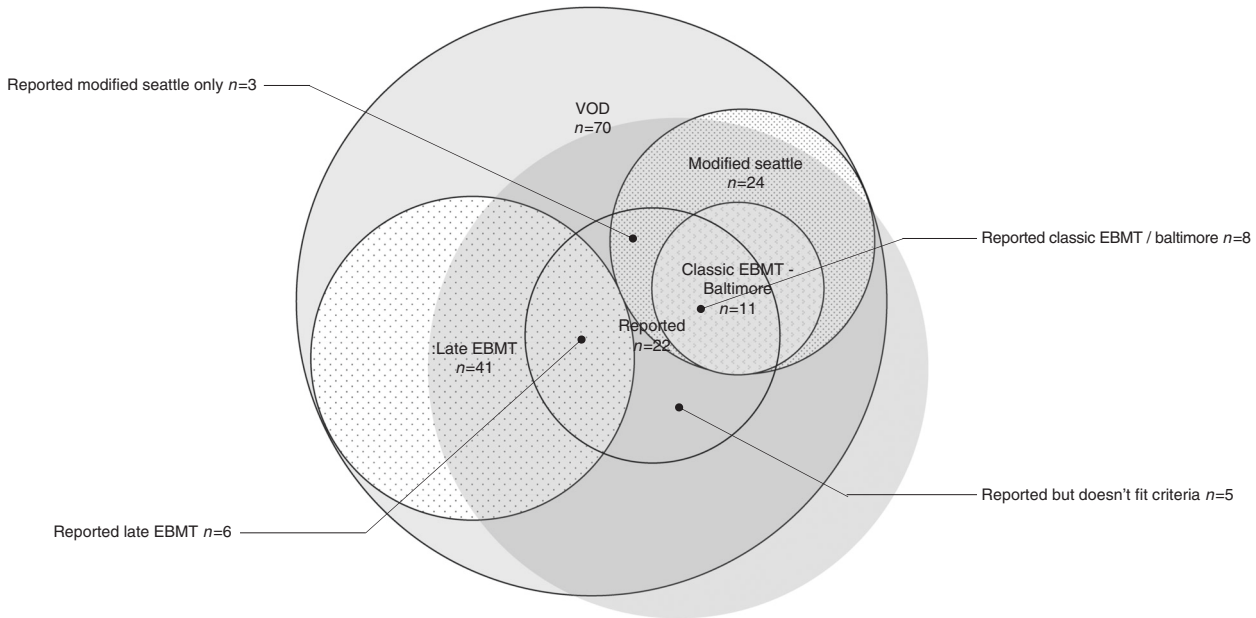

Fig. 1 VOD diagnosis per scoring system. VOD Veno-occlusive disease, EBMT European Society for Blood and Marrow Transplantation.

Table 3 Multivariate Analysis.

Outcome	Variables	OR	95% CI	*p* value
VOD	CR1 vs other	0.3	0.13–0.67	0.004
	Hepatic comorbidity or Gentuzumab use before transplant	6.6	2.14–20.53	0.001

Stepwise selection of variables associated with a p value <5% in univariate analysis + diagnosis and age at transplant.

VOD veno-occlusive disease, *CR1* first complete remission.

well beyond the 3-week period, and even months after transplant. This concept might therefore be behind the oversight of VOD/SOS diagnosis, as a high level of clinical attention is required to make this diagnosis, further emphasizing the importance of the EBMT criteria for late VOD/SOS extending beyond the traditional window [3].

Finally, the only consistent criterion suspicious of VOD/SOS was an elevated bilirubin level present in 87% of patients, others, such as ascites and hepatomegaly being present in only around half of diagnosed patients. These findings further highlight the heterogeneity of the disease presentation.

The main limitations of this study revolve around its retrospective nature. In fact, our ability to apply the VOD/SOS scoring criteria was limited by the availability of provided data and is therefore potentially underreported. Furthermore, very limited data was available to confirm or refute alternative hypotheses of MOF-related death, such as the original disease, sepsis, GVHD, and treatment toxicities to name a few, as the diagnosis of MOF was provided by centers. Finally, no post-mortem pathology was available to confirm the VOD/SOS diagnosis in patients that fit its criteria.

Conclusion

Our study is the first of its kind to investigate the hidden incidence of VOD/SOS post-alloHCT as an underlying cause of MOF. Our results suggest that VOD/SOS related MOF is a widely under-reported cause of death, accounting for around 27% of deaths attributed to MOF of unknown origin with no previous VOD/SOS diagnosis. Furthermore, it is highly suggested that patients with VOD/SOS related MOF have a far worse outcome with a significantly lower survival, which is attributable to both the relatively early incidence of VOD/SOS post-transplant and its highly accelerated progression and dismal course if untreated. Patient presentations however were also frequently consistent with a VOD/SOS diagnosis well beyond the classically defined 3-week post-transplant window, which could explain the oversight of this entity usually considered an early transplant complication. While the MOF concept is a widely used cause of death post-alloHCT, having precise categorization of cause-specific death from MOF should allow not only for better understanding of entities such as VOD/SOS, but also for disease-specific therapeutic interventions such as defibrotide which would greatly contribute to improved patient outcome.

Compliance with ethical standards

Conflict of interest MM reports grants and lecture honoraria from Janssen, Sanofi, and Jazz Pharmaceuticals; lecture honoraria from Celgene, Amgen, Bristol-Myers Squibb, Takeda, and Pfizer; and grants from Roche, all outside the submitted work. JAS reports lecture honoraria from Jazz, Janssen, Sanofi, Gilead and Mallinckrodt, and chairing NHS England Specialised Commissioning Clinical Reference Group for Blood and Marrow Transplantation, all outside the submitted work. FB has received travel grants and/or speaker honoraria from Celgene, AbbVie, Novartis, Pfizer and Sanofi. PJ has received travel grants and/or lecture honoraria from Novartis, Bristol-Myers Squib and Janssen, all outside the submitted work

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