

Clinical application of liver stiffness measurement in patients with cavernous transformation of portal vein

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Abstract. The clinical outcomes differ between patients with cavernous transformation of the portal vein (CTPV) with and without cirrhosis. Therefore, invasive liver biopsy may be needed for the differential diagnosis of patients with CTPV with or without cirrhosis. The present study aimed to investigate the diagnostic efficacy of liver stiffness measurements (LSM) for the prediction of cirrhosis in patients with CTPV. A total of 20 patients with CTPV, 34 with chronic hepatitis B (CHB)-related cirrhosis and 20 healthy volunteers, were retrospectively recruited in the study. CTPV was diagnosed with contrast-enhanced computed tomography (CT) and ultrasound for the abdomen. LSM values were detected for each patient, while liver biopsy was performed in each patient in the CTPV and cirrhosis groups. The results demonstrated that LSM values were significantly lower in the CTPV group (12.5 kPa; range, 6.8-21.5 kPa) compared with the CHB-related cirrhosis group (21.0 kPa; range, 15.5-27.2 kPa; $P=0.017$). However, this was still higher compared with healthy volunteers (4.9 kPa; range 4.0-5.8 kPa; $P<0.001$). In addition, CTPV patients with cirrhosis (17.7 kPa; range, 13.9-30.8 kPa) exhibited significantly increased LSM values compared with those without cirrhosis (6.4 kPa; range, 5.7-7.8 kPa; $P<0.001$). Furthermore, LSM values in CTPV patients without cirrhosis were slightly higher compared with those of healthy volunteers ($P=0.003$),

while no statistically significant difference was observed in LSM between CTPV patients with cirrhosis and CHB-related cirrhosis group. These findings indicated that LSM values could be used for the differential diagnosis of CTPV patients with or without cirrhosis. However, further validation studies are needed.

Introduction

Cavernous transformation of the portal vein (CTPV), also known as portal cavernoma, is a relatively rare condition resulting from chronic portal vein thrombosis and/or occlusion, which leads to the formation of numerous periportal or intrahepatic venous collaterals (1). Since it was first reported in 1869, CTPV remains a disease with insidious clinical presentation and is a common cause of portal hypertension (2).

Since various factors causing chronic portal vein thrombosis and/or occlusion can lead to CTPV, its etiology is not clear. CTPV is an uncommon finding in adults whose cause usually cannot be identified (3). In some patients, CTPV may be associated with congenital anomalies or neonatal umbilical vein sepsis (4). Additionally, secondary portal vein thrombosis with CTPV may often be accompanied by cirrhosis (5). The clinical outcomes differ between the CTPV patients with or without liver cirrhosis (6). However, CTPV patients without cirrhosis often present with characteristic imaging features, such as hypertrophy of the caudate lobe, mimic chronic liver disease and cirrhosis (7). Therefore, differential diagnosis of different types of CTPV may be difficult, and a significant number of cases may need to undergo invasive liver biopsy (8).

Transient elastography (TE) is a simple non-invasive method used to assess liver stiffness (LS) (9). Although the diagnostic value of LS measurements (LSM) has been well evaluated in liver fibrosis and cirrhosis in chronic liver diseases, such as chronic hepatitis B, hepatitis C and non-alcoholic steatohepatitis (9), its role in patients with CTPV remains to be identified. Since LSM has a high diagnostic value in the prediction of cirrhosis, the present study hypothesized that LSM may be a valuable non-invasive tool for the differential diagnosis of CTPV patients with or without cirrhosis. Therefore, the present study aimed to evaluate the diagnostic power of LSM in predicting cirrhosis in patients with CTPV.

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Patients and methods

Patients. Consecutive patients diagnosed with CTPV and simultaneously underwent liver biopsy were retrospectively recruited in Zhongshan Hospital, Fudan University between January 2013 and December 2017. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Institutional Review Board of the Zhongshan Hospital, Fudan University. Written informed consent was obtained from all patients. All recruited patients underwent contrast-enhanced 64-slice spiral computed tomography (CT) and TE. CT scans were independently reviewed by two radiologists. Patients who met any of the following criteria were excluded from the study: History of a variceal bleed in the previous 6 weeks; jaundice; malignant tumor or any previous shunt surgery. Patients with poor CT image quality or missing data were also excluded.

Two control groups were included in the study: Patients with chronic hepatitis B (CHB)-related cirrhosis and healthy volunteers. Retrospective liver TE data from age-matched cirrhosis patients with histologically proven CHB ($n=34$) were recorded between January 2013 and December 2017. All patients provided written consent to undergo TE examination and permit the inclusion of their data in future studies without disclosing their identity. Similarly, age-matched healthy volunteers ($n=20$) were also included in the study, after obtaining informed consent.

Laboratory examination, imaging and upper gastrointestinal endoscopy. Blood tests included serum bilirubin, alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), γ -glutamyl transpeptidase (GGT), serum albumin, platelet count, international normalized ratio (INR) and relevant tests for evaluation of the etiology of the liver disease (markers for hepatitis B and hepatitis C viruses). CTPV was diagnosed based on contrast-enhanced CT and ultrasound for the abdomen (1). In the CTPV and cirrhosis groups, the endoscopic findings were recorded and subsequently graded according to the criteria proposed at the Baveno V Consensus Conference (10). Endoscopic examinations were independently performed by two experienced endoscopists with good agreement in grading esophageal varices ($\kappa=0.96$).

LSM by transient elastography. LSM was assessed for each patient using the FibroScan® apparatus (Echosens) with an M-probe following an overnight fast. Measurements were performed according to the Liver Stiffness Study Group 'Elastica' of the Italian Association for the Study of the Liver (11). At least 10 successful measurements for each patient were evaluated. Only LSs with a success rate of $>60\%$ and interquartile range of $<30\%$ were considered reliable (12,13). The physicians who undertook all the examinations had prior experience with at least 1,000 TE procedures.

Liver histology and quantification of fibrosis. Ultrasonography-guided percutaneous liver biopsies were performed for all patients in the CTPV and cirrhosis groups. Liver biopsy samples >15 mm in length and with ≥ 10 portal tracts were considered eligible. The fibrosis staging (F) and inflammatory activity (A) were determined by one pathologist, blinded to patients' clinical characteristics, according to the METAVIR system (14).

Measurement of hepatic vein pressure gradient (HVPG). Following an overnight fast, HVPG was measured using a standard procedure (15-17). HVPG is defined as the difference between the wedged hepatic venous pressure and free hepatic venous pressure. Radiologists were blinded to clinical data.

Statistical analysis. All statistical analyses were performed using SPSS software version 20.0 (IBM Corp.). Continuous variables are summarized as the mean \pm SD or median and interquartile range and categorical variables as frequency and percentage. Unpaired Student's t-test and Mann-Whitney U test were applied for comparison between two groups. Differences between the groups were analyzed by one-way ANOVA and Kruskal-Wallis test, followed by Bonferroni's post hoc test for multiple comparisons. χ^2 and Fisher's exact tests were applied to compare categorical variables. The area under the receiver operating characteristic curve (AUROC) was used to evaluate the diagnostic values of each significant parameter. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Patient characteristics. In the present study, 20 patients (9 males, 11 females) with CTPV were retrospectively enrolled between January 2013 and December 2017. The mean age was 49.0 ± 3.6 years. Among 20 patients, CTPV etiology was associated with hepatitis B ($n=10$), alcohol consumption ($n=1$) and autoimmune hepatitis ($n=1$), while 8 patients were cryptogenic. All patients exhibited varying degrees of esophageal varices confirmed via upper gastrointestinal endoscopy, while 12 subjects (60%) had a history of hemorrhage (Table I).

In addition, 34 CHB-related cirrhosis patients (F4; liver biopsy proven) and 20 healthy volunteers were enrolled in the same period. All healthy subjects were asymptomatic and were screened to rule out underlying liver diseases determined by normal abdominal ultrasonography, normal liver function tests and negative serology results for hepatitis B and C. The baseline characteristics of 20 patients with CTPV and control groups are shown in Table I. There were no statistically significant differences in age among the three groups.

Comparison of LS, HVPG and serum parameters in CTPV and control groups. Compared with patients with CHB-related cirrhosis, AST and ALP levels were significantly higher in patients with CTPV. Hemoglobin, platelet, white blood count and albumin levels were significantly lower, while AST, ALP, GGT and INR levels were significantly higher in patients with CTPV compared with healthy volunteers (Table I).

LS values in the CTPV group (12.5 kPa; range, 6.8-21.5 kPa) were significantly lower compared with the CHB-related cirrhosis group (21.0 kPa; range, 15.5-27.2 kPa; $P=0.018$), however, they were significantly higher compared with healthy volunteers (4.9 kPa; range, 4.0-5.8 kPa; $P<0.001$; Table I and Fig. 1A).

There was no statistically significant difference in HVPG values between the CTPV (12.0 mmHg; range, 6.5-18.8 mmHg) and CHB-related cirrhosis groups (15.0 mmHg; range, 10.8-18.0 mmHg; $P=0.319$; Table I and Fig. 2A). However, HVPG values in CTPV patients with cirrhosis (17.0 mmHg;

Table I. Clinical characteristics of the patients.

Characteristic	Patients with CTPV (n=20)	Patients with cirrhosis (n=34)	P-value ^a	Healthy controls (n=20)	P-value ^b
Age (years)	49.0±13.6	51.7±9.9	0.453	47.5±13.5	0.728
Sex (M:F)	11:9	26:8	0.006	12:8	0.343
Hemoglobin (g/l)	99.0 (80.8, 120.3)	102.0 (80.8, 122.0)	0.680	153.5 (141.8, 164)	<0.001
Platelet (10 ⁹ /l)	90.0 (77.3, 104.3)	82.5 (70.8, 98.5)	0.258	188.0 (150.1, 212.5)	<0.001
White blood count (10 ⁹ /l)	2.9 (2.1, 3.7)	2.3 (1.8, 3.5)	0.441	5.5 (4.5, 6.7)	<0.001
Total bilirubin (μmol/l)	14.3 (10.3, 17.8)	18.5 (10.4, 26.7)	0.081	14.4 (10.3, 19.4)	0.779
Albumin (g/l)	38.0 (35.0, 41.8)	36.0 (32.8, 38.3)	0.053	48.3 (46.3, 50.0)	<0.001
ALT (IU/l)	21.0 (14.0, 30.3)	19.5 (14.8, 31.0)	0.865	21.3 (14.5, 31.5)	0.860
AST (IU/l)	39.0 (29.0, 46.0)	26.0 (19.8, 45.0)	0.011	22.5 (18.0, 27.0)	<0.001
ALP (IU/l)	72.0 (52.5, 92.3)	85.0 (72.5, 119.8)	0.030	45.5 (42.3, 55.8)	<0.001
GGT (IU/l)	51.0 (29.3, 78.5)	32.5 (17.8, 70.0)	0.452	24.0 (20.3, 32.8)	0.002
INR	1.12 (1.00, 1.26)	1.14 (1.04, 1.22)	0.865	1.03 (0.98, 1.07)	0.021
Hemorrhage history, n (%)	12 (60%)	12 (35%)	0.095	-	-
Esophageal varices grade	3 (2, 3.75)	3 (2, 4)	0.422	-	-
Gastric varices, n (%)	15 (75%)	23 (68%)	0.759	-	-
HVPG (mmHg)	12.0 (6.5, 18.8)	15.0 (10.8, 18.0)	0.319	-	-
METAVIR fibrosis score (n)			<0.001		-
F0-1	7	0		-	-
F2-3	1	0		-	-
F4	12	34		-	-
LS (kPa)	12.5 (6.8, 21.5)	21.0 (15.5, 27.2)	0.017	4.9 (4.0, 5.8)	<0.001

Results are expressed as the raw values (and percentage) for qualitative variables and as the median (and inter-quartile range) for quantitative variables. ^aPatients with CTPV vs. patients with cirrhosis; ^bPatients with CTPV vs. healthy control subjects. CTPV, cavernous transformation of the portal vein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, γ-glutamyltransferase; INR, international normalized ratio; HVPG, hepatic vein pressure gradient; LS, liver stiffness.

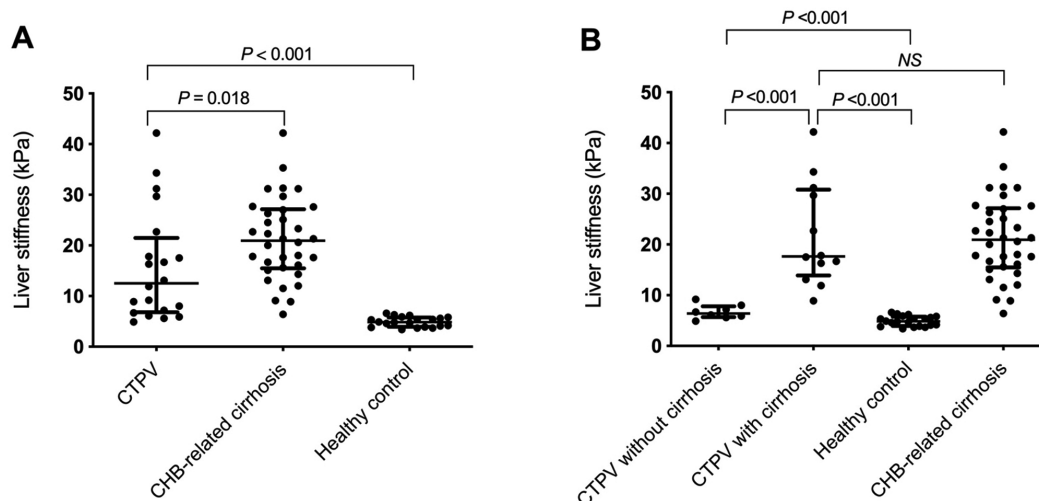


Figure 1. LS in CTPV and control groups. (A) Individual LS values in patients with CTPV, CHB patients with cirrhosis and healthy control subjects. (B) Individual LS values in CTPV patients with or without cirrhosis, CHB patients with cirrhosis and healthy control subjects. LS, liver stiffness; CTPV, cavernous transformation of the portal vein; CHB, chronic hepatitis B.

range, 13.1-22.0 mmHg) were significantly increased compared with CTPV patients without cirrhosis (6.0 mmHg; range, 5.0-8.8 mmHg; $P<0.001$; Table II and Fig. 2B).

Association between LSM and cirrhosis in patients with CTPV. In the CTPV group, liver biopsy showed preserved acinar architecture and normal hepatocytes in 7 (35%) patients. A total of

Table II. Characteristics of CTPV patients with or without cirrhosis.

Characteristic	Patients with CTPV		P-value
	Cirrhosis (n=12)	Non-cirrhosis (n=8)	
Age (years)	57.4±7.9	36.4±9.9	<0.001
Sex (M:F)	7:5	4:4	0.714
Hemoglobin (g/l)	98.0 (80.8, 120.3)	99.0 (76.5, 120.3)	0.938
Platelet (10 ⁹ /l)	90.0 (79.5, 98.0)	95.0 (76.0, 105.0)	0.908
White blood count (10 ⁹ /l)	2.7 (2.1, 4.2)	3.0 (1.5, 3.3)	0.877
Total bilirubin (μmol/l)	13.5 (10.3, 17.4)	14.9 (10.8, 20.0)	0.521
Albumin (g/l)	35.0 (35.0, 40.5)	39.5 (38.0, 42.8)	0.035
ALT (IU/l)	24.0 (14.0, 35.5)	17.0 (14.0, 28.8)	0.485
AST (IU/l)	44.0 (29.0, 49.0)	36.5 (30.3, 42.0)	0.561
ALP (IU/l)	77.0 (58.0, 97.3)	67.5 (43.5, 80.8)	0.164
GGT (IU/l)	57.5 (34.5, 90.3)	36.0 (21.0, 54.0)	0.217
INR	1.17 (1.00, 1.26)	1.06 (0.99, 1.25)	0.727
HBsAg positive, n (%)	9 (75%)	1 (13%)	0.020
Hemorrhage history, n (%)	7 (58%)	5 (63%)	0.852
Esophageal varices grade	3 (2, 4)	3 (2, 4)	0.748
Gastric varices, n (%)	8 (67%)	7 (88%)	0.603
HVPG (mmHg)	17.0 (13.1, 22.0)	6.0 (5.0, 8.8)	<0.001
LS (kPa)	17.7 (13.9, 30.8)	6.4 (5.7, 7.8)	<0.001

Results are expressed as the raw values (and percentage) for qualitative variables and as the median (and inter-quartile range) for quantitative variables. CTPV, cavernous transformation of the portal vein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, γ -glutamyltransferase; INR, international normalized ratio; HVPG, hepatic vein pressure gradient; LS, liver stiffness; HBsAg, hepatitis B surface antigen.

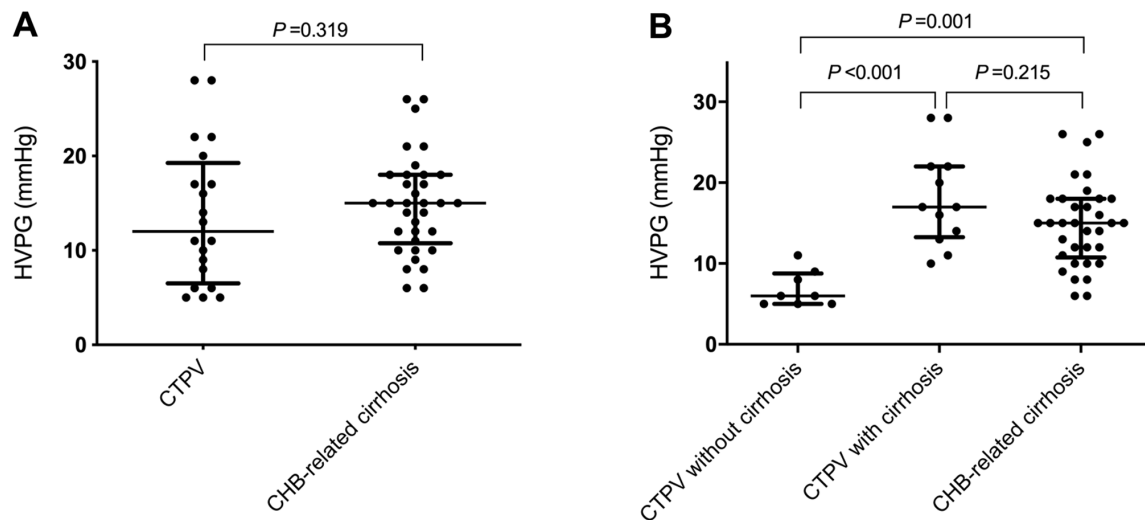


Figure 2. HVPG in CTPV and control groups. (A) Individual HVPG values in patients with CTPV and CHB patients with cirrhosis. (B) Individual HVPG values in CTPV patients with or without cirrhosis and CHB patients with cirrhosis. HVPG, hepatic vein pressure gradient; CTPV, cavernous transformation of portal vein; CHB, chronic hepatitis B.

7 patients exhibited no or mild signs of fibrosis (F0-1), while 1 patient showed significant fibrosis (F2-3) and the remaining 12 patients were diagnosed with cirrhosis (F4; Table I). Based on histological evaluation, patients with CTPV were divided into two different subgroups: Cirrhosis and non-cirrhosis

groups. The demographic and clinical characteristics of CTPV patients with or without cirrhosis are presented in Table II. Patients with CTPV in the cirrhosis group were significantly older (57.4±7.9 vs. 36.4±9.9 years; $P<0.001$) and were characterized by increased hepatitis B surface antigen

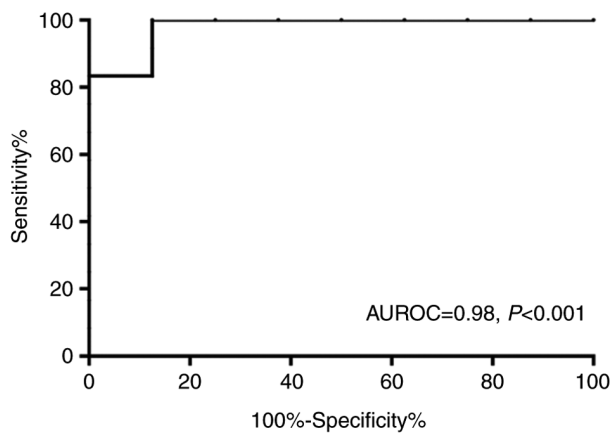


Figure 3. ROC curves for LS for the prediction of cirrhosis in patients with CTPV. AUROC, area under the receiver operating characteristic curve; LS, liver stiffness; CTPV, cavernous transformation of the portal vein.

positivity compared with the non-cirrhosis group. In addition, the clinical outcome of CTPV differs between patients with cirrhosis and patients without cirrhosis. However, the imaging manifestations of these two types of CTPV may be similar (Fig. S1). Therefore, differential diagnosis is difficult and liver biopsy is occasionally required.

LS values in CTPV patients with cirrhosis (17.7 kPa; range, 13.9-30.8 kPa) were significantly higher compared with the CTPV non-cirrhosis group (6.4 kPa; range, 5.7-7.8 kPa; $P<0.001$; Table II and Fig. 1B). Furthermore, the AUROC value evaluating the diagnostic value of LSM in cirrhosis ($F=4$) was 0.98 (Fig. 3). The LSM cut-off value was set at 9.0 kPa, and the sensitivity and specificity rates for the detection of cirrhosis were 92 and 88%, respectively (data not shown).

Additionally, there was no statistically significant difference in LS values between CTPV patients with cirrhosis (17.7 kPa; range, 13.9-30.8 kPa) and patients with CHB-related cirrhosis (21.0 kPa; range, 15.5-27.2 kPa; $P=1.000$; Fig. 1B). However, LS values in CTPV patients without cirrhosis (6.4 kPa; range, 5.7-7.8 kPa) were significantly higher compared with those of healthy volunteers (4.9 kPa; range, 4.0-5.8 kPa; $P<0.001$; Fig. 1B).

Discussion

The present study aimed to evaluate the diagnostic potential of the non-invasive method, LS, for predicting cirrhosis in patients with CTPV. The results demonstrated that LS values were higher in patients with CTPV compared with healthy controls. In addition, LS values were significantly increased in CTPV patients with cirrhosis compared with those without cirrhosis. These findings indicated that CTPV patients with cirrhosis may exhibit a poorer prognosis compared with those without cirrhosis. In addition to the complications that may be caused by portal hypertension, CTPV-cirrhotic patients may also suffer from cirrhosis-related complications. Therefore, LSM may be used for the differential diagnosis of CTPV patients with or without cirrhosis.

To the best of our knowledge, this is the first study to evaluate the clinical application of LSM via TE in patients with CTPV. In the present study, the AUROC value, evaluating

the diagnostic value of LS in cirrhosis, was 0.98, while the sensitivity and specificity rates for the detection of cirrhosis were 92 and 88%, respectively, with a cut-off value of 9.0 kPa. However, the cut-off value used in this study was significantly lower than that applied for the diagnosis of cirrhosis in other chronic liver diseases. Varying cut-offs have been proposed for the diagnosis of cirrhosis according to the etiology of liver disease, ranging from 9.7 kPa in hepatitis B to 22.7 kPa in alcoholic liver disease (18). According to the recent American Gastroenterological Association Institute Technical Review on the Role of Elastography in Chronic Liver Diseases (2017), the cut-offs proposed for the diagnosis of cirrhosis were 12.5, 11 and 12.5 kPa for hepatitis C, hepatitis B and alcoholic liver disease, respectively (19). However, most of these cut-off values have been defined in a single population using ROC curves to maximize sensitivity and specificity and have not been applied to a validation cohort (18). Therefore, the differences between cut-offs may be associated with differences in cirrhosis prevalence in the studied populations, known as spectrum bias (18).

A limited number of studies have evaluated LSM in patients with extrahepatic portal vein obstruction (EHPVO). EHPVO is another disorder of the portal venous system, which is characterized by occlusion of the portal vein, resulting in the formation of collateral vessels (20). EHPVO leads to pre-hepatic portal hypertension, while some patients may be accompanied by CTPV (21). Sharma *et al* (22) demonstrated a statistically significant difference ($P=0.001$) in LS values via TE between patients with EHPVO (6.7 kPa) and healthy volunteers (4.6 kPa). However, a recent study in EHPVO showed that LS values via 2D shear wave elastography were similar to normal liver (23). Unlike CTPV, EHPVO is rarely accompanied by cirrhosis, while histological examination revealed that the architectural pattern of the liver is preserved (21). Among 20 CTPV patients enrolled in the study, 8 non-cirrhotic patients were also diagnosed with EHPVO according to the expanding consensus in portal hypertension of the European Association for the Study of the Liver (24). LS values using TE in CTPV patients with EHPVO (6.4 kPa; range, 5.7-7.8 kPa) were significantly lower compared with patients without EHPVO (17.7 kPa; range, 13.9-30.8 kPa; $P<0.001$). However, further studies including more available data from patients are required to evaluate the clinical efficacy of LSM in CTPV.

Consistent with the results obtained by Sharma *et al* (22), the median LS value of CTPV patients without cirrhosis was 6.4 kPa (range, 5.7-7.8 kPa), which was significantly higher compared with age-matched healthy controls. The increased LS values may be associated with deprivation of portal blood to the liver, which in turn may influence the functions of the hepatic parenchyma (22,25). Additionally, hepatic hemodynamic changes may also explain this finding. A recent case report suggested that the false-positive results obtained using TE, namely portal vein thrombosis, may be caused by hepatic arterial buffer response. Although four biopsies were performed with no evidence of cirrhosis, the patient exhibited increased LS values, indicating cirrhosis. Therefore, the authors speculated that this observation could be caused by compensatory arterial buffer response to the portal vein obstruction in the hepatic vasculature and by arterial flow,

which in turn could lead to increased elastography grade of the liver (26).

However, there were some limitations of the present study. Firstly, due to the retrospective nature of the study and the small number of patients with CTPV, a further large-scale, prospective study is required to evaluate the aforementioned results. In addition, the thresholds for evaluating sensitivity and specificity were determined on the basis of the present study population, therefore, the diagnostic performance of LSM via TE could be overestimated due to spectrum bias.

In conclusion, the present study demonstrated that patients with CTPV exhibited higher LS values compared with healthy controls. Furthermore, CTPV patients with cirrhosis had higher LS values compared with those without cirrhosis. Therefore, LSM may be used for the differential diagnosis of CTPV patients with or without cirrhosis. However, further validation studies are required.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

SW and WJ conceived the study and organized the manuscript. YS and WM analyzed the data and wrote the manuscript. LL collected clinical data. YH analyzed and interpreted the patient data. YH, YS AND LL contributed to manuscript revision. All authors read and approved the final manuscript.

Ethics approval and consent participate

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Institutional Review Board of the Zhongshan Hospital, Fudan University (approval no. B2013-068). Written informed consent was obtained from all patients.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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