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Novel Ultrasonographic Scoring System of Sinusoidal Obstruction Syndrome after Hematopoietic Stem Cell Transplantation

Mutsumi Nishida [1,2,*], Kaoru Kahata [3], Eiko Hayase [1,3], Akio Shigematsu [3], Megumi Sato [2,4], Yusuke Kudo [1,2], Satomi Omotehara [1,2], Takahito Iwai [1,2], Junichi Sugita [3], Hitoshi Shibuya [2], Chikara Shimizu [1], Takanori Teshima [1,3]

[1] *Division of Laboratory and Transfusion Medicine, Hokkaido University Hospital, Sapporo, Japan*
[2] *Diagnostic Center for Sonography, Hokkaido University Hospital, Sapporo, Japan*
[3] *Department of Hematology, Hokkaido University Hospital, Sapporo, Japan*
[4] *Department of Radiological Technology, Hokkaido University Hospital, Sapporo, Japan*

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A B S T R A C T

Sinusoidal obstruction syndrome (SOS)/hepatic veno-occlusive disease (VOD) is a well-documented complication after hematopoietic stem cell transplantation (HSCT). Transabdominal ultrasonography (US) enables the visualization of blood flow abnormalities and is therefore useful for the diagnosis of SOS/VOD. We herein prospectively evaluated accuracy of a novel US diagnostic scoring system of SOS/VOD based on US findings. We carried out US in 106 patients on day 14 and when SOS/VOD was suspected after allogeneic HSCT. Among 106 patients, 10 patients (9.4%) were diagnosed as SOS/VOD by Baltimore or Seattle criteria. According to univariate analysis of 17 US findings (US-17 screening), we established a novel scoring system (HokUS-10) consisting of 10 parameters, such as gallbladder wall thickening, ascites, and blood flow signal in the paraumbilical vein. The sensitivity and specificity were 100% and 95.8%, respectively. Diagnostic performance of the HokUS-10 was significantly better than US-17 screening. In 4 of 10 patients US detection of SOS/VOD preceded to clinical diagnosis. The HokUS-10 scoring system is useful in the diagnosis of SOS/VOD; however, our results should be validated in other cohorts.

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INTRODUCTION

Sinusoidal obstruction syndrome (SOS), also known as hepatic veno-occlusive disease (VOD), is 1 of the life-threatening complications after hematopoietic stem cell transplantation (HSCT) [1]. Typical clinical presentations of SOS/VOD include body weight gain, painful hepatomegaly, ascites, and jaundice [2,3]. The incidence of SOS/VOD after HSCT varies from 5% to 60% [4-10], depending on types of conditioning regimen and cancer treatments before HSCT. SOS/VOD is induced by damage of the hepatic sinusoidal endothelial cells by cytotoxic agents, such as busulfan, cyclophosphamide, gemtuzumab ozogamicin, and inotuzumab ozogamicin [10]. The sinusoidal endothelial cell damage hinders the outflow of sinusoid by embolization, leading to upstream congestion and portal hypertension. Transabdominal ultrasonography (US) accompanied with Doppler imaging is useful to detect blood flow abnormalities in SOS/VOD [11-17]. Previous studies identified several parameters to be screened by US to detect SOS/VOD [18,19]. In this prospective study we developed a novel US-based scoring system of SOS/VOD.

METHODS

Patients

Patients aged 16 and over who underwent allogeneic HSCT from January 2009 to September 2013 in Hokkaido University Hospital were enrolled. US was performed before conditioning therapy (pre-HSCT) and on day 14 after HSCT. When SOS/VOD was suspicious or diagnosed, additional US was performed. Diagnosis of SOS/VOD was made according to either Baltimore criteria [2] or modified Seattle criteria [3]. Patients who had not developed SOS/VOD by day 21 were defined as the control group. This study was approved by the institutional review board (009-0353), and written informed consent was obtained from all patients in accordance with the Declaration of Helsinki.

US Scanning

Gray-scale and color Doppler US evaluation was performed using standard US equipment by 5 registered medical sonographers (M.N., M.S, Y.K.,

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* Correspondence and reprint requests: Mutsumi Nishida, PhD, Division of Laboratory and Transfusion Medicine, N14 W5, Kita-ku, Sapporo 060-8648, Japan.
E-mail addresses: mutuni@med.hokudai.ac.jp, mutuni@gmail.com (M. Nishida).

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Table 1
Patient Characteristics

Characteristics	SOS/VOD Group (n = 10)	Control Group (n = 96)	*P*
Median age, yr (range)	40 (21-66)	45 (16-66)	.70
Male/female	5/5	54/42	.71
Disease			
Leukemia/MDS	7	67	.61
Lymphoma/myeloma	3	22	
Nonmalignant diseases	0	7	
Prior history of HSCT	2	9	.29
Stem cell source			
BM/PBSC/CB	4/3/3	58/17/21	.82
Donor			
Related/unrelated	3/7	26/70	.84
Conditioning regimen			
RIC/MAC	6/4	57/39	.52
TBI-containing myeloablative regimen	4	36	.79
Use of busulfan	3	24	.68
History of GO	2	8	.23

MDS indicates myelodysplastic syndrome; BM, bone marrow; PBSC, peripheral blood stem cell; CB, cord blood; RIC, reduced-intensity conditioning; MAC, myeloablative conditioning; TBI, total body irradiation; GO, gemtuzumab ozogamicin.

S.O, and T.I) in gastroenterology and hepatology with more than 5 years of experience. All sonographic findings and measurements were verified by a registered senior medical sonographer (M.N.). Based on the previous studies [18,19], 17 parameters were evaluated for US screening (US-17 screening) [17]: hepatomegaly in the (1) left lobe and (2) right lobe, (3) splenomegaly, (4) dilatation of the main portal vein (PV), (5) hepatofugal flow in the main PV, (6) decreased velocity of the PV, (7) dilatation of the paraumbilical vein (PUV), (8) appearance of blood flow signal in the PUV, (9) gallbladder wall thickening, (10) ascites, (11 to 13) narrowing of the 3 hepatic veins, (14 to 16) waveform planarization of the 3 hepatic veins, and (17) increased resistive index of the hepatic artery. More details are described in the Supplementary Data.

Statistical Analysis

Univariate analysis was performed to evaluate each US finding. Comparison between the 2 groups was analyzed by the Mann-Whitney U test. Receiver operating characteristic curve was used to evaluate the diagnostic accuracy. Significant difference of diagnostic performance was evaluated by the McNemer test. Statistical analyses were performed using standard statistical software (IBM SPSS Statistics version 22.0 for Mac OS [Chicago, IL] and JMP Pro 12.2.0 [Cary, NC]).

RESULTS

Patients Characteristics

During the study period 142 patients were registered, of which 36 were excluded. Among them, 1 patient did not undergo HSCT. Thirty-five patients did not have US scans within day 21 after HSCT. None of them showed any clinical signs of SOS/VOD. The characteristics of the remaining 106 patients analyzed in this study are shown in Table 1.

Ursodeoxycholic acid and low-molecular-weight heparin were given to all patients. Ten patients (9.4%) were diagnosed as SOS/VOD within 21 days after HSCT, of which 9 patients met Baltimore criteria [2] and 1 patient (no. 65) was diagnosed by modified Seattle criteria [3] (Table 2). None of the patients had liver biopsy. A diagnosis of SOS/VOD was made a median of 12.5 days (range, 3 to 20) after allogeneic HSCT and before neutrophil engraftment in 8 patients. There was no statistically significant difference between the SOS/VOD patients and control subjects with regard to age, disease, history of prior HSCT, donor type, intensity of conditioning therapy, and use of busulfan or history of gemtuzumab ozogamicin use [8,20,21] (Table 1).

Scores from the Hokkaido US-based scoring system consisting of 10 parameters (HokUS-10) tended to be higher in patients with multiorgan failure, with median ± standard error scores of 6.5 ± 1.0 in patients without multiorgan failure and 8.0 ± 2.1 in patients with multiorgan failure. However, the difference was not statistically significant ($P = .61$), probably because of the small number of patients. US was not performed at most severe timing of SOS/VOD.

Selection of 10 Parameters from US-17 Screening

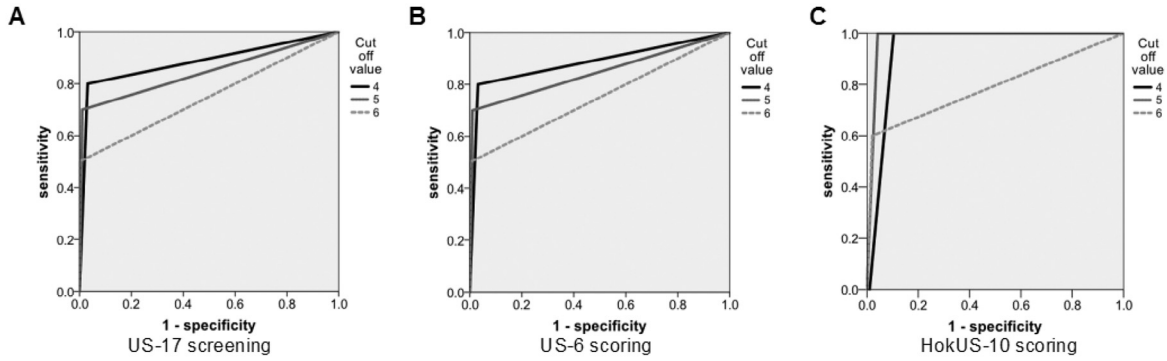
US-17 screening showed excellent diagnostic value for SOS/VOD, with 100% of sensitivity and 81.3% of specificity, when positivity was defined by detection of more than 4 points (Figure 1). However, it took more than 30 minutes per patient to scan throughout 17 parameters.

To improve the feasibility and convenience of US study without impairing accuracy, we performed univariate analysis to identify useful US parameters to detect SOS/VOD (Table 3). Univariate analysis identified 6 of 17 parameters that were significantly associated with SOS/VOD diagnosis: ascites, PUV blood flow signal, gallbladder wall thickening, PUV dilatation, increased vertical diameter of the hepatic right lobe, and PV dilatation ($P < .05$). Although there was no significant association in univariate analysis, we evaluated 4 more parameters: increased vertical diameter of the hepatic left robe, increased resistive index of the hepatic artery, decrease in PV flow velocity, and contraflow of PV, because hepatomegaly was 1 of the major diagnostic features of SOS/VOD, increased resistive index reflected increased blood flow pressure caused by sinusoidal obstruction in SOS/VOD [16,19,22], and decreased PV flow velocity and contraflow represent portal hypertension as a result of centrilobular vein

Table 2
Details of the Patients Who Developed SOS/VOD

Patient No.	Age/sex	Disease	Disease Status at HSCT	Donor/Stem Cell Source	Conditioning	Engraftment (day)	SOS/VOD Diagnosis (day)	Presence of MOF	100-Day Survival (day)
57	25/F	AML	Non-CR	Match related/PBSC	Flu/Mel	12	13	Yes	Alive
65	21/M	AML	Non-CR	Mismatch related/PBSC	Flu/CY/Bu/TBI	22	7	No	Alive
66	66/M	NHL	Non-CR	Match unrelated/BM	Flu/Bu/TBI	18	16	Yes	Death (70)
82	40/F	AML	Non-CR	Match unrelated/BM	HDAC/TBI	21	5	Yes	Death (31)
124	62/M	AML	CR	Mismatch/CB	Flu/Bu/TBI	17	20	Yes	Death (27)
133	60/F	ALL	CR	Match related/PBSC	Flu/Bu/TBI	18	3	No	Alive
147	36/M	MDS	Non-CR	Mismatch unrelated/BM	CY/ TBI	22	13	Yes	Alive
148	22/F	HL	Non-CR	Mismatch unrelated/BM	Flu/Mel	Graft failure	8	Yes	Death (21)
152	40/F	ALL	Non-CR	Mismatch/CB	VP/CY/TBI	23	12	No	Alive
189	44/M	NHL	Non-CR	Mismatch/CB	CY/TBI	20	13	No	Alive

MOF indicates multiorgan failure; AML, acute myeloid leukemia; CR, complete remission; Flu, fludarabine; Mel, melphalan; CY, cyclophosphamide; Bu, busulfan; HDAC, high-dose Ara-C; ALL, acute lymphoblastic leukemia; HL, Hodgkin lymphoma; VP, etoposide.



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Cut-off value	AUC		
	US-17 screening	US-6 scoring	HokUS-10
4	0.901	0.884	0.919
5	0.843	0.845	0.980
6	0.764	0.750	0.792

E

	US-17 screening	US-6 scoring	HokUS-10 scoring
Number of parameters	17	6	10
Maximum scores	19	8	13
Cut-off value	4	4	5
True positive	10 (9.4%)	8 (7.5%)	10 (9.4%)
True negative	78 (73.6%)	93 (87.7%)	92 (86.8%)
False negative	0 (0%)	2 (1.9%)	0 (0%)
False positive	18 (17.0%)	3 (2.8%)	4 (3.8%)
Sensitivity (%)	100	80	100
Specificity (%)	81.3	96.9	95.8
Positive predictive value (%)	35.7	95.3	71.4
Negative predictive value (%)	100	72.7	100

Figure 1. Receiver operating characteristic (ROC) curve analysis of US-17 screening, HokUS-6 scoring, and HokUS-10 scoring systems. (A-C) ROC curves to determine the cut-off values with the highest diagnostic performance by US-17 screening (A), HokUS-6 scoring (B), and HokUS-10 scoring (C). (D) Area under the ROC curves calculated by each cut-off value. (E) Diagnostic performances of the US-17, HokUS-6, and HokUS-10 when the cut-off values determined by ROC curves were used.

obstruction [10,19,22]. Among the 10 parameters PUV diameter, blood flow signal in PUV, and amount of ascites were statistically weighed according to the lowest *P* value and high odds ratio (Table 4). It took about 30 and 15 minutes to complete US-17 and HokUS-10, respectively. By reducing measurement parameters from 17 to 10, examination time was shortened. Assessing 3 hepatic vein diameters and waveforms (total of 6 measurements) especially took time.

Table 3
Univariate Analysis of US-17 Parameters

US Item	*P*	Odds Ratio	95% Confidence Interval
Presence of ascites	<.001	32.309	6.202-168.314
Appearance of PUV blood flow signal	<.001	27.300	5.778-128.981
Gallbladder wall thickening	<.001	1.540	1.247-1.902
PUV dilatation	.001	7.337	2.290-23.505
Hepatic right lobe vertical diameter increase ≧ 110 mm	.002	1.084	1.030-1.141
PV dilatation	.025	1.425	1.045-1.942
PV mean velocity decrease	.067	.917	.836-1.006
Hepatic artery RI* elevation	.070	1898.384	.544-6,626,616.11
Hepatic left lobe vertical diameter increase ≧ 70 mm	.581	1.016	.961-1.073
Middle HV narrowing	.142	1.271	.923-1.751
Left HV narrowing	.244	1.196	.885-1.616
Right HV narrowing	.662	.936	.694-1.261
Spleen long axis increase	.974	1.123	.001-1408.0
Left HV waveform planarization	.999	0	0-NA
Middle HV waveform planarization	.999	0	0-NA
Right HV waveform planarization	.705	.727	.139-3.803
Contraflow of PV blood flow	1	1.723×10^{8}	0-NA

RI indicates resistive index; HV, hepatic vein; NA, data not correctly calculated.
* RI was calculated by $V_{max} - V_{min}/V_{max}$.

Sensitivity and Specificity of HokUS-10 in the Diagnosis of SOS/VOD

We investigated the efficacy and effectiveness of the new scoring systems, which consisted of 6 (HokUS-6) or 10 (HokUS-10) selected parameters in the diagnosis of SOS/VOD. First, we determined the cut-off value of HokUS-6 and -10 to efficiently detect SOS/VOD. The area under the receiver operating characteristic curve became largest at 4 points by HokUS-6 and 5 points by HokUS-10 (Figure 1). The number of true-positive, true-negative, false-negative, and false-positive cases were 8, 93, 2, and 3 by HokUS-6 and 10, 92,

Table 4
HokUS-10 Scoring

Parameters	Description	Points
Hepatic left lobe vertical diameter	≧70 mm	1
Hepatic right lobe vertical diameter	≧110 mm	1
Gallbladder wall thickening	≧6 mm	1
PV diameter	≧12 mm	1
PUV diameter	≧2 mm	2
Amount of ascites	Mild	1
	Moderate to severe	2
PV mean velocity	<10 cm/s	1
Direction of PV flow	Congestion or hepatofugal	1
Appearance of PUV blood flow signal	Yes	2
Hepatic artery RI	≧.75	1

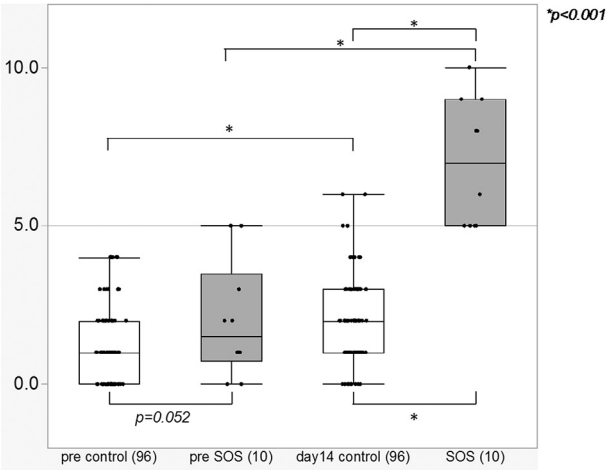

Figure 2. HokUS-10 scores in patients with or without SOS/VOD. HokUS-10 scores before (pre-HSCT) and after HSCT in the control group (n = 96) and SOS/VOD group (n = 10). The scores after HSCT in the control group were obtained by routine US scan on day 14. In the SOS/VOD group scores were obtained either by routine scan on day 14 or occasional scan. Each dot represents a patient. The lines in each graph are maximum, upper quartile, median, lower quartile, and minimum from the top. *$P < .001$.

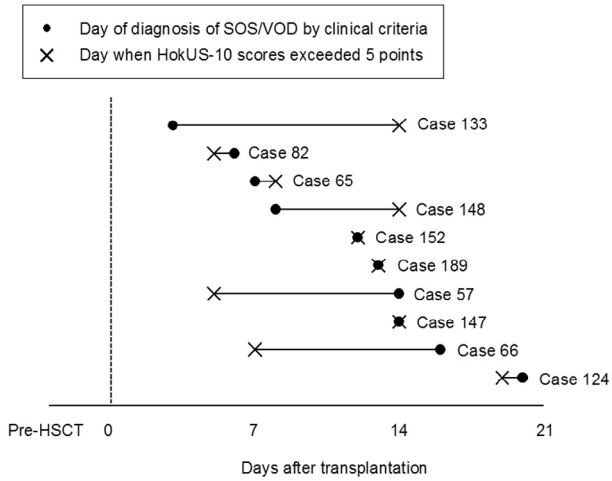

Figure 3. Time course of clinical diagnosis and US detection of SOS/VOD. Day of SOS/VOD diagnosis (●) and day of detection of SOS/VOD by the HokUS-10 (X) are depicted for each patient.

0, and 4 by HokUS-10, respectively. The sensitivity, specificity, positive predictive value, and negative predictive value were 80.0%, 96.9%, 95.3%, and 72.7% by HokUS-6 and 100%, 95.8%, 71.4%, and 100% by HokUS-10, respectively (Figure 1). Both new scoring systems improved diagnostic performance significantly compared with the US-17 ($P < .001$). Specificity and positive predictive value were equivalently better in the HoKUS-6 and HokUS-10 than the US-17. However, sensitivity and negative predictive value were inferior in the HokUS-6 when comparing with the US-17 and HokUS-10. According to these results we concluded that the HokUS-10 was a better predictive scoring system than the others. Four cases showing false positivity by HokUS-10 included engraftment syndrome, hyperacute graft-versus-host disease, and subclinical SOS/VOD.

The median score of the HokUS-10 in the SOS/VOD group was 7 (range, 5 to 10) at diagnosis, which was significantly higher than that of control subjects (median, 2; range, 0 to 6) on day 14 (Figure 2, $P < .0001$). Pre-HSCT scores tended to be higher in the SOS/VOD group compared with control subjects (Figure 2, $P = .052$). Interestingly, the scores on day 14 in the control group were significantly higher than those for pre-HSCT (Figure 2, $P < .001$), suggesting conditioning-mediated hepatic injury.

Figure 3 shows a time course of clinical diagnosis and US detection of SOS/VOD. US detection of SOS/VOD preceded its clinical diagnosis in 4 patients (82, 57, 66, and 124), clinical diagnosis was made following US detection on the same day in 3 patients (147, 152, and 189). In 3 patients (133, 148 and 65), US examination was not performed before clinical diagnosis was made because of rapid progression of the disease.

DISCUSSION

Diagnosis of SOS/VOD after HSCT is based on clinical criteria including weight gain, ascites, hepatomegaly, and jaundice [2,3]. Previous studies showed efficacy of imaging such as US, computed tomography, and magnetic resonance imaging to detect abnormalities associated with SOS/VOD [15-19,22-25]. In particular, US is a highly sensitive tool to detect hemodynamic change in the liver. However, diagnostic criteria of SOS/VOD by US remain to be investigated.

The advantage to the use of US for SOS/VOD is its ability to detect blood flow abnormalities responsible for the pathogenesis of SOS/VOD. For example, gallbladder wall thickening reflects congestion of the cystic vein returning to the portal venous system downstream of sinusoids and is 1 of the most sensitive parameters with the lowest P values in our study. In addition, US is a "point of care" diagnostic device and available at bedside with minimal invasiveness.

US-17 screening showed excellent diagnostic value, with 100% sensitivity and 81.3% specificity, but was not easy to perform, and we developed a more simplified scoring system, the HokUS-10, to further improve feasibility and specificity without impairing sensitivity by selecting parameters that were statistically weighted based on univariate analysis. The HokUS-10 achieved 100% sensitivity and 95.8% specificity. Specificity of the HokUS-10 was statistically superior to US-17 screening and sensitivity was superior to the HokUS-6.

Two patients had engraftment syndrome and hyperacute graft-versus-host disease, both of which are characterized by fluid retention due to capillary leak syndrome mediated by hypercytokinemia [26-28]. Two patients with subclinical SOS/VOD also showed false positivity. There were 4 patients in whom US diagnosis preceded clinical diagnosis of SOS/VOD, indicating predictive value of the HokUS-10. We performed US evaluation 14 days after HSCT. Considering the median day of clinical diagnosis of SOS/VOD was day 12.5 in our study, earlier US screening could be useful in patients suspicious of SOS/VOD. Earlier detection of SOS/VOD by US and intervention may help to improve prognosis of patients.

We proposed a new US-based scoring system that would be useful to detect SOS/VOD with high sensitivity and specificity. Limitations of our study include the small number of patients and lack of validation study. Further studies are required to validate the effectiveness of the HokUS-10 scoring system.

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at doi:10.1016/j.bbmt.2018.05.025.

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