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**Refined ultrasonographic criteria for sinusoidal obstruction syndrome after
hematopoietic stem cell transplantation**

Running title: Ultrasonographic criteria for SOS/VOD

Original article

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Conflict of Interest Disclosure

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Abstract

Hepatic sinusoidal obstruction syndrome (SOS)/veno-occlusive disease is a life-threatening complication after hematopoietic stem cell transplantation (HSCT). We previously reported the efficacy of the Hokkaido Ultrasonography (US)-based scoring system (HokUS-10) for US findings. To establish easier criteria, we retrospectively evaluated US findings of 441 patients including 30 patients with SOS using HokUS-10 scoring system. According to logistic regression analysis, we established the novel diagnostic criterion HokUS-6. In the presence of ascites, US diagnosis was made by the presence of two of the 6 parameters, moderate amount of ascites, appearance of para-umbilical vein blood flow signal, gallbladder wall thickening, portal vein dilatation, and velocity decrease, and hepatic artery resistive index increase. The AUC, sensitivity, and specificity of HokUS-6 were 0.974 (95% confidence intervals: 0.962-0.990), 95.2%, and 96.9%, respectively. The scores were significantly higher in patients with severe SOS than in those with nonsevere SOS ($p = 0.013$). Furthermore, the scores before HSCT were significantly higher in patients who developed SOS than in controls ($p = 0.001$). The HokUS-6 are easy and useful way for the diagnosis and identification of the risk of SOS.

Key Words

Sinusoidal obstruction syndrome, Veno-occlusive disease, Ultrasonography, Color Doppler, Hematopoietic stem cell transplantation

1 **Introduction**

2 Hepatic sinusoidal obstruction syndrome (SOS)/veno-occlusive disease (VOD) is a
3 life-threatening complication after hematopoietic stem cell transplantation (HSCT).
4 Severe SOS/VOD rapidly develops into multiple organ failure with a high mortality rate
5 exceeding 80% [1]. SOS/VOD is induced by damage to hepatic sinusoidal endothelial
6 cells and hepatocytes in zone 3 of the hepatic acinus by cytotoxic agents and irradiation
7 [2]. Defibrotide has been approved worldwide for the treatment of SOS/VOD.
8 However, defibrotide has the limited therapeutic effect on severe SOS/VOD. Thus,
9 early diagnosis and treatment is critical for the better outcome of SOS/VOD [3].

10 Ultrasonography (US) is an easy and useful tool for the diagnosis of SOS/VOD [2, 4-
11 7]. We recently established a novel scoring system for US findings related to
12 SOS/VOD: the Hokkaido US-based scoring system (HokUS-10) [8]. In this study, we
13 evaluated the efficacy of the more convenient and universal criteria of US. Also, we
14 investigated the relationship between the US scoring system and SOS/VOD severity,
15 and the risk estimation prior to HSCT.

16

17 **Patients and methods**

18 Patients who underwent allogeneic HSCT from January 2008 to June 2019 at
19 Hokkaido University Hospital were enrolled. US was performed before conditioning
20 therapy (pre-HSCT) and on day 14 after HSCT. When one or more of symptoms such
21 as body weight increasing, persistent platelets refractoriness, bilirubin increasing or right
22 upper quadrant pain were identified, SOS/VOD was clinically suspected, and an
23 additional US was performed. Clinical diagnosis of SOS/VOD was made according to
24 either the EBMT [9]/Baltimore criteria [10] or modified Seattle criteria [11]. Patients

1 who had not developed SOS/VOD by day 21 after HSCT were defined as the non-
2 SOS/VOD group. Severe SOS/VOD was defined as dialysis dependency and/or
3 respiratory failure, which required oxygen supplementation or ventilator dependency
4 [12]. Acute GVHD was diagnosed according to the guideline by consensus conference
5 on acute GVHD grading [13]. This study was approved by the institutional review
6 board (018-0127). Informed consent was obtained from all patients according to the
7 Declaration of Helsinki.

8
9

10 **US scanning**

11 Grayscale and color Doppler US evaluations were performed using convex transducers
12 (center frequency, 3.75~6 MHz) and linear transducers (center frequency, 7.5 MHz)
13 equipped with Aplio™ XG/500/i800 and Viamo (Canon Medical Systems Corp.,
14 Otawara, Japan) by 7 medical sonographers with more than 5 years of experience. All
15 sonographic findings and measurements were verified by a registered senior medical
16 sonographer. HokUS-10 [8] consists of 10 parameters: 1) hepatomegaly in the left lobe
17 and 2) right lobe, 3) dilatation of the main portal vein (PV), 4) hepatofugal flow in the
18 main PV, 5) decreased velocity of the PV, 6) dilatation of the para-umbilical vein
19 (PUV), 7) appearance of blood flow signal in the PUV, 8) gallbladder (GB) wall
20 thickening, 9) ascites, and 10) increased resistive index of the hepatic artery (HA-RI).
21 Ascites was graded into 3 levels, none, presence and moderate. A moderate amount of
22 ascites was originally defined by the presence of ascites in all of the subhepatic space,
23 spleno-renal interspace, and Douglas pouch (maximum thickness \geq 1 cm at least at the
24 2 sites).

1

2 **Statistical analysis**

3 We used highly reliable statistical analysis as the boot strapping method, which was
4 introduced by transparent reporting of a multivariable prediction model for individual
5 prognosis or diagnosis (TRIPOD) guidelines [14] to construct and validate the predictive
6 model. Logistic regression models with Firth's correction [15] were performed to evaluate
7 each US parameter of HokUS-10 associated with the diagnosis of SOS/VOD. Akaike's
8 information criterion [16] was used for variable selection from all combinations of US
9 findings. A receiver operating characteristic (ROC) curve was used to evaluate the
10 diagnostic accuracy. Discrimination was measured with the use of the area under the ROC
11 curve (AUC). All measures of predictive performance, such as sensitivity, specificity,
12 positive predictive value, negative predictive value, and AUC, were adjusted for optimism
13 by using the median 2.5 percentile and 97.5 percentiles from 10,000 bootstrapped samples.
14 The bootstrap method is a resampling technique used to estimate statistics on a population
15 by sampling a dataset replacement. A desirable diagnostic performance can be presented
16 with confidence intervals (CI), which is not available with other methods such as cross-
17 validation. Wilcoxon rank-sum test was used to compare HokUS-6 of SOS/VOD with
18 acute GVHD accompanied by ascites. Severity and prediction of SOS/VOD were
19 evaluated using the Cochran-Armitage trend test. Statistical analyses were performed
20 using SAS 9.4 and JMP Pro 14.0.0 (Cary, NC).

21

22 **Results**

23 **Patient characteristics**

24 Four hundred forty-one patients were enrolled including age under 16 years old. The

1 characteristics of the patients are shown in Table 1. Ursodeoxycholic acid and low
2 molecular weight heparin were given to all the patients as prophylaxis for SOS/VOD.
3 Sixteen patients did not undergo US examination before HSCT. Thirty patients (6.8%)
4 were diagnosed with SOS/VOD within 21 days after HSCT, of which 14 patients met
5 EBMT classical [9]/Baltimore criteria [10], and 16 patients met modified Seattle criteria
6 [11] (Table 2). None of the patients had liver biopsy for diagnosis. A clinical diagnosis of
7 SOS/VOD was made at a median of 14 days, ranging from 3 to 21 days after allogeneic
8 HSCT. In which, seven and 19 patients fulfilled HokUS-6 criteria earlier than clinical
9 diagnosis and on the same day with clinical diagnosis, respectively.

10 **US parameters**

11 A total of 1,019 US scans were performed in 441 patients. The rates of valid data for the
12 10 parameters of HokUS-10 are shown in Supplementary Table 1 (Table S1). GB wall
13 thickening and hepatomegaly were not evaluable in 15 and 2 patients due to a history of
14 cholecystectomy and hepatectomy, respectively. HA-RI, PUV diameter, and PV velocity
15 were evaluable in 99.3%, 99.4%, and 99.3% of US scans, respectively, while the presence
16 of ascites and PV blood flow signals were evaluable in all US scans. The median
17 evaluability of the 10 parameters was 99.6% (95% CI: 98.6 to 100).

18 **Predictive model and diagnostic value**

19 To develop easier US criteria without impairing accuracy, all parameters of HokUS-10
20 were entered into a logistic regression model using logistic regression analysis to
21 specify feasible ultrasonographic parameters associated with SOS/VOD based on
22 Akaike's information criterion. The top 10 high performance models are listed in Table
23 S2. To maximize the sensitivity, we chose the second effective model, which included 6
24 out of 10 parameters (HokUS-6). Because all patients with SOS/VOD had ascites, the

1 presence of ascites regardless of its amount was set to a necessary condition. Moderate
2 amount of ascites and 5 other frequently observed findings (appearance of PUV blood
3 flow signal, GB wall thickening, PV dilatation, and velocity decrease, and HA-RI
4 increase) were selected. Representative US images of SOS/VOD are shown in Figure 1.
5 The logistic regression model shown in Table 3 was the best prediction model evaluated
6 by Akaike's information criteria. The highest AUC was achieved when two or greater
7 criteria were present (AUC:0.974, 95% CI: 0.962-0.990, Figure 2). A flow chart of the
8 HokUS-6 diagnostic system was shown in Figure 3. The sensitivity and specificity of
9 HokUS-6 were 95.2% and 96.9%, respectively, while those of HokUS-10 were 96.7%
10 and 97.6%, respectively (Figure 3).

11 In this cohort, 70 of 441 patients (15.9%) developed acute GVHD within 21 days.
12 Thirty of 70 patients had ascites, but the mean HokUS-6 score in these patients was
13 significantly lower than that in patients with SOS/VOD (0.4 ± 0.7 vs. 3.1 ± 1.1 , $P <$
14 0.001). Among 30 patients with acute GVHD, SOS/VOD was diagnosed clinically in 2
15 patients and ultrasonographically in 6 patients.

16 We further investigated using simple sum of positive criteria of HokUS-6 as “HokUS-
17 6 scoring system” for evaluation of severity and prediction of SOS/VOD. The HokUS-6
18 scoring was significantly higher in severe SOS/VOD cases than in nonsevere patients,
19 with average scores of 2.6 in nonsevere patients and 5.8 in severe patients ($p=0.013$,
20 Figure 4). Pre-HSCT HokUS-6 scoring in SOS/VOD patients were significantly higher
21 than those in non-SOS/VOD patients (Figure 5, $p = 0.001$).

22

23 **Discussion**

1 We recently established the HokUS-10 scoring system [8] based on 17 findings of the
2 US-17 screening [8]. Although HokUS-10 is easier than US-17 screening, it is still time
3 consuming and requires technical skill to evaluate all 10 parameters. It took about 15
4 minutes and 10 minutes in HokUS-10 and HokUS-6, respectively.

5 First, the presence of ascites should be evaluated using focused assessment with
6 sonography for trauma (FAST). When ascites is present, US diagnosis of SOS/VOD can
7 be made by detecting two findings out of the 6 parameters. Acute GVHD is not rarely
8 complicated with ascites. Although HokUS-6 score was generally lower in acute GVHD
9 than in SOS/VOD, SOS/VOD is sometimes complicated with acute GVHD. Thus,
10 clinical confirmation of SOS/VOD diagnosis is important.

11 When ascites is not present, SOS/VOD can be excluded. HokUS-6 is also convenient
12 in diagnosing SOS/VOD, since there is no need to go through all 6 criteria, only two
13 positive findings are needed. Even in patients with cholecystectomy/hepatectomy or
14 missing validated data, HokUS-6 criteria can effectively diagnose SOS/VOD by
15 obtaining 2 positive findings.

16 US is highly sensitive for detecting hemodynamic changes in zone 3 of the liver
17 caused by sinusoidal obstruction. Eighty percent of blood flow into the liver is supplied
18 via the PV. In SOS/VOD, the diameter of the PV increases and the blood flow of the PV
19 decreases. Since the remaining 20% blood flow is supplied by HA, HA-RI should be an
20 important finding. Congestion of sinusoids increases resistance to peripheral blood
21 flow. GB wall swelling is caused by congestion of the cystic vein returning to the portal
22 venous system. Additionally, one of the distinctive parameters is PUV recanalization,
23 which is well known to be detected in portal hypertension. Thus, all the HokUS-6
24 parameters reflect the pathophysiology of SOS/VOD, and the scoring of 6 parameters

1 are associated with the severity of the disease. HokUS-6 was useful for early diagnosis,
2 and pathophysiological based US criteria could be a promising tool to help clinical
3 diagnosis of SOS/VOD.

4 As for high HokUS-6 scoring prior to HSCT, eight out of 28 SOS/VOD (2 patients did
5 not have US prior HSCT) patients had ascites, seven had a high HA-RI, and six had a
6 PUV blood flow signal prior to HSCT. A high HokUS-6 scoring pre-HSCT reflects
7 preexisting liver damage and predicted the development of SOS/VOD. These findings
8 may encourage us to use defibrotide as the intensive prophylaxis strategy or preemptive
9 treatment for SOS/VOD, as well as more close monitoring of the patients.

10 In summary, refined HokUS-6 criteria are useful to detect early pathophysiological
11 changes, severity and risk estimation of SOS/VOD. The limitations of our study include
12 its retrospective single-center design and lack of validation. Further multicenter
13 prospective studies are warranted to validate the effectiveness of the HokUS-6 criteria.

14

15 **Competing Interests**

16 The authors declare no competing financial interests.

17

18 **Authorship**

19 M. N. is participated in the research design, the writing of the paper, the
20 performance of the research and data analysis. J. S. and S. T. are participated in
21 research design, the data analysis and the review of the paper. T. I., M. S., Y. K., S.
22 O., T. H. and R. S. are participated in the performance of the research. H.S. and A.

- 1 I. are participated in the review of the paper. I. Y. and T. T. are participated in the
- 2 research design, data analysis and the writing and review of the paper.

References

1. Cheuk DK. Hepatic veno-occlusive disease after hematopoietic stem cell transplantation: Prophylaxis and treatment controversies. *World J Transplant.* 2012;2(2):27-34.
2. Mohty M, Malard F, Abecassis M, Aerts E, Alaskar AS, Aljurf M, et al. Sinusoidal obstruction syndrome/veno-occlusive disease: current situation and perspectives-a position statement from the European Society for Blood and Marrow Transplantation (EBMT). *Bone Marrow Transplant.* 2015;50(6):781-9.
3. Kernan NA, Grupp S, Smith AR, Arai S, Triplett B, Antin JH, et al. Final results from a defibrotide treatment-IND study for patients with hepatic veno-occlusive disease/sinusoidal obstruction syndrome. *Br J Haematol.* 2018;181(6):816-27.
4. Brown BP, Abu-Yousef M, Farner R, LaBrecque D, Gingrich R. Doppler sonography: a noninvasive method for evaluation of hepatic veno-occlusive disease. *AJR Am J Roentgenol.* 1990;154(4):721-4.
5. Herbetko J, Grigg AP, Buckley AR, Phillips GL. Venooclusive liver disease after bone marrow transplantation: findings at duplex sonography. *AJR Am J Roentgenol.* 1992;158(5):1001-5.
6. Lassau N, Leclere J, Auperin A, Bourhis JH, Hartmann O, Valteau-Couanet D, et al. Hepatic veno-occlusive disease after myeloablative treatment and bone marrow transplantation: value of gray-scale and Doppler US in 100 patients. *Radiology.* 1997;204(2):545-52.
7. Park JE, Choi YH, Cheon JE, Kim WS, Kim IO, Ryu YJ, et al. Gallbladder wall oedema and ascites are independent predictors of progression to hepatic veno-occlusive disease for children with hematopoietic stem cell transplantation. *Eur J Radiol.* 2018.
8. Nishida M, Kahata K, Hayase E, Shigematsu A, Sato M, Kudo Y, et al. Novel Ultrasonographic Scoring System of Sinusoidal Obstruction Syndrome after Hematopoietic Stem Cell Transplantation. *Biol Blood Marrow Transplant.* 2018;24(9):1896-900.
9. Mohty M, Malard F, Abecassis M, Aerts E, Alaskar AS, Aljurf M, et al. Revised diagnosis and severity criteria for sinusoidal obstruction syndrome/veno-occlusive disease in adult patients: a new classification from the European Society for Blood and Marrow Transplantation. *Bone Marrow Transplant.* 2016;51(7):906-12.
10. Jones RJ, Lee KS, Beschoner WE, Vogel VG, Grochow LB, Braine HG, et al. Venooclusive disease of the liver following bone marrow transplantation. *Transplantation.* 1987;44(6):778-83.

11. McDonald GB, Hinds MS, Fisher LD, Schoch HG, Wolford JL, Banaji M, et al. Venous-occlusive disease of the liver and multiorgan failure after bone marrow transplantation: a cohort study of 355 patients. *Ann Intern Med*. 1993;118(4):255-67.
12. Yakushijin K, Atsuta Y, Doki N, Yokota A, Kanamori H, Miyamoto T, et al. Sinusoidal obstruction syndrome after allogeneic hematopoietic stem cell transplantation: Incidence, risk factors and outcomes. *Bone Marrow Transplant*. 2016;51(3):403-9.
13. Przepiorka D, Weisdorf D, Martin P, Klingemann HG, Beatty P, Hows J, et al. 1994 Consensus Conference on Acute GVHD Grading. *Bone Marrow Transplant*. 1995;15(6):825-8.
14. Moons KG, Altman DG, Reitsma JB, Ioannidis JP, Macaskill P, Steyerberg EW, et al. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): explanation and elaboration. *Ann Intern Med*. 2015;162(1):W1-73.
15. Firth D. Bias Reduction of Maximum-Likelihood-Estimates. *Biometrika*. 1993;80(1):27-38.
16. Nagashima K, Sato Y. Information criteria for Firth's penalized partial likelihood approach in Cox regression models. *Stat Med*. 2017;36(21):3422-36.

Figure Legends

Figure 1. Representative US images of SOS/VOD.

Moderate amount of ascites is seen in the surrounding of the liver (a), pelvic cavity (b), and the surrounding of the spleen (c). Edematous wall thickening (10.5mm) of the gall bladder (d). Dilatation of the main portal trunk (14.0mm) (e). Hepatofugal color Doppler blood flow signal in PUV (f). Decreased blood flow velocity in portal vein measured by pulse Doppler analysis (g). Increased RI in PHA by pulse Doppler analysis (h). US; ultrasonography, GB; gall bladder, IVC; inferior vena cava, U.B.; urinary bladder, PV; portal vein, PUV; paraumbilical vein, UP; umbilical vein, PHA; proper hepatic artery, HA; hepatic artery, RI; resistive index

Figure 2. Area under the ROC curve of each cut off value on HokUS-6 and diagnostic performance.

Upper panel: the ROC curve of the positive number of criteria in HokUS-6.

AUC=0.974 (95% CI: 0.962-0.990). N=441. Lower panel: the diagnostic performances of each cut off value of HokUS-6 diagnostic system.

Figure 3. Diagnostic system of HokUS-6

When ascites is present, US diagnosis of SOS/VOD can be made by detecting additional two findings out of the 6 criteria. The table below shows the diagnostic performance of HokUS-6 diagnostic system statistically adjusted by the bootstrap method. N=441.

Figure 4. Comparison of HokUS-6 scoring between non-severe SOS/VOD and severe SOS/VOD

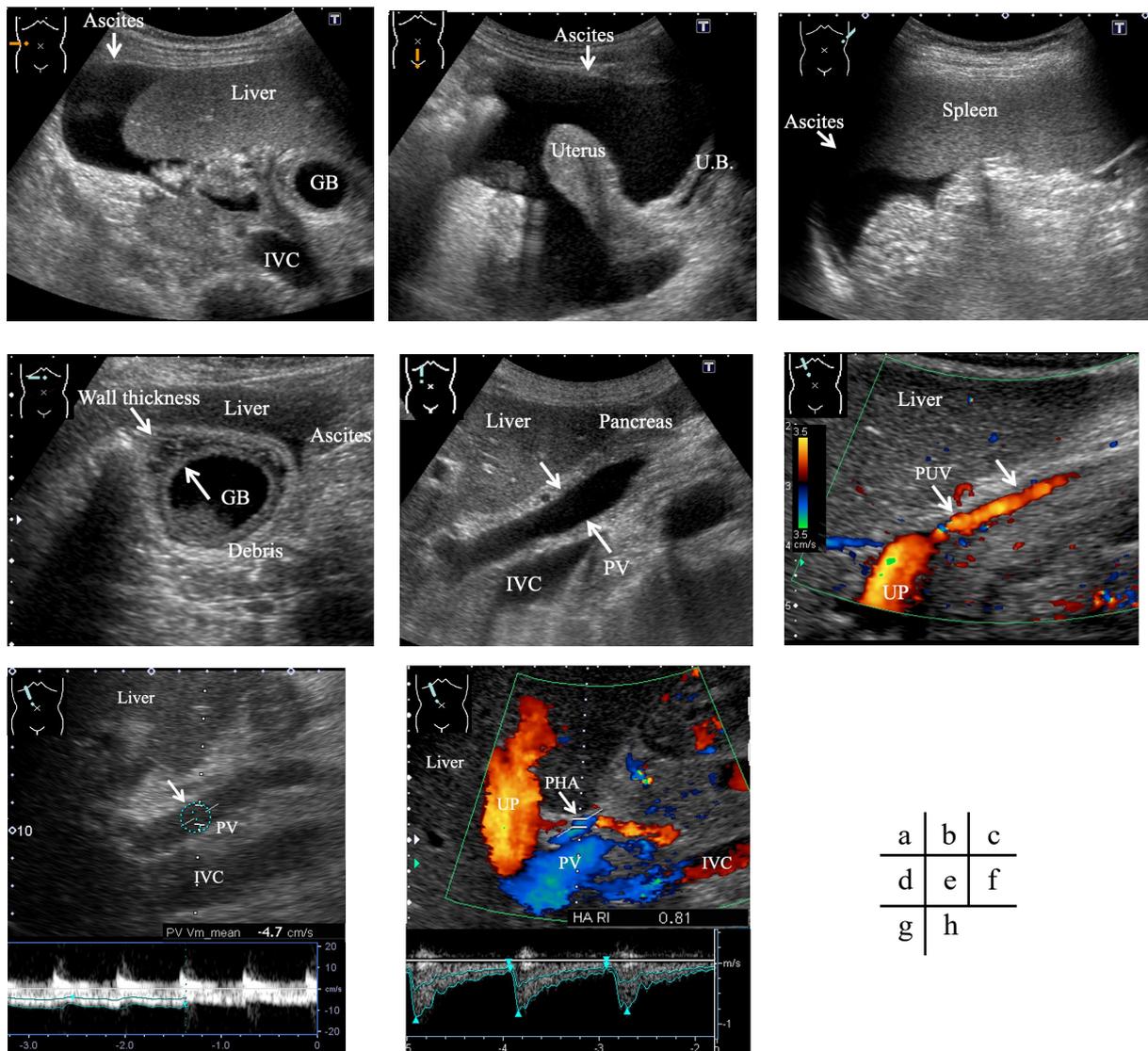
As the HokUS-6 score increases, the number of severe SOS increase. Thus, the HokUS-6 scoring showed significant differences between non-severe SOS/VOD and severe SOS/VOD by the Cochran-Armitage trend test (P=0.013).

Figure 5. Prediction of developing SOS/VOD after HSCT by HokUS-6 scoring

The patients diagnosed with SOS/VOD had a tendency toward a higher HokUS-6 scoring prior to HSCT than those without SOS/VOD by the Cochran-Armitage trend test (p<0.001). Sixteen patients without US prior to HSCT were excluded.

Figure 1.

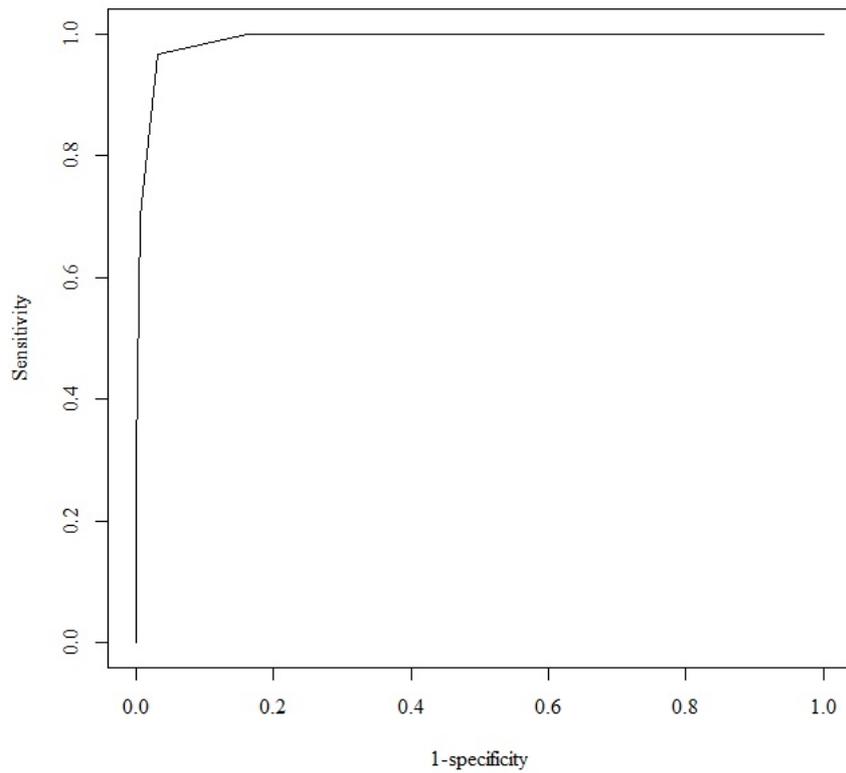
Representative US images of SOS/VOD.



a	b	c
d	e	f
g	h	

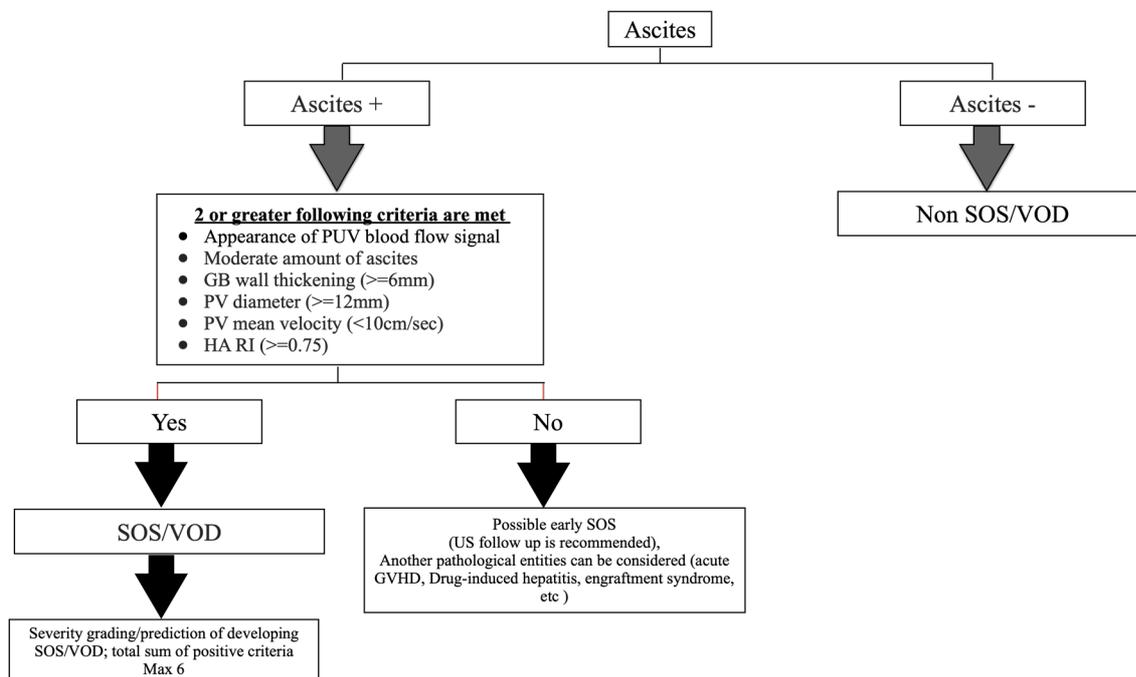
Figure 2.

Area under the ROC of each cut off value on HokUS-6 and diagnostic performance.



Cut off value (positive number of criteria in HokUS-6)	Sensitivity (%)	Specificity (%)
1	100	83.7
2	96.7	96.8
3	70.0	99.3
4	30.0	100
5	10.0	100
6	3.3	100

Figure 3. Diagnostic system of HokUS-6



PUV; paraumbilical vein, GB; gall bladder, PV; portal vein, HA; hepatic artery, RI; resistive index, GVHD; Graft versus host disease

	HokUS-6	HokUS-10
AUC (95% CI)	0.974 (0.962 - 0.990)	0.992 (0.9827 - 0.9966)
Sensitivity % (95% CI)	95.2 (93.3 - 100.0)	96.7 (81.9 - 100.8)
Specificity % (95% CI)	96.9 (95.6 - 98.1)	97.6 (95.5 - 98.7)
Positive predictive value % (95% CI)	69 (58.3 - 80.8)	74.4 (58.8 - 85.6)
Negative predictive value % (95% CI)	99.6 (99.6 - 100.0)	99.8 (98.5 - 100.1)

AUC; area under the curve, C.I.; confidential interval

Figure 4. Comparison of HokUS-6 scoring between nonsevere SOS/VOD and severe SOS/VOD

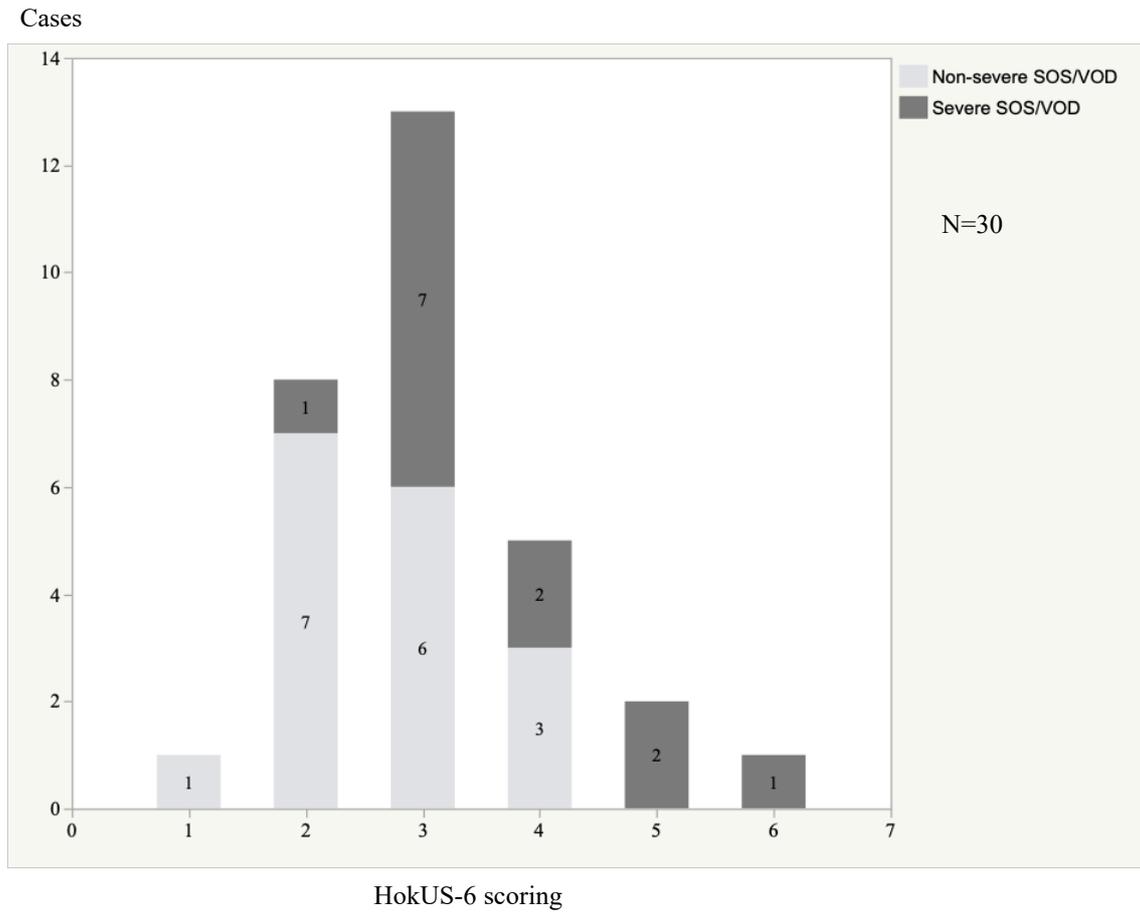


Figure 5. Prediction of developing SOS/VOD after HSCT by HokUS-6 scoring

The patients diagnosed with SOS/VOD had a tendency toward a higher HokUS-6 score prior to HSCT than those without SOS/VOD by the Cochran-Armitage trend test (p=0.0002). Sixteen patients including 2 SOS/VOD without US prior to HSCT were excluded.

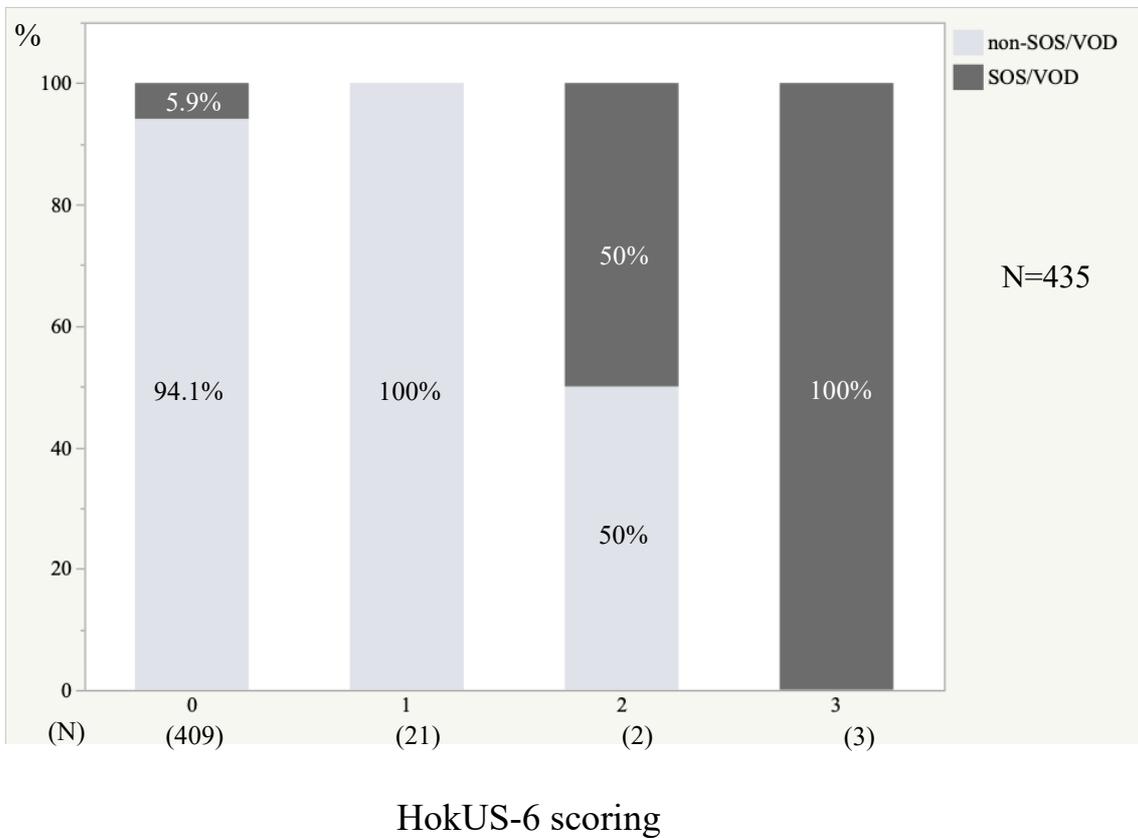


Table 1. Patient characteristics

Characteristics	Total	Non-SOS/VOD	SOS/VOD
Number of patients (age under 16)	441 (75)	411 (72)	30 (3)
Median age (range)	42 (0-70)	42 (0-70)	44.0 (6-66)
Male/female	258/183	239/172	19/11
Disease			
Leukemia/MDS	332	308	24
Lymphoma/myeloma	48	44	4
Other malignancies	31	30	1
Nonmalignant diseases	30	29	1
Prior history of HSCT	83	73	10
Stem cell source			
BM/PB/CB	117/207/117	106/195/110	11/12/7
Donor			
Related/unrelated/auto	154/260/27	144/241/26	10/19/1
Disease status at HSCT			
CR/non-CR/NA*	232/177/32	219/161/31	13/16/1
Conditioning regimen			
MAC/RIC	230/211	216/195	14/16
TBI-containing	334	311	23
Use of busulfan	203	194	9
History of GO	21	18	3

Abbreviations: MDS, myelodysplastic syndrome; BM, bone marrow; PB, peripheral blood stem cell; CB, cord blood; RIC, reduced intensity conditioning; MAC, myeloablative conditioning; TBI, total body irradiation; GO, gemtuzmab ozogamicin; *NA, not assessed in patients with non-malignant diseases

Table 2. Details of the patients who developed SOS/VOD

Characteristics	
Engraftment day after HSCT (range)	18 (10-33)
Clinical SOS/VOD diagnosis day after HSCT (range)	14 (3-24)
EBMT classical/Baltimore criteria / modified Seattle criteria (N)	14/16
SOS/VOD diagnosis by HokUS-10 day after HSCT (range)	13.5 (3-21)
The first day of the onset of clinical signs of SOS/VOD (range)	10 (1-18)
Presence of severe SOS/VOD (N)	13
100-day mortality, N (range of day after HSCT)	10 (21-95)

Abbreviations: EBMT, European Society for Blood and Marrow Transplantation

Table 3. The best prediction logistic model evaluated by Akaikes information criteria

Parameter	Estimated log odds ratio	Standard error
PV mean velocity (≤ 10 cm/s)	2.10	0.92
Appearance of PUV blood flow signal	3.78	0.99
PV diameter (≥ 12 mm*)	2.62	0.82
Moderate amount of ascites	5.89	1.46
GB wall thickening (≥ 6 mm)	1.65	0.90
Hepatic artery RI (> 0.75)	1.16	0.80

Notes; *3~11 mm for patients under 16 years old according to their age (Patriquin, et al. 1990),

Abbreviations: PV, portal vein; PUV, para-umbilical vein; GB, gallbladder; RI, resistive index

* RI is calculated by $V_{max} - V_{min} / V_{max}$