


















ORIGINAL ARTICLE

# Usefulness of virtual touch tissue quantification for predicting the presence of esophageal varices in patients with liver cirrhosis

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## Key words

esophageal varices, hepatic venous pressure gradient, liver cirrhosis, virtual touch tissue quantification.

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**Declaration of conflict of interest:** None.

## Abstract

**Background and Aim:** Measuring the hepatic venous pressure gradient (HVPG) is an established technique to detect increased portal pressure and predict the presence of esophageal varices (EVs); however, the risk of the test is greater than the information it provides. This study aimed to clarify the usefulness of virtual touch tissue quantification (VTQ), which assesses liver stiffness, in predicting the presence of EVs in patients with liver cirrhosis by comparing it with HVPG.

**Methods:** Two hundred seventeen patients with liver cirrhosis underwent VTQ, HVPG measurement, and upper endoscopy. Patients were divided into three groups: group V, hepatitis C virus liver cirrhosis ( $n = 40$ ); group A, alcoholic liver cirrhosis ( $n = 116$ ); and group N, other liver cirrhosis ( $n = 61$ ). In each group, we performed linear regression analysis of VTQ and HVPG data. The accuracy of VTQ and HVPG measurement in predicting the presence of EVs and high-risk EVs (EV category F2 and F3) was assessed by area under the receiver operating characteristic curve (AUROC).

**Results:** VTQ was significantly correlated with the HVPG in the whole patients and in each group, and both VTQ and HVPG values were significantly higher in patients with EVs and high-risk EVs than in those without. The AUROC for the presence of EVs for VTQ was 0.76 in the whole sample, 0.76 in group V, 0.79 in group A, and 0.67 in group N; and for HVPG, 0.92, 0.94, 0.93, and 0.88, respectively. For VTQ, the AUROC for the presence of high-risk EVs was 0.78 in the whole sample, 0.78 in group V, 0.73 in group A, and 0.73 in group N; and for HVPG, it was 0.85, 0.82, 0.85, and 0.82, respectively.

**Conclusion:** VTQ was reliable at predicting the presence of EVs and high-risk EVs. Therefore, we propose that VTQ is a useful, noninvasive tool for predicting the presence of EVs in daily medical care.

## Introduction

Portal hypertension is a common consequence of liver disease and is characterized by progressive liver tissue fibrogenesis and extensive vascular changes in both the liver and the splanchnic compartment.<sup>1</sup> The standard way to evaluate portal hypertension in patients with chronic liver disease is to measure the hepatic venous pressure gradient (HVPG).<sup>2</sup> The standard threshold for developing complications is an HVPG >10 mm Hg. An HVPG above this threshold is considered to indicate clinically significant portal hypertension,<sup>3</sup> which is associated with a higher risk of esophageal varices (EVs), clinical decompensation, and death

after liver resection.<sup>4–7</sup> An HVPG >12 mm Hg is considered to indicate severe portal hypertension and is linked to a higher risk of acute variceal bleeding.<sup>8,9</sup> Measurement of the HVPG is useful for estimating the degree of portal hypertension, but it is an invasive technique.

Many publications have reported on the measurement of liver stiffness, a noninvasive technique, as an alternative approach for assessing portal hypertension. The company Echosens performed pioneering work on liver stiffness measurements by liver elastography and developed the FibroScan device, which mechanically measures induced shear waves in the liver

by transient elastography (TE). Later, the company Siemens developed an alternative method for measuring liver stiffness, virtual touch tissue quantification (VTQ); this technique assesses the velocity of induced shear waves by Acoustic Radiation Force Impulse (ARFI) and uses software that can be integrated into modern ultrasound machines.<sup>10</sup>

Established evidence indicates that TE has good sensitivity and specificity for diagnosing liver fibrosis and cirrhosis, and it has been a popular test for these diseases in the past few years.<sup>11,12</sup> TE also demonstrated quite high sensitivity, specificity, and accuracy in identifying clinically significant portal hypertension.<sup>13</sup> Recently, VTQ has been suggested as an alternative method for noninvasive assessment of liver fibrosis and portal hypertension. VTQ is reported to be able to predict the presence of EVs, so it has been suggested as a guiding noninvasive screening tool for EVs that require endoscopic evaluation.<sup>14-16</sup> However, the correlation between VTQ and the etiology and stage of EVs has not been adequately studied. Therefore, the present study aimed to evaluate the usefulness of VTQ by assessing these correlations in patients with liver cirrhosis and portal hypertension and by comparing VTQ with HVPg.

## Methods

**Patients.** We studied 217 patients with portal hypertension due to liver cirrhosis who underwent VTQ, measurement of the HVPg, and upper endoscopy at our hospital between November 2012 and April 2019. Exclusion criteria were biliary obstruction disease, venous outflow blockage, or congestive heart failure disease. The patients were divided into three groups according to the liver cirrhosis etiology: group V, hepatitis C virus (HCV) liver cirrhosis ( $n = 40$ ); group A, alcoholic liver cirrhosis ( $n = 116$ ); and group N, liver cirrhosis due to other causes ( $n = 61$ ). Group N included patients with liver cirrhosis due to non-alcoholic steatohepatitis ( $n = 36$ ), autoimmune hepatitis ( $n = 5$ ), primary biliary cholangitis ( $n = 6$ ), and unknown causes ( $n = 14$ ). We also divided the patients into two groups on the basis of the severity of their liver cirrhosis: patients with hepatic encephalopathy, variceal bleeding, or uncontrollable ascites were categorized as having decompensated liver cirrhosis ( $n = 114$ ), and those without these symptoms were categorized as having compensated liver cirrhosis ( $n = 103$ ). Data for this study were obtained from blood samples collected early in the morning and patients were asked to fast for 12 h before measurement of the VTQ, HVPg, or endoscopy.

**Measurement of liver stiffness by VTQ.** To measure liver stiffness by VTQ, we downloaded additional software to a Siemens ACUSON S2000 ultrasound machine (Siemens Healthcare GmbH, Erlangen, Germany). In this procedure, by performing a routine abdominal ultrasonography, the radiologist selects a suitable 10 mm  $\times$  6 mm region of interest (ROI) in the right liver lobe while scanning through an intercostal space. The probe then generates a short-lived shear wave with a high-frequency (up to 600 Hz) ultrasound push pulse. The velocity of the induced shear wave, which moves at right angles to the original pulse, is transduced by the same probe. In our study, we measured the velocity of the shear wave passing through the ROI five times and calculated the median value.

**Measurement of HVPg.** The HVPg was measured by introducing a 5-Fr balloon catheter (balloon diameter: 9 mm) into a major hepatic vein via the transjugular approach. We obtained a mean of 3 HVPg readings. Written informed consent for the measurement of HVPg was obtained from each patient after the potential complications of the procedure had been explained.

**Endoscopic evaluation and grading of EVs.** Expert endoscopists at our institution evaluated and graded the EVs. EVs were classified into four groups: F0, no EVs; F1, small EVs in a straight line; F2, between F1 and F3; and F3, thick EVs resembling a rosary. The EV (–) group of patients was defined as those with the EV category F0; and the EV (+) group of patients, as those with an EV category F1 and above. Low-risk EVs were defined as EV category F0 and F1, and high-risk EVs, as category F2 and F3.

**Statistical analysis.** Correlations between variables were analyzed by Spearman's correlation test. Continuous variables were compared between two groups by Mann–Whitney U test, and between multiple groups, by Dunn's test. Receiver operating characteristics (ROC) curves were prepared to determine the usefulness of VTQ and HVPg in predicting the presence of EVs. The DeLong test was used to compare the area under the receiver operating characteristic curves (AUROCs) of VTQ and HVPg in the subgroups.

Analyses were performed with STATFLEX version 6 (Osaka, Japan) and BellCurve for Excel version 3.20 (Social Survey Research Information Co., Ltd., Tokyo, Japan).

The study was approved by the Ethical Review Board of Toho University Medical Center, Omori Hospital (M19186).

## Results

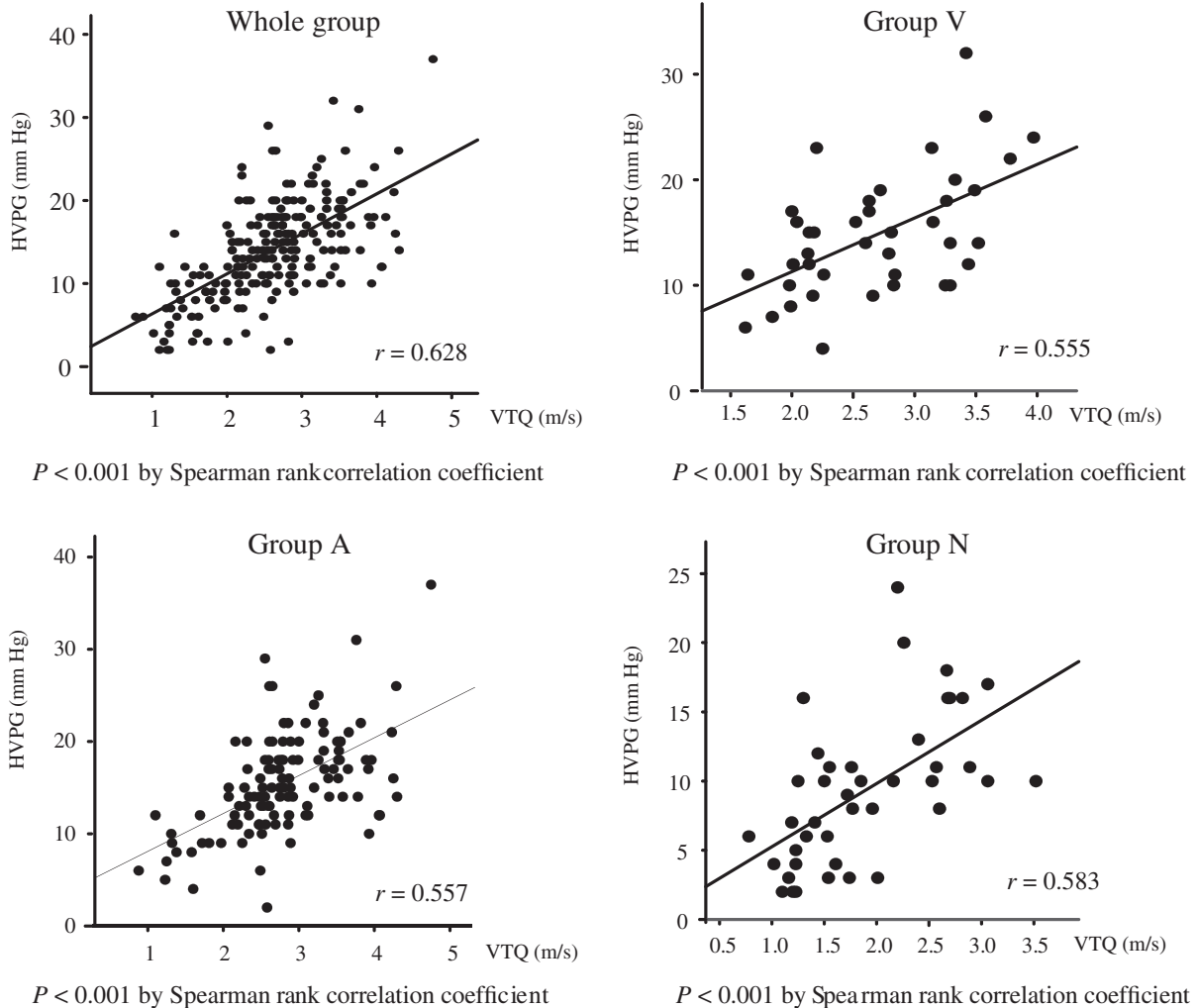
**Patients.** The mean age of the whole group of patients was 62 years; of group V, 67 years; of group A, 60 years; and of group N, 62 years. The results of laboratory tests in the whole group of patients and groups V, A, and N are presented in Table 1. The mean Child–Pugh score was 7.6 in the whole group of patients, 8.0 in group V, 7.9 in group A, and 6.7 in group N. The mean VTQ and HVPg values were 2.6 m/s and 14.1 mm Hg in the whole group of patients, 2.7 m/s and 14.8 mm Hg in group V, 2.8 m/s and 15.5 mm Hg in group A, 2.2 m/s and 10.8 mm Hg in group N, respectively. EVs were present in 172/217 (79.3%) of the whole group of patients, 32/40 (80.0%) of group V, 98/116 (84.5%) of group A, and 42/61 (68.9%) of group N. High-risk EVs were present in 122/217 (56.2%) of the whole group of patients, 22/40 (55.0%) of group V, 78/116 (67.2%) of group A, and 24/61 (39.3%) of group N. The number of patients with decompensated liver cirrhosis was 114/217 (52.5%) in the whole group of patients, 21/40 (52.5%) in group V, 73/116 (62.9%) in group A, and 20/61 (33.3%) in group N.

**Correlation between VTQ and HVPg.** We found a significant positive correlation between VTQ and HVPg (Spearman's  $\rho = 0.63$ ,  $P < 0.001$ ) in the whole group of patients. The correlation was also significant in each of the three groups:

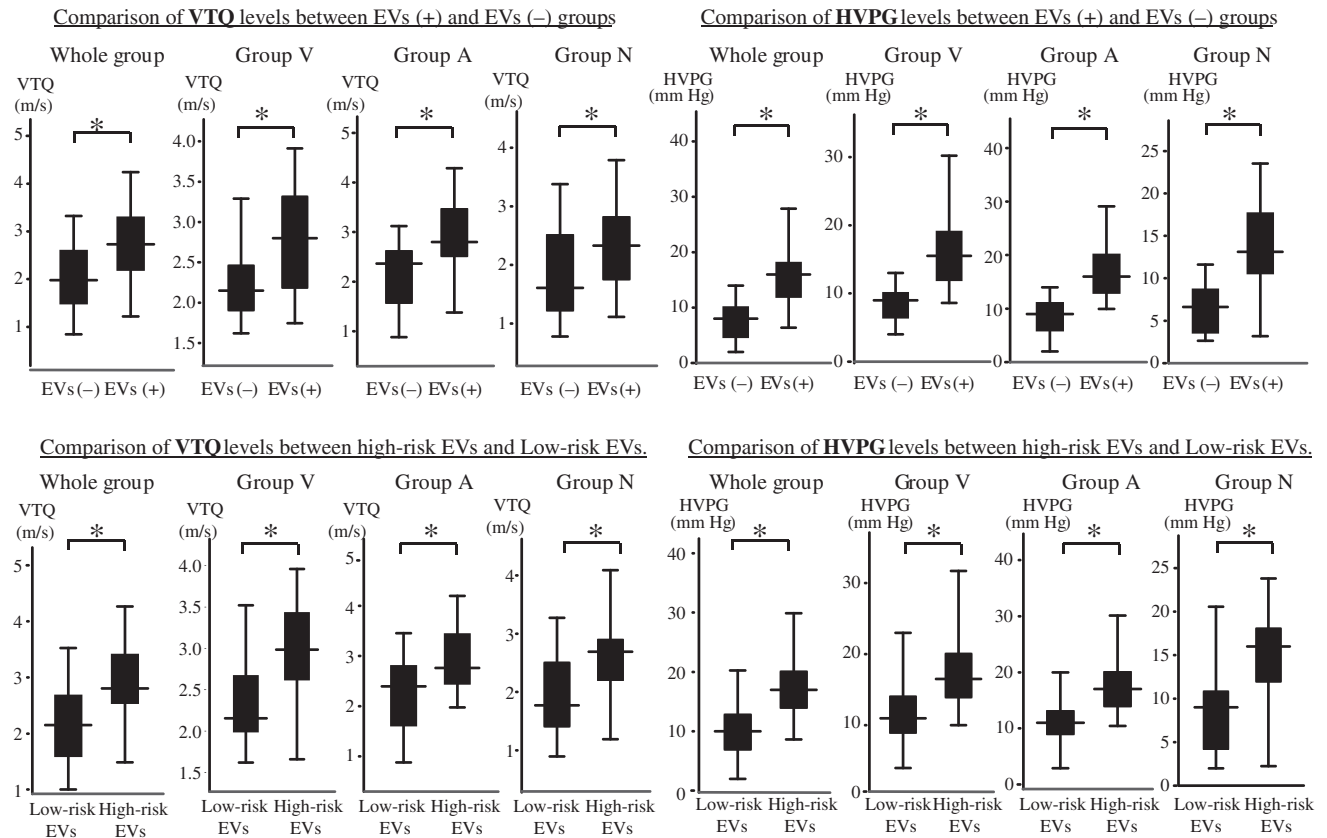
**Table 1** Clinical characteristics of the 217 patients and the comparisons of each variable between group V, group A, and group N

	All patients	Group V	Group A	Group N	P value
No. of Patients	217	40	116	61	
Gender (M/F)	154/63	24/16	97/19*	33/28*	<0.01*
Age (y.o)	62 ± 11	67 ± 11*	60 ± 11*	62 ± 12	<0.01*
AST (U/L)	50 ± 35	51 ± 16*	56 ± 44**	37 ± 16*,**	<0.01*,**
ALT (U/L)	32 ± 36	36 ± 16*	34 ± 47**	27 ± 17*,**	<0.01*,**
Alb (g/dl)	3.1 ± 0.7	2.9 ± 0.7*	3.0 ± 0.6**	3.4 ± 0.7*,**	<0.01*,**
Bil (mg/dl)	1.8 ± 1.9	1.5 ± 0.8	2.1 ± 2.3*	1.3 ± 1.6*	<0.01*
Platelet (x10 <sup>4</sup> /μl)	10.9 ± 5.6	8.6 ± 3.9*	11.6 ± 5.7*	11.1 ± 5.9	<0.01*
CPS	7.6 ± 1.9	8.0 ± 1.6*	7.9 ± 2.0**	6.7 ± 1.9*,**	<0.01*,**
BMI (kg/m <sup>2</sup> )	23.7 ± 4.4	23.1 ± 3.6	23.4 ± 4.6	24.6 ± 4.4	N.S.
VTQ (m/s)	2.6 ± 0.7	2.7 ± 0.6*	2.8 ± 0.8**	2.2 ± 0.7*,**	<0.01*,**
HVPG(mmHg)	14.1 ± 5.9	14.8 ± 5.8*	15.5 ± 5.5**	10.8 ± 5.7*,**	<0.01*,**
No. of Patients with EVs (- / +)	45/172	8/32	18/98*	19/42*	<0.05*
No. of Patients with Low / High risk EVs	95/122	18/22	38/78*	37/24*	<0.01*
Stage of cirrhosis Compensated / Decompensated	103/114	19/21	43/73*	41/20*	<0.01*

Alb, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Bil, bilirubin; BMI, body mass index; CPS, Child-Pugh score; EVs, esophageal varices; HVPG, hepatic venous pressure gradient; NS, not significant; VTQ, virtual touch tissue quantification.



**Figure 1** Linear regression analysis between virtual touch tissue quantification (VTQ) and hepatic venous pressure gradient (HVPG) in whole and each group.



**Figure 2** Comparison of virtual touch tissue quantification (VTQ) and hepatic venous pressure gradient (HVP) levels between esophageal varices (EVs) (+) and EVs (-) group (upper panel) and between high-risk EVs and low-risk EVs (lower panel).

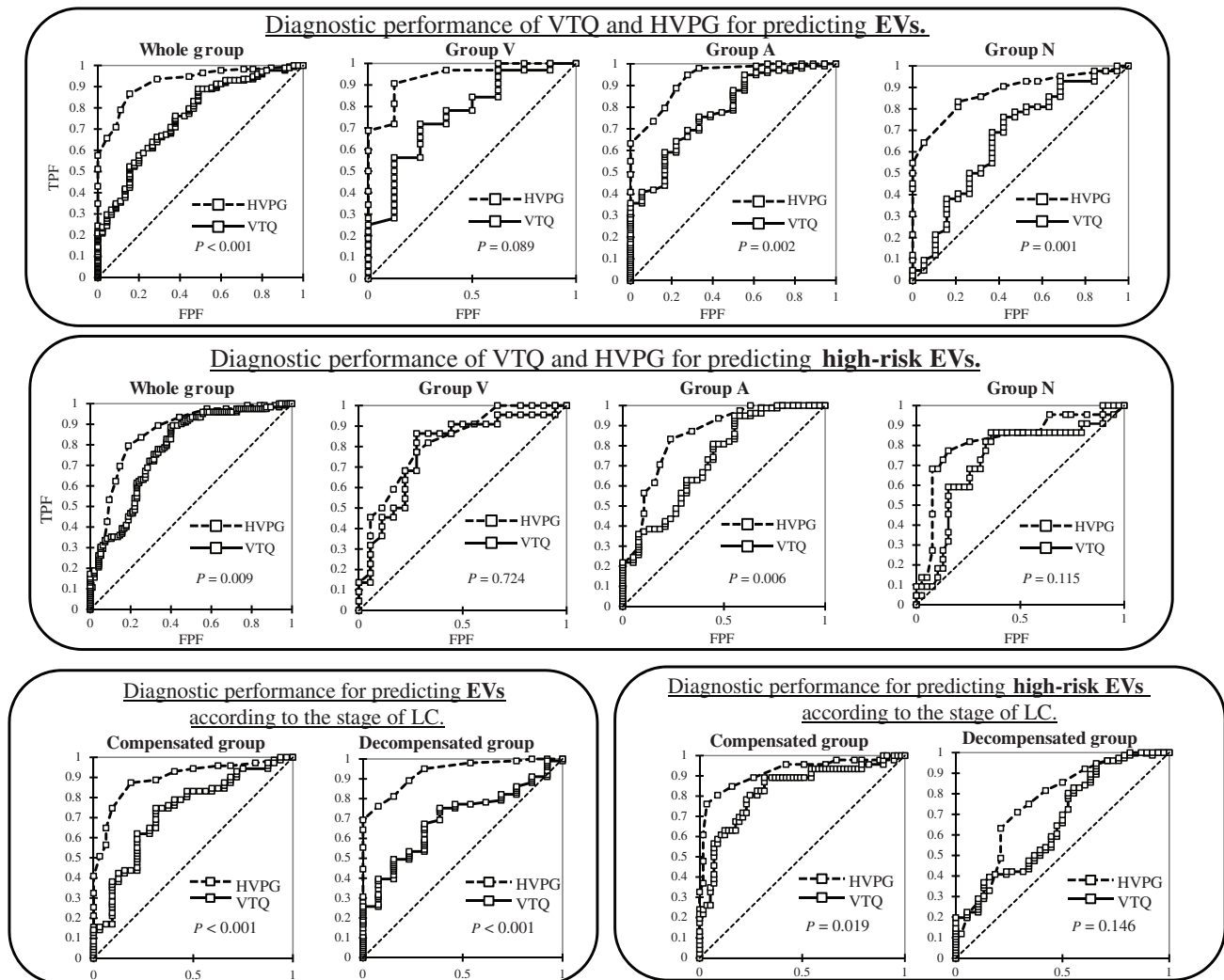
group V,  $\rho = 0.56$ ,  $P < 0.001$ ; group A,  $\rho = 0.56$ ,  $P < 0.001$ ; group N,  $\rho = 0.58$ ,  $P < 0.001$  (Fig. 1).

**Comparison of VTQ and HVP levels between the EV (-) and EV (+) groups.** Figure 2 (upper panel) shows the VTQ and HVP values in the EVs (+) and EV (-) groups in the whole group of patients and in each of the three etiology groups. VTQ was significantly higher in the EV (+) group than in the EV (-) group in the whole group ( $P < 0.001$ ) and in each etiology group (group V,  $P < 0.05$ ; group A,  $P < 0.001$ ; and group N,  $P < 0.05$ ). Similarly, the HVP was significantly higher in the EV (+) group than in the EV (-) group in the whole group ( $P < 0.001$ ) and in each etiology group ( $P < 0.001$  in groups V, A, and N).

**Diagnostic performance of VTQ and HVP in predicting the presence of EVs.** Figure 3 (upper panel) shows the ROC curves for the performance of VTQ and HVP in predicting the presence of EVs in the whole group and each of the three etiology groups. In the whole group, the diagnostic capability of HVP for predicting the presence of EVs was satisfactory (AUROC = 0.92;  $P < 0.001$ ; 95% confidence interval [CI], 0.88–0.96) and that of VTQ was moderate (AUROC = 0.76;  $P < 0.001$ ; 95% CI, 0.68–0.84). In the whole group, HVP had significantly higher diagnostic capability than VTQ ( $P < 0.001$ ).

In group V, HVP had satisfactory diagnostic capability for predicting the presence of EVs (AUROC = 0.94;  $P < 0.001$ ; 95% CI, 0.86–1.02), and VTQ had moderate diagnostic capability (AUROC = 0.76;  $P = 0.0081$ ; 95% CI, 0.57–0.95); in this group, a comparison of the AUROC between HVP and VTQ showed no significant difference ( $P = 0.089$ ). In group A, HVP had satisfactory diagnostic capability for predicting the presence of EVs (AUROC = 0.93;  $P < 0.001$ ; 95% CI, 0.88–0.99) and VTQ had moderate diagnostic capability (AUROC = 0.79;  $P < 0.001$ ; 95% CI, 0.68–0.90); in this group, the diagnostic capability of HVP was significantly higher than that of VTQ ( $P = 0.002$ ). In group N, HVP had satisfactory diagnostic capability for predicting the presence of EVs (AUROC = 0.88;  $P < 0.001$ ; 95% CI, 0.79–0.96), but VTQ had unsatisfactory capability (AUROC = 0.67;  $P = 0.0287$ ; 95% CI, 0.52–0.83); in this group, the diagnostic capability of HVP was significantly higher than that of VTQ ( $P = 0.001$ ). Table 2 (upper panel) summarizes the diagnostic performance of VTQ and HVP for predicting the presence of EVs.

**Comparison of VTQ and HVP levels between high-risk EVs and low-risk EVs group.** Figure 2 (lower panel) shows the VTQ and HVP values for the low- and high-risk groups in the whole group of patients and in each of the three etiology groups. VTQ was significantly higher in the high-



**Figure 3** Diagnostic performance of virtual touch tissue quantification (VTQ) and hepatic venous pressure gradient (HVPG) for predicting esophageal varices (EVs) (upper panel) and high-risk EVs (middle panel). Diagnostic performance of VTQ and HVPG in predicting the presence of EVs and high-risk EVs in patients with compensated and decompensated liver cirrhosis (lower panel). FPF, false positive fraction; TPF, true positive fraction.

risk group than in the low-risk group in the whole group ( $P < 0.001$ ) and in each etiology group (group V,  $P = 0.002$ ; group A,  $P < 0.001$ ; and group N,  $P = 0.003$ ). Similarly, the HVPG value was significantly higher in the high-risk group than in the low-risk group in the whole group ( $P < 0.001$ ) and in each etiology group (group V,  $P < 0.001$ ; group A,  $P < 0.001$ ; and group N,  $P < 0.001$ ).

**Diagnostic performance of VTQ and HVPG in predicting the presence of high-risk EVs.** Figure 3 (middle panel) shows the ROC curves for VTQ and HVPG for predicting the presence of high-risk EVs in the whole group and each of the three etiology groups. In the whole group, HVPG had satisfactory diagnostic capability for predicting the presence of high-risk EVs (AUROC = 0.85;  $P < 0.001$ ; 95% CI, 0.80–0.90), and VTQ had moderate diagnostic capability (AUROC = 0.78;  $P < 0.001$ ; 95% CI, 0.72–0.84); HVPG had

significantly higher diagnostic capability than VTQ ( $P = 0.009$ ). In group V, HVPG had satisfactory diagnostic capability for predicting the presence of high-risk EVs (AUROC = 0.82;  $P < 0.001$ ; 95% CI, 0.68–0.95) and VTQ had moderate diagnostic capability (AUROC = 0.78;  $P < 0.001$ ; 95% CI, 0.63–0.93); in this group, no significant difference was found between the AUROC of HVPG and that of VTQ ( $P = 0.724$ ). In group A, HVPG had satisfactory diagnostic capability for predicting the presence of high-risk EVs (AUROC = 0.85;  $P < 0.001$ ; 95% CI, 0.77–0.93) and VTQ had moderate diagnostic capability (AUROC = 0.73;  $P < 0.001$ ; 95% CI, 0.63–0.83); in this group, the diagnostic capability of HVPG was significantly higher than that of VTQ ( $P = 0.006$ ). In group N, HVPG had satisfactory diagnostic capability for predicting the presence of high-risk EVs (AUROC = 0.82;  $P < 0.001$ ; 95% CI, 0.70–0.94) and VTQ had moderate diagnostic capability (AUROC = 0.73;  $P = 0.0012$ ; 95% CI, 0.59–0.87); in this group, the comparison of the

**Table 2** Diagnostic performance of virtual touch tissue quantification (VTQ) and hepatic venous pressure gradient (HVPG) for predicting esophageal varices (EVs) (upper panel) and high-risk EVs (lower panel)

Group	AUROC	95% CI	<i>P</i> value	Cutoff	FPF	TPF	OR
Diagnostic performance of VTQ for predicting EVs							
All patients	0.76	0.68–0.84	<0.001	1.99	0.49	0.88	7.90
Group V	0.76	0.57–0.95	0.0081	2.26	0.25	0.71	7.33
Group A	0.79	0.68–0.90	<0.001	2.60	0.28	0.70	6.09
Group N	0.67	0.52–0.83	0.0287	1.76	0.42	0.78	4.89
Diagnostic performance of HVPG for predicting EVs							
All patients	0.92	0.88–0.96	<0.001	11	0.16	0.87	36.4
Group V	0.94	0.86–1.02	<0.001	11	0.13	0.90	65.3
Group A	0.93	0.88–0.99	<0.001	11	0.28	0.95	47.8
Group N	0.88	0.79–0.96	<0.001	9	0.21	0.83	18.2
Diagnostic performance of VTQ for predicting high-risk EVs							
All patients	0.78	0.72–0.84	<0.001	2.28	0.40	0.89	11.6
Group V	0.78	0.63–0.93	<0.001	2.52	0.28	0.86	16.5
Group A	0.73	0.63–0.83	<0.001	2.52	0.45	0.81	5.19
Group N	0.73	0.59–0.87	0.0012	2.15	0.36	0.86	11.3
Diagnostic performance of HVPG for predicting high-risk EVs							
All patients	0.85	0.80–0.90	<0.001	14	0.19	0.80	16.6
Group V	0.82	0.68–0.95	<0.001	14	0.28	0.77	8.84
Group A	0.85	0.77–0.93	<0.001	14	0.24	0.83	16.1
Group N	0.82	0.70–0.94	<0.001	12	0.15	0.77	18.7

AUROC, area under the receiver operating characteristic curve; FPF, false positive fraction; OR, odds ratio; TPF, true positive fraction.

AUROC between HVPG and VTQ found no significant difference ( $P = 0.115$ ). Table 2 (lower panel) summarizes the diagnostic performance of VTQ and HVPG for predicting the presence of high-risk EVs.

#### **Diagnostic performance of VTQ and HVPG in predicting the presence of EVs and high-risk EVs according to the stage of liver cirrhosis.**

Figure 3 (lower panel, left side) shows the ROC curves for the diagnostic performance of VTQ and HVPG in predicting the presence of EVs in patients with compensated and decompensated liver cirrhosis. In both groups, the diagnostic capability of HVPG for predicting the presence of EVs was satisfactory (compensated group, AUROC = 0.90,  $P < 0.001$ , 95% CI, 0.83–0.96; decompensated group, AUROC = 0.93,  $P < 0.001$ , 95% CI, 0.88–0.99). The diagnostic capability of VTQ for predicting the presence of EVs was moderate in the compensated group (AUROC = 0.73;  $P < 0.001$ ; 95% CI, 0.62–0.84), but it was not as good in the decompensated group (AUROC = 0.69;  $P < 0.0035$ ; 95% CI, 0.56–0.83). Table 3 (upper panel) summarizes the diagnostic performance of VTQ and HVPG in predicting the presence of EVs classified according to the stage of liver cirrhosis.

Figure 3 (lower panel, right side) shows the ROC curves for the diagnostic performance of VTQ and HVPG in predicting the presence of high-risk EVs in patients with compensated and decompensated liver cirrhosis. In the compensated group, the diagnostic capabilities of VTQ and HVPG were satisfactory (VTQ, AUROC = 0.83,  $P < 0.001$ , 95% CI, 0.75–0.91; HVPG, AUROC = 0.92,  $P < 0.001$ , 95% CI, 0.86–0.97). In the decompensated group, the diagnostic capability of HVPG was moderate, but that of VTQ was unsatisfactory (HVPG,

AUROC = 0.75,  $P < 0.001$ , 95% CI, 0.65–0.85; VTQ, AUROC = 0.67,  $P = 0.002$ , 95% CI, 0.56–0.78).

Table 3 (lower panel) summarizes the diagnostic performance of VTQ and HVPG in predicting the presence of high-risk EVs classified according to the stage of liver cirrhosis.

#### **VTQ cutoff values for predicting the presence of EVs and high-risk EVs.**

Table 4 (upper panel) shows the diagnostic values when a VTQ cutoff of 1.99 m/s was applied for predicting EVs in each of the three groups and in the different stages of cirrhosis; the cutoff value was calculated by the AUROC for predicting EVs in the whole group. Significant, good diagnostic values were found in group V ( $P = 0.004$ , with 37.5% sensitivity [Se], 96.9% specificity [Sp], 75% positive predictive value [PPV], 86.1% negative predictive value [NPV], and 85% accuracy), group A ( $P < 0.001$ , with 44.4% Se, 94.9% Sp, 61.5% PPV, 90.2% NPV, and 87.1% accuracy), and the compensated group ( $P < 0.001$ , with 68.8% Se, 74.7% Sp, 55% PPV, 84.1% NPV, and 72.8% accuracy). In group N, the cutoff had moderate diagnostic value ( $P = 0.018$ , with 63.2% Se, 69% Sp, 48% PPV, 80.6% NPV, and 72.8% accuracy) but worse diagnostic value in the decompensated group ( $P = 0.083$ , with 7.7% Se, 99% Sp, 50% PPV, 89.3% NPV, and 88.6% accuracy).

Table 4 (lower panel) shows the diagnostic values for the prediction of high-risk EVs when a VTQ cutoff of 2.28 m/s was applied to each of the three groups and to the different stages of cirrhosis; the cutoff was calculated on the basis of the AUROC for predicting high-risk EVs in the whole group. The diagnostic values were satisfactory in group V ( $P < 0.001$ , with 72.2% Se, 86.4% Sp, 81.3% PPV, 79.2% NPV, and 80% accuracy), in group A ( $P < 0.001$ , with 44.7% Se, 94.9% Sp, 80.9% PPV, 77.9% NPV, and 78.5% accuracy), in the compensated group

**Table 3** Diagnostic performance of virtual touch tissue quantification (VTQ) and hepatic venous pressure gradient (HVPG) for predicting esophageal varices (EVs) (upper panel) and high-risk EVs (lower panel) according to the stage of liver cirrhosis (LC)

Group	AUROC	95% CI	P value	cutoff	FPF	TPF	OR	Group	AUROC	95% CI	P value	cutoff	FPF	TPF	OR
Diagnostic performance of VTQ for predicting EVs according to the stage of LC															
Compensated	0.73	0.62–0.84	<0.001	1.99	0.29	0.74	7.1	Compensated	0.90	0.83–0.96	<0.001	10	0.19	0.87	28.2
Decompensated	0.69	0.56–0.83	0.0035	2.60	0.38	0.73	4.4		0.93	0.88–0.99	<0.001	13	0.15	0.81	23.7
Diagnostic performance of VTQ for predicting high-risk EVs according to the stage of LC															
Compensated	0.83	0.75–0.91	<0.001	2.04	0.32	0.89	17.7	Compensated	0.92	0.86–0.97	<0.001	13	0.09	0.80	42.8
Decompensated	0.67	0.56–0.78	0.0021	2.55	0.53	0.80	3.66		0.75	0.65–0.85	<0.001	16	0.29	0.71	6.02

AUROC, area under the receiver operating characteristic curve; CI, confidence interval; FPF, false positive fraction; OR, odds ratio; TPF, true positive fraction.

( $P < 0.001$ , with 77.2% Se, 78.3% Sp, 81.5% PPV, 73.5% NPV, and 77.7% accuracy), and in the decompensated group ( $P < 0.001$ , with 34.2% Se, 94.7% Sp, 76.5% PPV, 74.2% NPV, and 74.6% accuracy). In group N, the diagnostic value was worse than in the other groups ( $P = 0.0047$ , with 69.2% Se, 68.2% Sp, 79.4% PPV, 55.6% NPV, and 68.9% accuracy).

## Discussion

Portal hypertension is a major complication of liver cirrhosis because it predisposes to the development of serious clinical manifestations, such as ascites, hepatic encephalopathy, and variceal bleeding. Until now, measurement of the HVPG has been the gold standard for confirming the presence and significance of portal hypertension, and many studies have shown its correlation with the presence of varices and the possibility of variceal bleeding. However, the measurement of HVPG is an invasive procedure and consequently difficult to perform in daily clinical practice. As alternatives to HVPG, several noninvasive methods—including elastography techniques—that can adequately evaluate liver fibrosis are currently used to assess the presence and severity of portal hypertension.

VTQ is one such noninvasive method. It can be used in routine diagnostic or surveillance scans to accurately measure liver stiffness in the presence of ascites because the push pulse is not attenuated and the optimal ROI can be detected with real-time imaging. VTQ has advantages over TE in that the TE impulse is attenuated by fat, requiring a modification in the form of the XL probe, whereas VTQ appears to be less affected by obesity.<sup>17,18</sup> Studies have also found no evidence that adjustments need to be made for age, sex, the depth of the subcutaneous fat layer, or the chosen ROI.<sup>19</sup> Various factors may have a significant effect on the measurement of liver stiffness, such as biliary obstruction or cholestasis, venous outflow blockage, congestive heart failure, meals, and exercise.<sup>20</sup> The most important confounding factors affecting the predictive accuracy of VTQ are as follows: (i) fatty change (either due to the primary disease or a comorbidity); (ii) inflammation; and (iii) a scan with high variability, expressed as an interquartile range to median ratio  $>0.3$ .<sup>21</sup> In the present study, HVPG had a strong positive correlation with VTQ in assessing portal hypertension in the whole group of patients with liver cirrhosis. The correlation was also seen in the three etiology-based groups, although in group N (the group included 36 patients [59%] with liver cirrhosis due to non-alcoholic steatohepatitis) the correlation was slightly weaker and scattered. As mentioned above, VTQ has some important confounding factors such as that inflammation, cholestasis, and fatty change of liver make its accuracy worse. Our findings show that AST and ALT were significantly lower in group N than in group V (the group with HCV-related liver cirrhosis) and group A (the group with alcohol-related liver cirrhosis) and that serum bilirubin was similar in all three groups indicates that the factors that decreased the accuracy of VTQ were not related to inflammation or cholestasis. Although body mass index did not differ between the groups, people with non-alcoholic steatohepatitis are known to have rich fat deposits in the liver. Therefore, measurement of liver stiffness might be less accurate in this group of patients, which would explain our results. Taken together, our findings indicate that VTQ may not be as useful for predicting the degree

**Table 4** The diagnostic values for the prediction of esophageal varices (EVs) when a virtual touch tissue quantification (VTO) cutoff of 1.99 (m/s) (upper panel) and for the prediction of high-risk EVs when a VTO cutoff of 2.28 (m/s) (lower panel)

The diagnostic values for the prediction of EVs when VTO cutoff of 1.99 (m/s)												
Etiologies and stage of cirrhosis.	VTO cutoff 1.99 (m/s)		EV (+) (n)	EV (-) (n)	Total (n)	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)	Accuracy (%) (95% CI)	OR (95% CI)	P value
	Group V	Over		31	5	36	37.5 (0.09–0.76)	96.9 (0.83–0.99)	75.0 (0.19–0.99)	86.1 (0.71–0.95)	85.0 (0.70–0.94)	18.6 (1.60–216)
Under			1	3	4							
Group A	Over		93	10	103	44.4 (0.21–0.69)	94.9 (0.88–0.98)	61.5 (0.32–0.86)	90.2 (0.83–0.95)	87.1 (0.79–0.93)	14.9 (4.08–54.3)	<0.001
	Under		5	8	13							
Group N	Over		29	7	36	63.2 (0.38–0.84)	69.0 (0.53–0.82)	48.0 (0.28–0.69)	80.6 (0.64–0.92)	67.2 (0.54–0.79)	3.82 (1.22–11.9)	0.018
	Under		13	12	29							
Compensated group	Over		53	10	63	68.8 (0.49–0.84)	74.7 (0.63–0.84)	55.0 (0.38–0.70)	84.1 (0.73–0.92)	72.8 (0.63–0.81)	6.48 (2.58–16.2)	<0.001
	Under		18	22	40							
Decompensated group	Over		100	12	112	7.7 (0.01–0.36)	99.0 (0.63–0.84)	50.0 (0.01–0.98)	89.3 (0.82–0.94)	88.6 (0.81–0.94)	8.33 (0.49–142)	0.083
	Under		1	1	2							

The diagnostic values for the prediction of high-risk EVs when VTO cutoff of 2.28 (m/s)												
Etiologies and stage of cirrhosis.	VTO cutoff 2.28 (m/s)		High-risk EV+ (n)	Low-risk EV+ (n)	Total (n)	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)	Accuracy (%) (95% CI)	OR (95% CI)	P value
	Group V	Over		19	5	24	72.2 (0.47–0.90)	86.4 (0.83–0.99)	81.3 (0.54–0.96)	79.2 (0.58–0.93)	80.0 (0.63–0.91)	16.5 (3.34–81.2)
Under			3	13	16							
Group A	Over		74	21	95	44.7 (0.29–0.62)	94.9 (0.87–0.98)	80.9 (0.58–0.95)	77.9 (0.68–0.86)	78.5 (0.69–0.86)	14.9 (4.55–49.3)	<0.001
	Under		4	17	21							
Group N	Over		15	12	27	69.2 (0.52–0.83)	68.2 (0.45–0.86)	79.4 (0.62–0.91)	55.6 (0.35–0.76)	68.9 (0.56–0.80)	4.82 (1.56–14.9)	0.0047
	Under		7	27	34							
Compensated group	Over		36	13	49	77.2 (0.64–0.87)	78.3 (0.64–0.89)	81.5 (0.69–0.91)	73.5 (0.56–0.86)	77.7 (0.68–0.85)	12.2 (4.79–31.0)	<0.001
	Under		10	44	54							
Decompensated group	Over		72	25	97	34.2 (0.19–0.51)	94.7 (0.87–0.99)	76.5 (0.50–0.93)	74.2 (0.64–0.83)	74.6 (0.66–0.82)	9.36 (2.79–31.4)	<0.001
	Under		4	13	17							

CI, confidence interval; NPV, negative predictive value; OR, odds ratio; PPV, positive predictive value.



of portal pressure in patients with liver cirrhosis due to non-alcoholic steatohepatitis as it is in patients with liver cirrhosis of other etiologies.

The HVPG is well known to correlate closely with the severity and prognosis of the symptoms of liver cirrhosis, including esophageal variceal bleeding.<sup>22</sup> Silkauskaitė *et al.* reported a positive relationship between HVPG and the size of EVs,<sup>23</sup> and Kim *et al.* also showed that the risk of variceal bleeding significantly increased as the HVPG increased.<sup>24</sup> In our study, HVPG had high diagnostic performance in predicting the presence of EVs and high-risk EVs, regardless of their etiology.

The HVPG reflects portal vein pressure directly, so—as expected—in the present study, it was found to have high diagnostic capability. In contrast, VTQ had moderate diagnostic performance in detecting the presence of EVs and high-risk EVs in the whole group of patients and the three etiology groups. Sherman *et al.*<sup>25</sup> reported that measurements of liver stiffness correlate well with the increases in portal pressure seen in early liver cirrhosis because the resistance to portal blood flow was proportional to the reduced compliance (i.e. effectively inversely proportional to the stiffness) of liver tissue resulting from the fibrosis and other processes occurring in chronic liver disease. However, initial studies of elastography with TE found that it did not correlate as well as expected with the occurrence of varices on endoscopy and HVPG measurements. The authors explained this finding as being related to the circulatory changes that evolve in later stages of portal hypertension, with increased portal inflow and vasodilation of the splanchnic circulation becoming more important in determining the rise in the HVPG and the development of EVs, over and above increased hepatic sinusoidal resistance.<sup>25</sup> As mentioned above, VTQ was influenced by many factors, including the circulatory changes resulting from the progression of liver cirrhosis, fatty change or inflammation of the liver, cholestasis, venous outflow blockage, congestive heart failure, meals, and exercise. Our study excluded patients with biliary obstruction disease, venous outflow blockage, or congestive heart failure disease, and patients fasted before we performed VTQ. Just over half of the patients in our study had decompensated liver cirrhosis, which might explain why VTQ did not correlate that well with the presence of EVs and high-risk EVs. In our study, HVPG had good diagnostic performance in predicting the presence of EVs in both the compensated and decompensated groups, but the diagnostic capability of VTQ was only moderate in the compensated group and even worse in the decompensated group. Furthermore, HVPG had good diagnostic performance in predicting the presence of high-risk EVs in the compensated group and moderate performance in the decompensated group, and VTQ had good diagnostic performance in the compensated group but worse performance in the decompensated group. Our results indicate that VTQ may not be as suitable as HVPG for classifying EVs and high-risk EVs in patients with decompensated liver cirrhosis, although it may have adequate diagnostic performance in patients with compensated liver cirrhosis. Certainly, HVPG had high diagnostic capability and was significantly better than VTQ in predicting the presence of EVs and high-risk EVs. However, HVPG is a highly invasive procedure and therefore difficult to use as a routine medical screening test. Our results indicate that the optimal VTQ cutoff values of 1.99 m/s for predicting EVs and 2.28 m/s for predicting high-risk

EVs produce adequate results. Although VTQ did not predict the presence of EVs and high-risk EVs as reliably as HVPG did, on the basis of the above we suggest that it is reliable enough to be used as a noninvasive method for diagnosing EVs in routine care.

Recently, a combination of modalities, that is, measurements of liver and spleen stiffness and platelet counts, has been suggested as a way to improve the prediction of the presence of EVs, which have prognostic significance in compensated liver cirrhosis. Bota *et al.*<sup>26</sup> reported that measurements of liver and spleen stiffness assessed by ARFI were good enough for predicting significant EVs. At the Baveno IV conference in 2015, it was recommended that a platelet count >150 and a liver stiffness, measured by TE, below 20 Kpa could be used as thresholds for avoiding surveillance endoscopy because they indicate a low likelihood of varices requiring treatment. A decision was reached by a consensus of experts on the basis of the high NPV for clinically significant portal hypertension demonstrated in clinical trials.<sup>2</sup> Sherman *et al.*<sup>25</sup> stated that an equivalent threshold for liver stiffness measurement by VTQ is likely to be developed in the near future, although further validation of this approach is required in longer-term studies. Therefore, although measuring liver stiffness by VTQ to assess EVs has many more confounding factors than measuring HVPG, in the future the accuracy of VTQ for predicting EVs may potentially be increased by combining it with other modalities.

In conclusion, VTQ was reliable at predicting the presence of EVs and high-risk EVs in patients with liver cirrhosis, except for in patients with non-alcoholic steatohepatitis or decompensated liver cirrhosis. Therefore, we propose that VTQ is a useful, noninvasive tool for predicting the presence of EVs in daily medical care.

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