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Original article

Assessment of hepatic veno-occlusive disease/sinusoidal obstruction syndrome using different scanning approaches for the ultrasonographic evaluation of portal vein blood flow and hepatic artery resistance index in hematopoietic stem cell transplant recipients

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Abstract

Purpose: Sinusoidal obstruction syndrome (SOS) is a fatal complication of hematopoietic stem cell transplantation (HSCT). Previously, we established a scoring system (Hokkaido ultrasound-based scoring system-10; HokUS-10) comprising 10 ultrasound parameters for SOS diagnosis. In HokUS-10, the portal vein time-averaged flow velocity (PV TAV) and hepatic artery resistance index (HA RI) are measured using subcostal scanning. However, measurement errors and delineation difficulties occur. Therefore, we aimed to prospectively evaluate PV TAV and HA RI measurements obtained via intercostal scanning as an alternative method to subcostal scanning and determine their cutoff values.

Methods: HokUS-10 was administered before and after HSCT. PV TAV and HA RI were measured on subcostal and right intercostal scans.

Results: We performed 366 scans on 74 patients. The median value (range) of PV TAV in the main and right portal veins was 15.0 cm/s (2.2–49.6 cm/s) and 10.5 cm/s (1.6–22.0 cm/s), respectively. A low correlation was observed between the two values ($r = 0.39$, $p < 0.01$). The highest diagnostic value of the right portal vein was less than 8.0 cm/s. The median value (range) of HA RI in the proper and right hepatic arteries was 0.72 (0.52–1.00) and 0.70 (0.51–1.00), respectively. A strong correlation was observed between the two values ($r = 0.65$, $p < 0.01$). The highest diagnostic value of the right HA RI was 0.72 or higher.

Conclusion: Quantitative measurement of PV TAV and HA RI using intercostal scanning can be appropriately performed as an alternative method to using subcostal scanning.

Keywords

ultrasonography, liver, sinusoidal obstruction syndrome, hepatic veno-occlusive disease, portal vein blood flow velocity, hepatic artery resistance index

Introduction

Hepatic sinusoidal obstruction syndrome (SOS) / hepatic veno-occlusive disease (VOD) are fatal complications that occur mainly after hematopoietic stem cell transplantation (HSCT). In 2016, the European Society for Blood and Marrow Transplantation (EBMT) proposed ultrasonography (US) parameters as a diagnostic criterion for SOS diagnosis [1]. In 2018, we reported the usefulness of the 10 US scoring system (Hokkaido US-based scoring system-10; HokUS-10) for the diagnosis of SOS [2] (Table 1). In HokUS-10, the portal vein time-averaged flow velocity (PV TAV) and hepatic artery resistance index (HA RI) are measured using subcostal scanning. The cutoff values for the main portal vein (MPV) and HA RI are less than 10 cm/s and 0.75 or higher, respectively. However, subcostal scanning often results in measurement errors owing to larger Doppler angle corrections and difficulty in delineation because the PV runs through deeper areas, and intestinal gas often interferes. In contrast, right intercostal scans are simpler, have less error, and are not affected by intestinal gas [3]. Therefore, we hypothesized that right intercostal scanning may be a beneficial alternative to subcostal scanning. In this study, we compared the PV TAV and HA RI values obtained using right intercostal and subcostal scans. In addition, we re-evaluated the cutoff values because the peripheral blood flow velocity and resistive index are usually smaller than those of the hepatic hilum.

Patients and Methods

Patients who underwent US before and after HSCT between May 2020 and September 2021, and were scored using HokUS-10, were enrolled in this study. The PV TAV and HA RI were measured on the same day using subcostal and right intercostal scans. Modified HokUS-10 was calculated using the scores of PV TAV and HA RI obtained via intercostal scanning. SOS diagnosis was based on the Modified Seattle [4] or Baltimore/EBMT criteria [5]. The ultrasound systems used were the Canon Aplio XG, Aplio 500, Aplio i800, Viamo, and Xario 200G, with a convex-type probe with a center frequency of 3.5–5.0 MHz.

Seven laboratory technologists and three radiological technologists performed US. Seven had more than three years of experience, and three had less than three years of experience. When US was performed by technologists with less than three years of experience, technologists with more than three

years of experience always rechecked the US.

US was performed in the morning under fasting conditions. PV TAV and HA RI were measured under natural respiration or light breath holding. The TAV of the MPV and right portal vein (PR) was measured on subcostal (Fig. 1a) and right intercostal scans (Fig. 1b), respectively. The proper hepatic artery RI (PHA RI) and right hepatic artery RI (RHA RI) were measured using subcostal scanning (Fig. 2a) and right intercostal scanning (Fig. 2b), respectively.

Statistical analyses were performed using Spearman's correlation coefficient (r) between MPV TAV and PR TAV, and between PHA RI and RHA RI. Significant differences were compared using the Mann–Whitney U test. The cutoff values of PR and RHA were calculated from the area under the receiver operating characteristic (ROC) curve analysis [6] for a cutoff value of approximate measurements data of PV TAV and HA RI obtained via subcostal scanning. Variations in the angle correction of the MPV and PR TAV measurements were compared using the Mann–Whitney U test. JMP Version 16.2.0 (SAS Institute Inc., Cary, NC, USA) was used for analysis.

Results

During the study period, 74 patients and 368 exams were enrolled in this study. Two exams in one patient were excluded because of portal vein thrombus. MPV TAV was excluded three times in two patients, due to markedly decreased PV blood flow and angle correction beyond 60° . PHA could not be detected four times in three patients. Ultimately, 363 PV TAV and 362 HA RI were measured in 74 patients (50 men, 24 women). Patient characteristics are shown in Table 2. The median age was 48 (range: 20–67) years, and the median body mass index was 22.1 (range: 15.6–36.2).

SOS was diagnosed in four patients (5%, four males), with a median age of 50 (range: 35–63) years, and the diagnosis of SOS was made at a median of 25 (range: 13–38) days after HSCT. In four patients with SOS, HokUS-10 scores were 7, 9, 5, and 6 based on subcostal and intercostal scans. Twenty-four PV TAV and 23 HA RI were measured in SOS patients. Summarized scoring data on HokUS-10 and modified HokUS-10 are shown in Table 3.

The median PV TAV was 15.0 cm/s (range: 2.2–49.6 cm/s) for MPV and 10.5 cm/s (range: 1.6–22.0 cm/s) for PR (Fig. 3a). MPV showed a significantly higher PV TAV than PR ($P < 0.01$). A low correlation was observed between the two values ($r = 0.39$, $p < 0.01$) (Fig. 3b). In the ROC

curve analysis, a PR cutoff value of 8.0 cm/s on the right intercostal scan showed the highest diagnostic value of 0.81 (Fig. 3c). The Doppler angle correction of MPV TAV tended to be larger than that of PR TAV, with a median value (95% CI) of 58° (55°–56°) for MPV and 30° (27°–30°) for PR (Supplementary Figure).

The median (range) RI of PHA and RHA was 0.72 (0.52–1.00) and RHA 0.70 (0.51–1.00), respectively (Fig. 4a). PHA showed a significantly higher value than RHA ($P < 0.01$). They were moderately concordant and showed a strong positive correlation ($r = 0.65$, $p < 0.01$) (Fig. 4b). ROC curve analysis showed the highest diagnostic value as 0.87 for RHA with a cutoff of 0.72 (Fig. 4c).

Discussion

In this study, both PV TAV and HA RI measured using the two different scanning approaches were moderately correlated. Therefore, quantitative measurement of PV TAV and HA RI using right intercostal scanning can be a substitute for evaluating PV and HA parameters. Cutoff values of 8.0 cm/s for PR and 0.72 for RHA were reasonable.

There were measurement difficulties using subcostal scanning three times with the PV TAV, and four times with the HA RI, whereas all measurements performed using intercostal scanning succeeded in this study. Intercostal scanning is therefore proposed as a substitutional measurement method for subcostal scanning.

The existing differences in the accuracy of measurements among US systems is a concern. Usually, portable US systems are adequate for performing US in a sterile room instead of using a high-grade large machine. In this study, portable US was used in five of the six excluded exams. The depth sensitivity of portable systems is thought to affect the measurements of PV TAV and HA RI obtained via the subcostal approach. Therefore, we must keep in mind the depth sensitivity when using a portable US system. However, our previous study [7] showed that the diagnostic performance when using four different types of US systems was good. Hence, differences between US systems should not be a major issue.

For PV TAV, the cutoff value in HokUS-10 was 10 cm/s in the MPV. According to previous reports, PV flow velocity decreases by approximately 70%–80% when the main trunk branches into primary and secondary branches [8, 9]. Furthermore, the cutoff value was reported as 7.0–8.0 cm/s.

This value is consistent with our results. Compared to the Doppler incidence angles, the angle tended to be larger in the subcostal scans. In a previous study with a linear probe, the deviation of the flow velocity value from the true value increased by 15% when the Doppler incidence angle was 60° ; however, it became an incompetent error value with a 50% increase when the Doppler incidence angle was 80° [10]. Based on these results, the effect of the slightly overestimated variability values was considered because of the larger angle in the subcostal approach. The Doppler incidence angle should be set within 60° , and setting the angle as small as possible is recommended. Achieving a smaller Doppler incidence angle using intercostal scanning would be appropriate.

A strong correlation was observed between the RI values obtained using the two scanning methods. RHA showed a significantly lower value than PHA, which is consistent with a previous report that the RI decreases as the RHA branches peripherally [11]. The cutoff value for HA RI in HokUS-10 was set at 0.75 PHA. In the present study, the cutoff value for RHA was significantly lower than that of PHA, and the highest diagnostic performance was obtained when the cutoff value of RHA was 0.72.

In patients with SOS, the MPV and RPV TAV were consistently above or below the cutoff values. The PHA RI was difficult to assess in one patient, whereas the RHA RI was measurable and did not increase. Thus, the HokUS-10 scores obtained using different approaches were consistent for all patients with SOS. This indicates that the onset of SOS was correctly detected in all patients.

Several reports have suggested the usefulness of elastography in diagnosing SOS [2,7,12-14]. Transient elastography (TE) showed a very good AUC (0.997) with moderate sensitivity (75%) [12]. There is some concern that the ability of TE to measure elasticity when ascites exists on the liver surface is limited since most SOS patients have ascites. Furthermore, TE has limited availability, it is expensive, and not all hospitals have access to it. While shear wave elastography (SWE) might be a useful tool instead of TE, previous reports of diagnosing SOS with 2D-SWE showed a good AUC (0.85 [12] and 0.84 [13]) but not enough sensitivity (80% [12] and 75% [13]). Since sensitivity is important to diagnose SOS, false negatives lead to treatment delay and unfortunate results. On the contrary, HokUS-10 showed very good sensitivity (100% [2] and 97% [7]) with a very good AUC (0.980 [2] and 0.992 [7]). So far, the

availability of US machines with SWE measurement capability is limited. We think that, currently, universally available conventional US is indispensable to diagnose SOS.

The right intercostal approach has several limitations. First, it cannot estimate the hemodynamics of the entire liver. Hemodynamic changes in the left lobe cannot be assessed. However, in patients with SOS, CT and MRI showed heterogeneous staining in the liver [15, 16], mainly in the hepatic limbus and right lobe of the liver [15], with hepatic volume predominating in the right lobe. Thus, hemodynamic evaluation of the right lobe only can be substitutable. Second, we were concerned about the wide range of angular corrections and large variability. However, because the RHA correlated with the PHA and its variability was similar to that of the PHA, measurement of the RHA may be an alternative when the main trunk is difficult to delineate. Third, inter- and intra-operator reliability of PV TAV and HA RI was investigated previously [17], but PV TAV and HA RI were not measured with subcostal and right intercostal scanning. Furthermore, this was a single center study with a limited sample size and few cases of SOS. A multicenter study with a larger number of participants that includes reliability estimations is needed to confirm our conclusion.

Conclusion

Quantitative measurement of PV and HA using intercostal scanning can be an appropriate alternative to subcostal scanning. A cutoff value of 8.0 cm/s for PR TAV and 0.72 for RHA RI on the right intercostal scan might be appropriate.

Acknowledgments

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Authorship

M. K., T. I., and M. N. participated in the study design, writing of the manuscript, research, and data analysis.

Y. K., S. O., and M. S. participated in the performance of the research.

J. S. and H. G. participated in the study design, data analysis, and manuscript review.

I. Y. performed statistical analysis.

T. T. participated in the study design, data analysis, and writing and reviewing of this paper.

Compliance with ethical standards

Conflicts of interest

Mutsumi Nishida has received a research grant and a speaker fee from Nippon Shinyaku, and a speaker fee from Pfizer. Hideki Goto has received research grants and speaker fees from Bristol Myers Squibb and Kyowa Kirin, a research grant from SymBio, and speaker fees from Novartis, Chugai Pharmaceutical, and Daiichi Sankyo. Isao Yokota has received a research grant from Nihon Medi-Physics, and speaker fees from Chugai Pharmaceutical and AstraZeneca. Takanori Teshima has received research grants and speaker fees from Chugai Pharmaceutical, Kyowa Kirin, Nippon Shinyaku, Sumitomo Pharma, and Astellas, research grants from Fuji Pharma, Asahi Kasei Pharma, Eisai, Ono Pharmaceutical, Shionogi, Priothera SAS, and Luca Science, speaker fees from AbbVie, Novartis, Bristol-Myers Squibb, Merck Sharp & Dohme, Celgene and Janssen, and participation on a Data Safety Monitoring Board or Advisory Board at Novartis, Meiji Seika Pharma, Daiichi Sankyo, Asahi Kasei Pharma, Astellas, AstraZeneca, Takeda, Janssen, Roche Diagnostics, Sumitomo Pharma, Celgene, and Sanofi. The rest of the authors declare that they have no conflicts of interest.

Ethical statement

This study was approved by the Institutional Review Board (019-0386), and written informed consent was obtained from all study participants in accordance with the World Medical Association Declaration of Helsinki:

Ethical principles for medical research involving human subjects, 2013.

Role of the funding source

There is none.

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Figure captions

Fig. 1 Measurement of main portal vein (MPV) time-averaged flow velocity (TAV) using subcostal scanning (a) and PR TAV using right intercostal scanning (b)

PV TAV was measured using the auto-tracing method, with Doppler angle correction within 60° , and the sample gate was set at more than two-thirds of the vessel diameter. MPV TAV was measured by identifying the MPV near the hepatic hilum after the confluence of the splenic and superior mesenteric

veins in the subcostal region. PR TAV was measured before the bifurcation of the anterior and posterior branches.

Fig. 2 Measurement of proper hepatic artery (PHA) resistive index (RI) via the subcostal approach (a) and right hepatic artery (RHA) RI via the right intercostal approach (b)

The maximum flow velocity (Vmax) and minimum flow velocity (Vmin) of the hepatic artery (HA) were measured using automatic or manual trace methods. The PHA RI was measured when the PHA branching from the common hepatic artery was identified. The RHA RI was measured using color Doppler in the right intercostal space to identify pulsatile blood flow signals in the ventral portal vein. HA RI was measured based on the average of three or more waveforms. The formula $(V_{\max} - V_{\min}) / V_{\max}$ was used to determine HA RI.

Fig. 3 Comparison of portal vein (PV) measurements obtained via subcostal and intercostal scanning

(a) Boxplot of main portal vein (MPV) and right portal vein (PR) time-averaged flow velocity (TAV). The median (range) PV TAV was 15.0 cm/s (2.2–49.6 cm/s) for the MPV and 10.5 cm/s (1.6–22.0 cm/s) for the PR. The MPV showed a significantly higher value than the PR ($p < 0.01$). (b) Correlation of MPV and PR TAV. There was a low correlation between them ($r = 0.39$, $p < 0.01$). (c) ROC curve in PR TAV. In the ROC curve analysis, the PR cutoff value was 8 cm/s using right intercostal scanning and showed the highest diagnostic value as 0.81 (Fig. 3c)

Fig. 4 Comparison of hepatic artery (HA) resistive index (RI) measurements using subcostal and intercostal scanning

(a) Boxplot of HA RI. The median (range) RI for the proper hepatic artery (PHA) was 0.72 (0.52–1.00), and that for the right hepatic artery (RHA) was 0.70 (0.51–1.00). The PHA showed a significantly higher value than the RHA ($p < 0.01$). (b) Correlation between PHA RI and RHA RI. They were moderately concordant and showed a strongly positive correlation ($r = 0.65$, $p < 0.01$). (c) Receiver operating characteristic (ROC) curve and area under the curve (AUC) for RHA RI. The ROC curve analysis showed the highest diagnostic value as 0.87 for the RHA with a cutoff of 0.72.

Supplementary Figure Boxplot of angle correction for main portal vein (MPV) and right portal vein (PR) time-averaged flow velocity (TAV) measurement

The Doppler angle correction of the MPV tended to be larger than that of the PR, with a median value (95% confidence interval [CI]) of 58° (55° –56°) for the MPV and 30° (27° –30°) for the PR.

Table 1. Hokkaido ultrasound-based scoring system-10 scoring

Parameters	Description	Points
Hepatic left lobe vertical diameter	≥ 70 mm	1
Hepatic right lobe vertical diameter	≥ 110 mm	1
Gallbladder 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 (TAV)	< 10 cm/s	1
Direction of PV flow	Congestion or hepatofugal	1
Appearance of PUV blood flow signal	Yes	2
*Hepatic artery RI	≥ 0.75	1

RI was calculated by the formula of $V_{\max} - V_{\min} / V_{\max}$

PV/portal vein, TAV/time-averaged flow velocity, PUV/paraumbilical vein, RI/resistive index

* Items examined in this study

Table 2. Characteristics of the study population

Patient characteristics (n = 74)	Number / Median (range)
Male / Female	50 / 24
Age (years)	48 (20–67)
BMI (kg/m ²)	22.1 (15.6–36.2)
Diagnosis	
AML	29 (39.2%)
ALL	13 (17.6%)
MDS	8 (10.8%)
Others	24 (32.4%)
Number of Examinations	366
Before / After HSCT	74 / 292

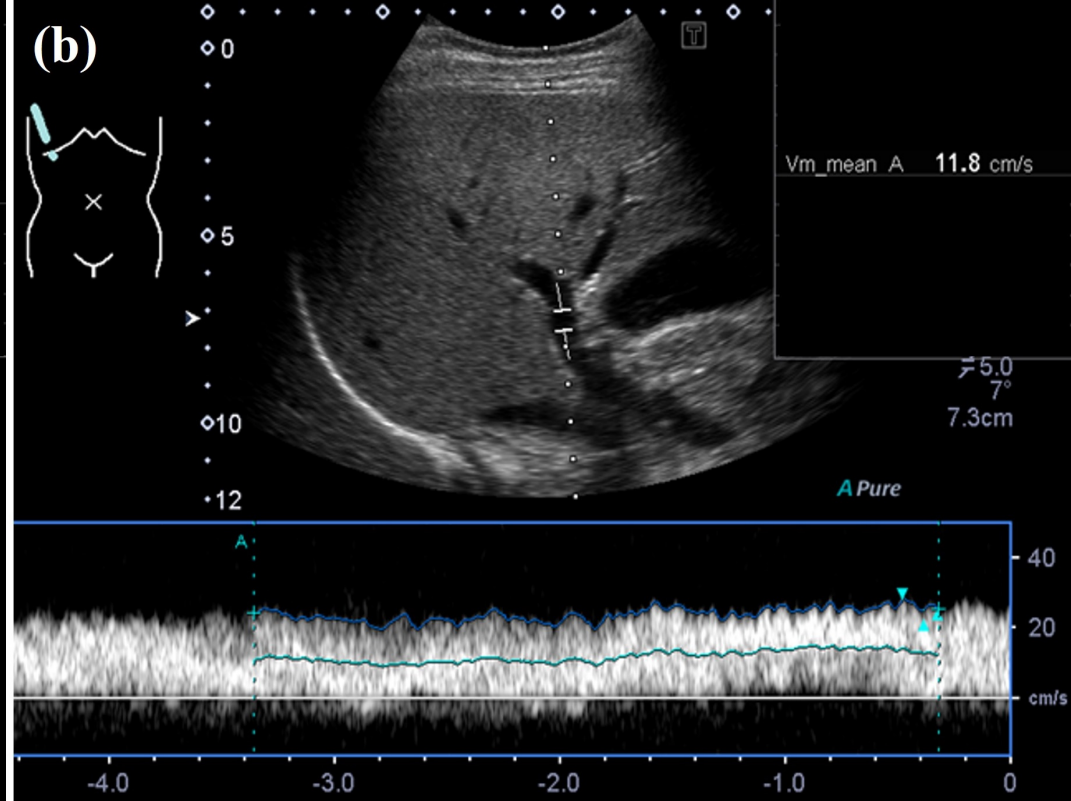
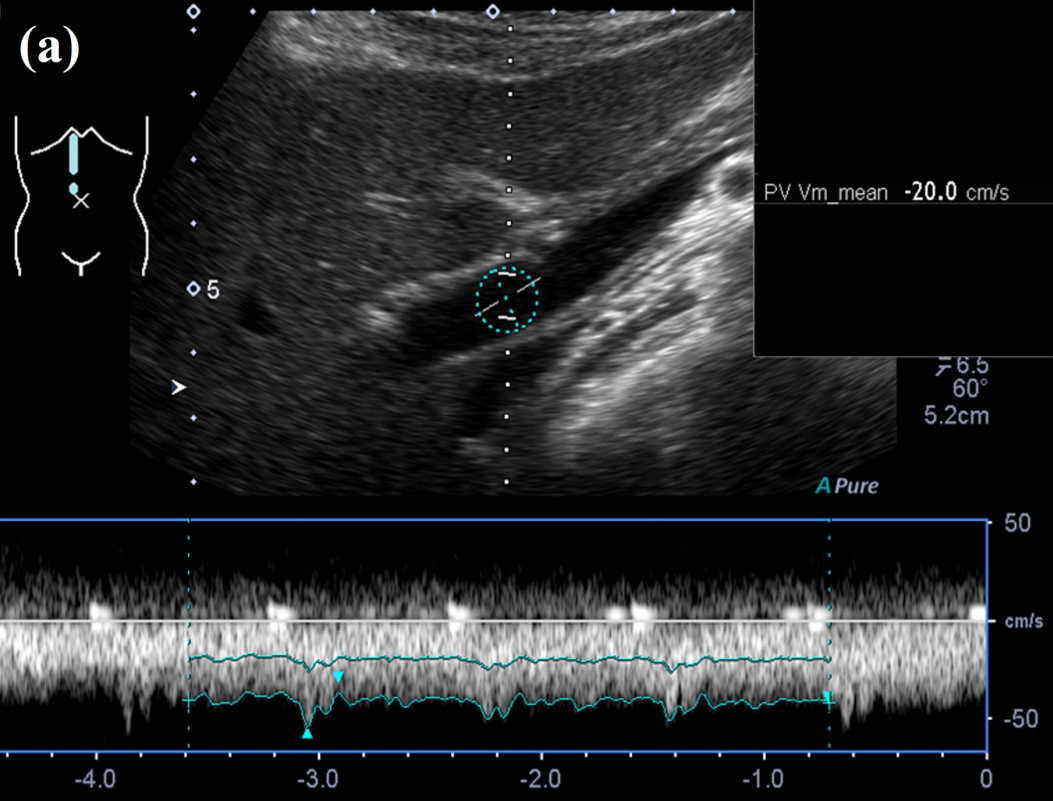
BMI body mass index, *AML* acute myeloid leukemia, *ALL* acute lymphoblastic leukemia, *MDS* myelodysplastic syndrome, *HSCT* hematopoietic stem cell transplantation

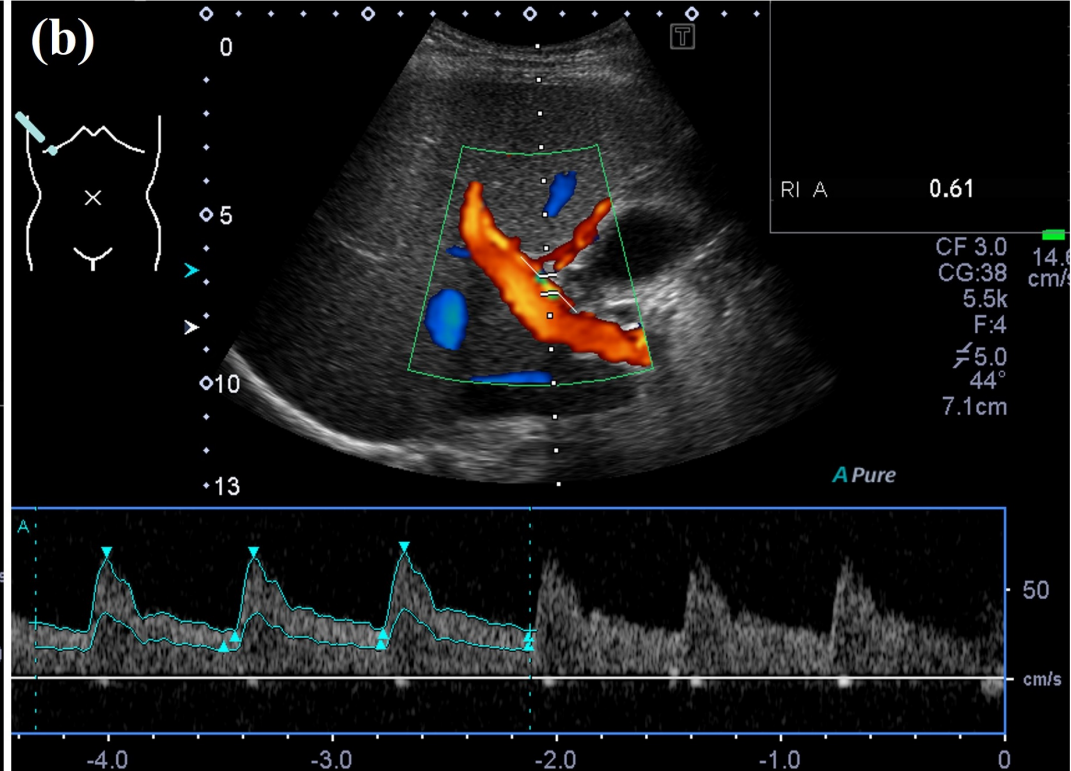
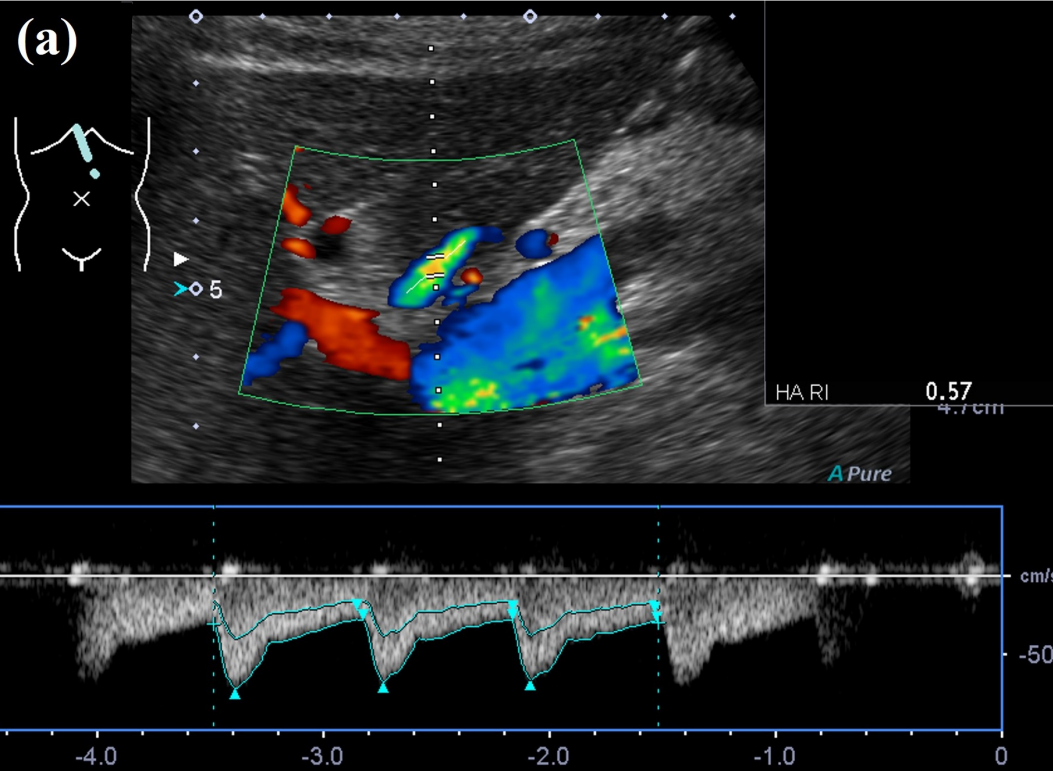
Table 3. Comparison of HokUS-10 and modified HokUS-10

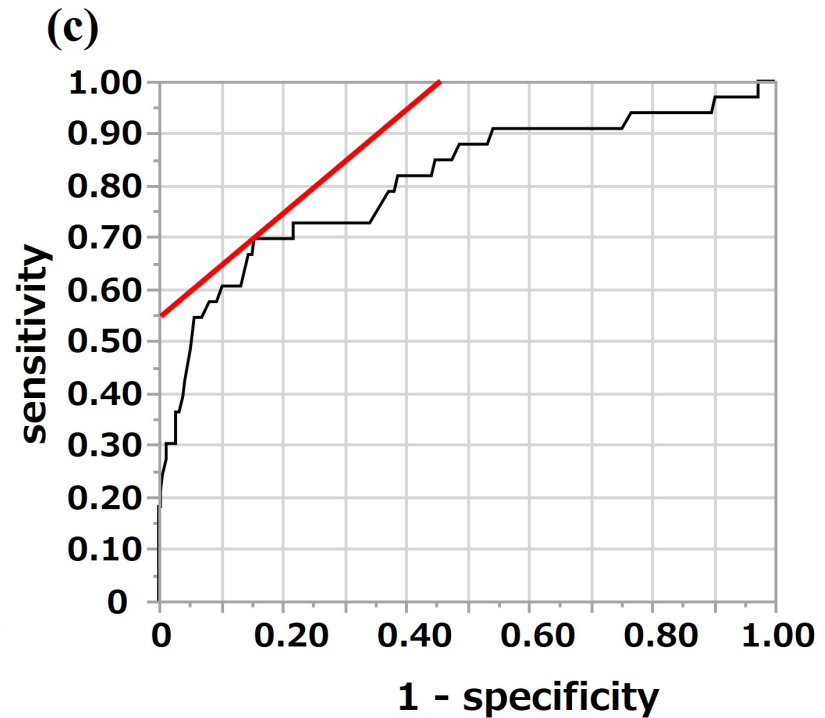
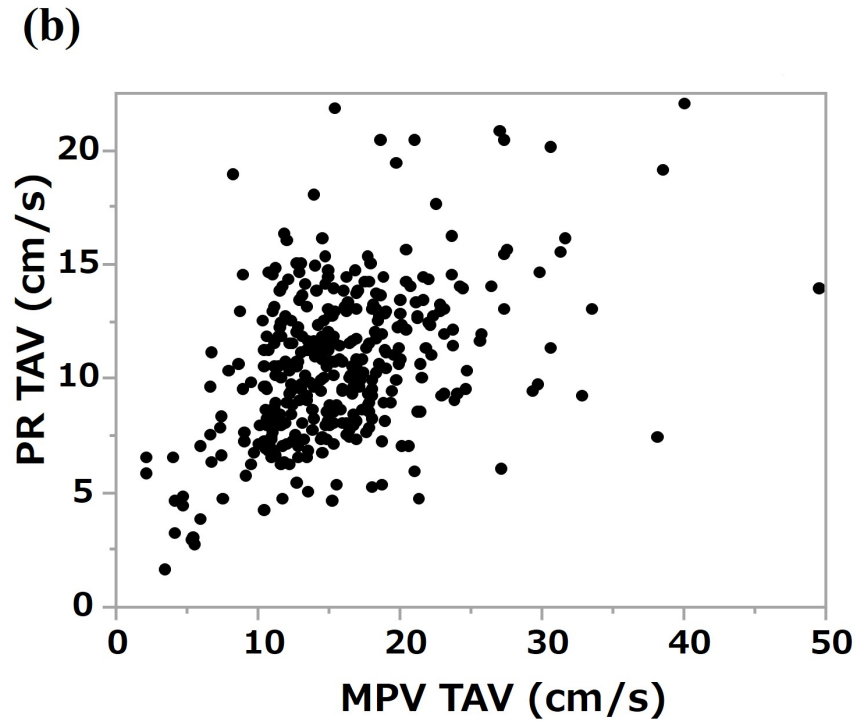
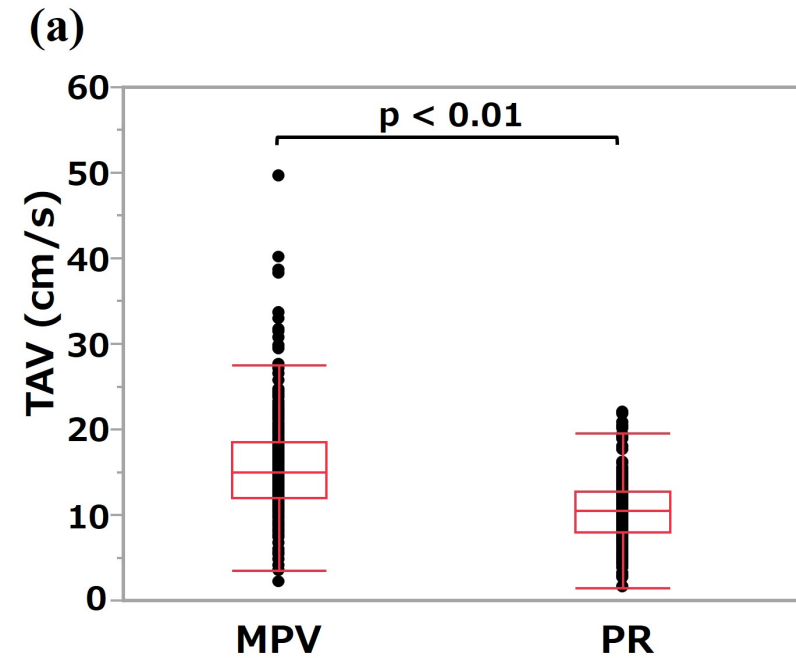
Scoring system (N=360)		HokUS-10 ¹											
	Score	0	1	2	3	4	5	6	7	8	9	10	11
Modified HokUS-10 ²	0	32	3	0	0	0	0	0	0	0	0	0	0
	1	19	81	11	0	0	0	0	0	0	0	0	0
	2	1	27	56	5	0	0	0	0	0	0	0	0
	3	0	3	20	27	4	0	0	0	0	0	0	0
	4	0	0	3	4	16	4	0	0	0	0	0	0
	5	0	0	0	0	9	10	1	0	0	0	0	0
	6	0	0	0	0	2	2	6	0	0	0	0	0
	7	0	0	0	0	0	1	0	2	0	0	0	0
	8	0	0	0	0	0	0	0	0	2	0	0	0
	9	0	0	0	0	0	0	0	0	0	3	1	0
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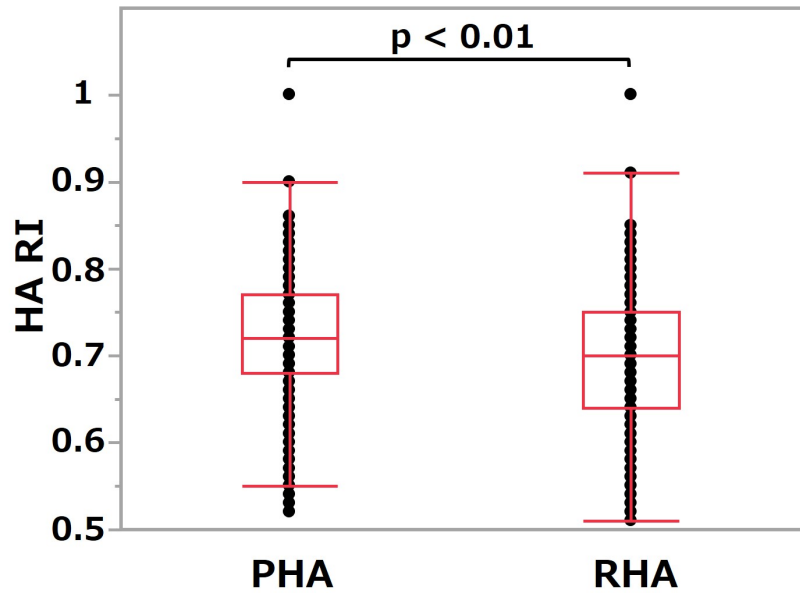
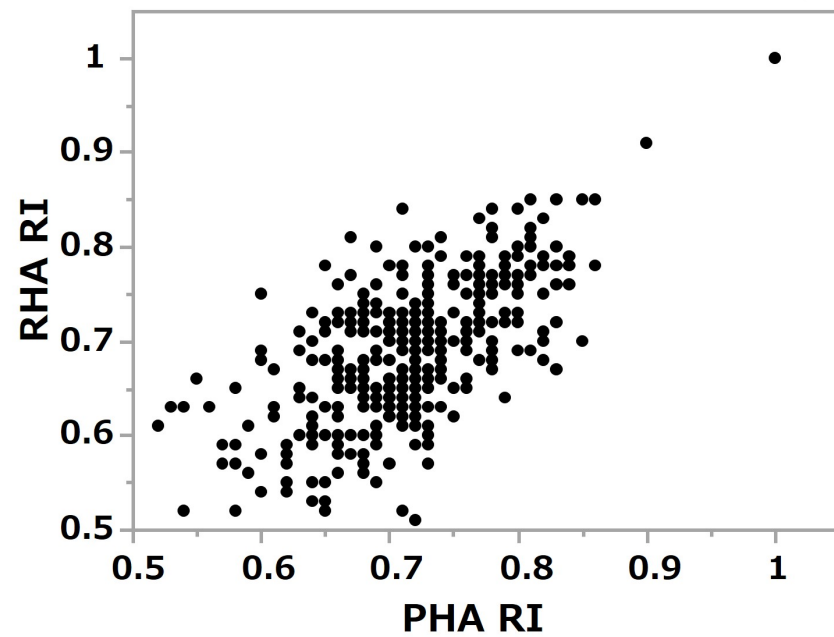
¹HokUS-10: PV TAV and HA RI were obtained via subcostal scanning. ²Modified HokUS-10: PV TAV and HA RI were obtained via intercostal scanning.

PV portal vein, *TAV* time-averaged flow velocity, *HA* hepatic artery, *RI* resistive index







(a)**(b)****(c)**