

Results of liver and spleen endoscopic ultrasonographic elastography predict portal hypertension secondary to chronic liver disease



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ABSTRACT

Background and study aims Assessment of endoscopic ultrasonography (EUS)-elastography of the liver and spleen may identify patients with portal hypertension secondary

to chronic liver disease. We aimed to evaluate use of EUS-elastography of the liver and spleen in identification of portal hypertension in patients with chronic liver disease.

Patients and methods This was a single-center, diagnostic cohort study. Consecutive patients with liver cirrhosis and portal hypertension underwent EUS-elastography of the liver and spleen. Patients without a history of liver disease were enrolled as controls. The primary outcome was diagnostic yield of liver and spleen stiffness measurement via EUS-elastography in prediction of portal hypertension secondary to chronic liver cirrhosis. Cutoff values were defined through Youden's index. Overall accuracy was calculated for parameters with an area under the receiver operating characteristic (AUROC) curve $\geq 80\%$.

Results Among the 61 patients included, 32 had cirrhosis of the liver. Liver and spleen stiffness was measured by the strain ratio and strain histogram, with sensitivity/(1 – specificity) AUROC values $\geq 80\%$. For identification of patients with cirrhosis and portal hypertension, the liver strain ratio (SR) had a sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of 84.3%, 82.8%, 84.4%, and 82.8%, respectively; the liver strain histogram (SH) had values of 87.5%, 69.0%, 75.7%, and 83.3%, respectively. EUS elastography of the spleen via the SR reached a sensitivity, specificity, PPV, and NPV of 87.5%, 69.0%, 75.7%, and 83.3%, respectively, whereas the values of SH were 56.3%, 89.7%, 85.7%, and 65.0%, respectively.

Conclusion Endoscopic ultrasonographic elastography of the liver and spleen is useful for diagnosis of portal hypertension in patients with cirrhosis.

Introduction

Chronic liver disease causes structural and functional changes in the liver and spleen, with subsequent development of portal hypertension. Liver biopsy is the gold standard for evaluation, grading, and monitoring of fibrosis, but the cost and risk of complications limit its applicability in clinical practice [1]. A high hepatic venous pressure gradient indicates portal hyper-

tension and predicts clinical decompensation in patients with cirrhosis of the liver, but the invasiveness of the test limits its applicability in clinical practice [2].

The diagnostic workup for liver cirrhosis and portal hypertension includes abdominal ultrasonography, esophagogastroduodenoscopy (EGD), and abdominal transient elastography, yet all of these approaches have roles and limitations. For example, transient elastography has limited applicability in pa-

tients with obesity or ascites [3–6]. In addition, although EGD is the current gold standard for evaluation of esophageal and gastric varices, as a surrogate finding of portal hypertension, nearly 14% of patients without esophageal varices by EGD have either gastric varices or gastric parietal abnormalities based on endoscopic ultrasonography (EUS) [7].

EUS, a minimally invasive imaging technique, offers endoscopic and elastographic evaluation of the liver and spleen, especially in patients with obesity, in a single diagnostic test. EUS is also able to detect paraesophageal and gastric varices, even if EGD indicates a negative result. In addition, EUS may allow detection of structural and functional changes in the splenic vasculature that are associated with portal hypertension in patients with cirrhosis, mainly with regard to azygos vein flow, which is directly associated with the hepatic venous pressure gradient [8]. Finally, EUS evaluation may allow for carrying out EUS-guided liver biopsy if needed, with comparable results to transjugular approaches [9].

Recently, spleen stiffness measurement has shown a significantly superior diagnostic odds ratio compared with liver stiffness measurement in prediction of esophageal varices in patients with chronic liver disease, with a significantly higher pooled sensitivity and area under the curve [4]. In addition, spleen stiffness exhibits high sensitivity for predicting esophageal varices in cirrhosis of different etiologies [10].

Nonetheless, EUS-elastography of the liver and spleen has not previously been evaluated for assessment of portal hypertension in patients with chronic liver disease. The aim of the present study was to evaluate use of EUS-elastography of the liver and spleen in diagnosis of portal hypertension secondary to liver cirrhosis.

Patients and methods

Study design

This was a prospective cohort study performed in a single tertiary academic center in Ecuador. The study protocol was approved by the local Institutional Review Board and registered at clinicaltrials.gov under the identifier NCT03155282. The study was conducted in accordance with the principles of the Declaration of Helsinki, and all participants signed a consent form before enrollment. All researchers had access to the study database and approved the final version of the manuscript.

Study population

Patients were recruited from the Gastroenterology and Endoscopy Division of the Ecuadorian Institute of Digestive Diseases from March 2017 to October 2017. The study population included a control group of patients who did not have a history of disease of the liver, biliary tract, or spleen. Controls were selected from patients undergoing EUS evaluation for the diagnostic workup of subepithelial lesions. These patients received transient elastography, and if the results were within normal parameters, they underwent EUS for liver and spleen elastography measurement as well as the evaluation of subepithelial lesions. Control patients were excluded if they had a history of hematological or coagulopathic disorders, hereditary spherocytosis, hemochromatosis, hepatolenticular degeneration, alcoholic liver disease, primary or secondary liver malignancy, acute or chronic infection with hepatotropic viruses, a history of liver disease secondary to nonalcoholic steatohepatitis, or a history of drug-induced hepatotoxicity.

The case group comprised patients with a known history of chronic liver disease, as based on clinical, laboratory, and transient elastography findings of liver cirrhosis, as well as confirmed portal hypertension with the presence of large esophageal varices detected by previous esophagogastroduodenoscopy (≤ 4 weeks before enrollment). All patients with liver cirrhosis were treatment-naïve at the time of EUS-elastography evaluation.

Study outcomes

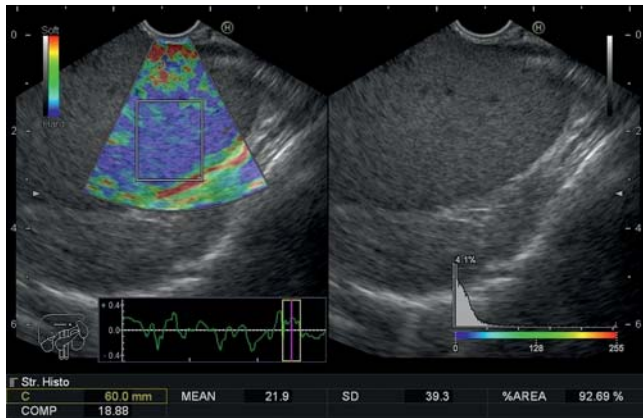
The primary outcome of the study was diagnostic yield of liver and spleen stiffness measurement via EUS-elastography in prediction of portal hypertension secondary to liver cirrhosis. The secondary outcome of the study was evaluation of azygos-vein diameter, mean velocity, and blood-flow volume index (BFVI) as markers of portal hypertension secondary to liver cirrhosis. We also performed subgroup analysis according to the etiology of chronic liver disease.

Endoscopic technique

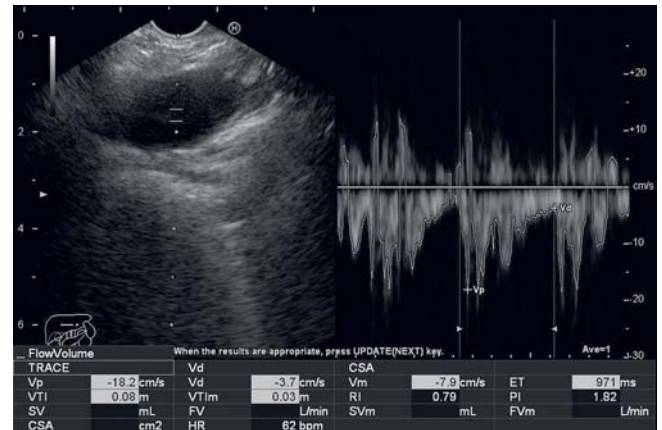
Three endoscopists (C.R-M., M.V., and R.D.) performed the EUS evaluations, and all were experienced in EUS and EUS-elastography (> 300 EUS procedures/year). The operators were blinded to patient medical histories and results of transient elastography. The procedures were performed under general anesthesia with the patients in the supine position. EUS evaluation was performed using a linear-array echoendoscope (EG-3870 UTK, Pentax Medical, Montvale, New Jersey, United States) attached to an ultrasonographic console (HI VISION Avius, Hitachi Medical Systems, Steinhaus, Switzerland).

Liver and spleen stiffness measurements by EUS-elastography were derived from the strain ratio (SR) and strain histogram (SH) of the elastography evaluations. The liver SR and SH were measured on the left hepatic lobe using the transgastric approach comparing the hepatic elastography against that of the normal gastric mucosal layer. For SR calculation, the region of interest included hepatic tissue (Area A) and tissue from the gastric mucosa (Area B). For the SH, the selected region of interest had a surface area of 60 mm^2 . Spleen SR and SH measurements were performed using the same protocol and transgastric approach. To avoid variability, the SR and SH were measured 10 times in the liver and 10 times in the spleen for each participant, and the respective median values were calculated, as performed for transient abdominal elastography. An example of spleen stiffness measurement evaluated by EUS-elastography is illustrated in ► **Fig. 1**.

For azygos vein hemodynamic features, vein diameter, mean velocity, and BFVI were measured once for each participant. The azygos vein diameter was originally measured in millimeters (mm) from the mediastinal stage. The mean velocity (V_{mean} [centimeters per second]) was calculated using EUS-Doppler.



► **Fig. 1** Endoscopic ultrasonographic elastography of the spleen. Measurement of spleen stiffness via a strain histogram.



► **Fig. 2** Measurement of the azygos vein diameter (left panel) under endoscopic ultrasonography (EUS) evaluation and EUS-Doppler flowmetry of the azygos vein for blood flow volume index evaluation (right panel).

The BFVI (cubic centimeters per second) was calculated as follows:

$$V(\text{cm/s})_{\text{mean}} \times \pi \times \left(\frac{\text{diameter (cm)}}{2}\right)^2$$

An example of azygos vein diameter measurement and Doppler evaluation of the azygos vein under EUS is shown in ► **Fig. 2**.

Transient elastography

Transient elastography was performed with the FibroScan system (Echosens, Paris, France) using the M probe after overnight fasting. Measurements were performed by a gastroenterologist (H.P-L.) with experience in transient elastography. The stiffness of the tissue was measured in kilopascals (kPa), with a minimum of 10 valid readings per patient; a $\geq 60\%$ success rate and an interquartile range $\leq 30\%$ were considered to indicate adequate quality of the assessment [11].

Statistical analysis

All statistical analyses were performed by the institutional statistician (M.P-T.), using R v3.6.3 (R foundation, Vienna, Austria). $P < 0.05$ was considered statistically significant. The sample size was calculated using the power.diagnostic.test function from the MKmisc package. The sample size was estimated considering a 100% specificity of transient elastography spleen stiffness for predicting severe (> 12 mm Hg) portal hypertension [5], with corresponding 13.1% disease prevalence, a $\delta = 10\%$, and α and β -errors of 5% and 20% respectively. Through previously described parameters, a sample size of four cases and 25 controls was estimated, with 80% statistical power. To respect the central limit theorem (30 observations are necessary to reach a Gaussian distribution), we approximated a 30-participant sample size for each study group.

Quantitative variables are described as the mean (standard deviation) or median (minimum-maximum range) according to their statistical distribution (Kolmogórov-Smirnov test). Qualitative variables are described as the frequency (%). Quantitative and qualitative variable comparisons among the study groups were performed with respective statistical hypothesis testing and illustrated with a boxplot when necessary. The asso-

ciation between liver stiffness measurements and transient elastography was verified by Spearman's rank correlation coefficient (ρ) and the results were illustrated in scatter plots. The liver stiffness measurement, spleen stiffness measurement, and azygos vein diameter (mm), mean velocity (cm/s), and BFVI (cm^3/s) cutoff values to optimally diagnose liver cirrhosis and portal hypertension were defined through Youden's index. The overall accuracy of those parameters was calculated only when they reached an area under the receiver operating characteristic (AUROC) curve $\geq 80\%$, individually as well as in the context of a pooled analysis. Subgroup analysis including only alcohol-related liver cirrhosis was developed when the sample size allowed it, keeping a 1:4 control vs. case relationship.

Results

A total of 61 patients were included in the study, with 32 in the case group and 29 in the control group. The median age was 60 years (range 18–82 years), and 36 patients (59%) were female. All patients underwent transient elastography prior to EUS evaluation and EUS evaluation was completed without any adverse events being reported.

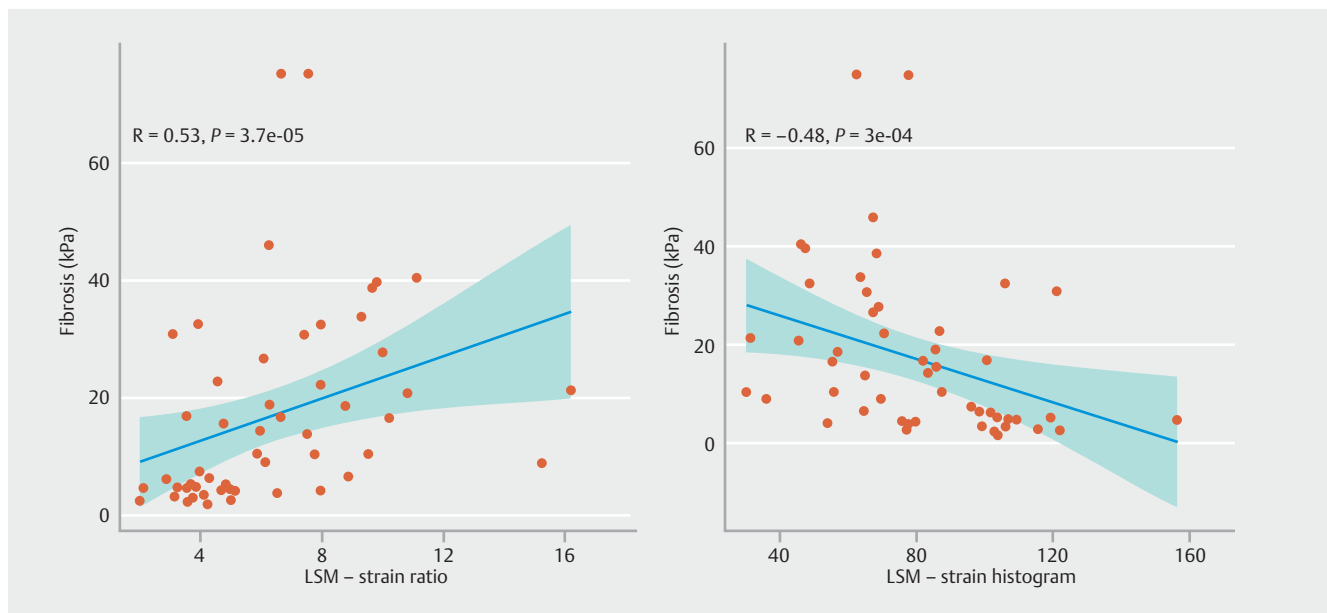
In the case group of 32 patients, the etiology of cirrhosis was nonalcoholic steatohepatitis in 20, alcoholic liver disease in 10, and hepatitis C virus infection in two. According to transient elastography, the median stiffness in this group was 21.30 kPa (range 9.00–75.00 kPa), with 75% of patients having a value > 14 kPa (liver cirrhosis). In the control group, the median stiffness was 4.48 kPa (range 1.90–7.50 kPa), and the values of all patients were within the normal limits (< 7.6 kPa). The transient elastography findings in both groups are shown in ► **Table 1**.

EUS-elastography of the liver

Liver stiffness measurements of SR determined by EUS-elastography correlated significantly and positively with the results of liver transient elastography ($\rho = 0.53$, $P < 0.01$). In contrast, liver stiffness measurements of SH on EUS-elastography had a

► **Table 1** Transabdominal transient elastography results in the case and control groups.

	Cirrhosis (n = 32)	Controls (n = 29)	P value
Fibrosis (kPa), median (range)	21.30 (9.00–75.00)	4.48 (1.90–7.50)	<0.001 ¹
Normal (<7.6 kPa), n (%)	0	29 (100.0)	<0.001 ²
Moderate (7.7–9.4 kPa), n (%)	3 ³ (9.4)	0	
Advanced (9.5–14.0 kPa), n (%)	5 ³ (15.6)	0	
Liver cirrhosis (>14.0 kPa), n (%)	24 (75.0)	0	
Interquartile range (kPa), median (range)	2.9 (0.0–11.5)	0.5 (0.2–2.4)	<0.001 ¹
Variability ([interquartile range]/[fibrosis]), median (range)	0.14 (0.00–0.32)	0.12 (0.04–0.32)	0.528 ¹

¹ Results of Mann-Whitney U test.² Results of Pearson's chi-squared test.³ Patients with large esophageal varices on previous esophagogastroduodenoscopy.► **Fig. 3** Scatter plots illustrating a significant directly and inversely proportional relationship between liver fibrosis vs. the liver stiffness measurement (LSM) strain ratio and histogram, respectively.

significant negative correlation with transient elastography ($\rho = -0.47$, $P < 0.01$) (► **Fig. 3**).

In patients with portal hypertension secondary to liver cirrhosis, the liver median SR was significantly higher (7.53 versus 3.97, $P < 0.001$) and the median SH significantly lower (67.38 versus 101.70, $P < 0.001$) relative to control patients (► **Table 2**). Compared with liver stiffness measurements of SR, we found a significant difference in comparison to controls in subanalysis of patients with portal hypertension secondary to alcohol-related cirrhosis (► **Table 3**).

The SR and SH determined by EUS-elastography of the liver had AUROC values of 84.8% and 81.1% (► **Fig. 4**), respectively, when using a cutoff value of 5.35 for the former and 87.4 for the latter (► **Table 4**). With these cutoff values, the SR had a sensitivity, specificity, positive predictive value (PPV) and nega-

tive predictive value (NPV) of 84.3%, 82.8%, 84.4%, and 82.8%, respectively, for diagnosis of portal hypertension secondary to cirrhosis in the study population (► **Table 5**).

EUS elastography of the spleen

In patients with portal hypertension secondary to liver cirrhosis, spleen median SR was significantly higher (12.10 versus 6.50, $P < 0.001$) and median SH significantly lower (39.63 versus 65.45, $P < 0.001$) relative to control patients (► **Table 2**). In subanalysis of patients with portal hypertension secondary to alcohol-related liver disease, we found a significant difference with respect to controls when comparing the spleen stiffness measurements of SR (► **Table 3**).

The SR and SH determined by EUS-elastography of the spleen had AUROC values of 81.5% and 80.0% respectively

► **Table 2** Endoscopic ultrasonographic elastography results in patients with cirrhosis and controls.

	Cirrhosis (n = 32)	Controls (n = 29)	P value
Liver stiffness measurement			
▪ Strain ratio, median (range)	7.53 (3.10–16.20)	3.97 (2.01–8.85)	<0.001 ¹
▪ Strain histogram, median (range)	67.38 (30.30–121.10)	101.70 (53.75–156.10)	<0.001 ¹
Spleen stiffness measurement			
▪ Strain ratio, median (range)	12.10 (4.92–50.64)	6.50 (2.34–18.40)	<0.001 ¹
▪ Strain histogram, median (range)	39.63 (14.40–91.50)	65.45 (28.45–111.60)	<0.001 ¹
Azygos-vein measurements			
▪ Diameter (mm), median (range)	8.30 (2.62–20.70)	5.10 (3.10–9.80)	0.002 ¹
▪ Mean velocity (cm/s), median (range)	6.55 (1.50–18.20)	4.60 (0.20–17.70)	0.049 ¹
▪ Blood-flow-volume index (cm ³ /s), median (range)	2.94 (0.08–23.3)	0.94 (0.02–5.47)	0.002 ¹

¹ Results of Mann-Whitney U test.

► **Table 3** Endoscopic ultrasonographic elastography results in patients with alcohol-related cirrhosis and controls.

	Alcohol-related cirrhosis (n = 10)	Controls (n = 29)	P value
Liver stiffness measurement			
▪ Strain ratio, median (range)	7.07 (3.55–11.10)	3.97 (2.01–8.85)	0.003 ¹
▪ Strain histogram, median (range)	67.90 (46.60–109.00)	101.70 (53.75–156.10)	0.011 ¹
Spleen stiffness measurement			
▪ Strain ratio, median (range)	12.10 (4.92–39.00)	6.50 (2.34–18.40)	0.001 ¹
▪ Strain histogram, median (range)	39.20 (21.50–87.10)	65.45 (28.45–111.60)	0.012 ¹
Azygos-vein measurements			
▪ Diameter (mm), median (range)	9.20 (5.60–13.80)	5.10 (3.10–9.80)	<0.001 ¹
▪ Mean velocity (cm/s), median (range)	10.70 (3.00–18.20)	4.6 (0.2–17.7)	0.008 ¹
▪ Blood-flow-volume index (cm ³ /s), median (range)	6.96 (2.76–14.00)	0.94 (0.02–5.47)	<0.001 ¹

¹ Results of Mann-Whitney U test.

(► **Fig. 4**), when using a cutoff value of 7.5 for the former and 39.9 for the latter (► **Table 4**). Based on these values, the SR had a sensitivity of 87.5% and an NPV of 83.3%, whereas the SH had a specificity of 89.7% and a PPV of 85.7% (► **Table 5**).

Azygos-vein hemodynamic parameters

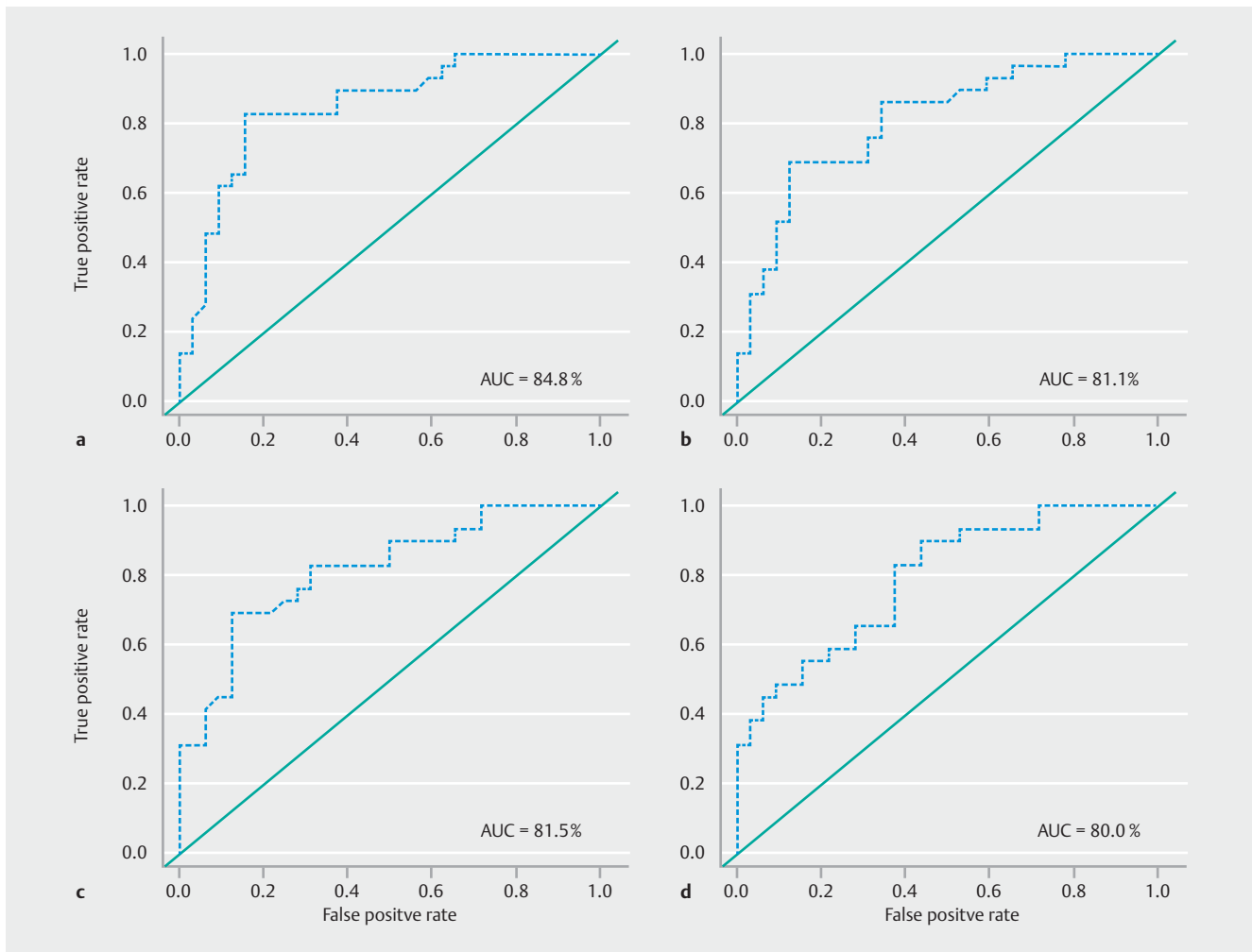
Compared with the control group, patients with portal hypertension secondary to liver cirrhosis had a significantly higher azygos-vein diameter (8.30 mm versus 5.10 mm, $P=0.002$), mean velocity (6.60 cm/s versus 4.60 cm/s, $P=0.049$), and BFVI (3.74 cm³/s versus 1.20 cm³/s, $P=0.001$) (► **Table 2**). These differences were significantly different when comparing control patients with those patients with portal hypertension secondary to alcohol-related liver cirrhosis with an azygos-vein diameter of

9.20 mm ($P < 0.001$), mean velocity of 10.7 cm/s ($P=0.008$), and BFVI of 6.96 cm³/s ($P < 0.001$) (► **Table 3** and ► **Fig. 5**).

For diagnosis of patients with cirrhosis and portal hypertension related to alcohol consumption the azygos vein diameter and BFVI had AUROC values of 91.5% and 94.9%, respectively. Azygos vein diameters >7.6 mm had a sensitivity of 90.0% and NPV of 95.7% for the diagnosis of these patients, and BFVI >2.75 mm³/s had a sensitivity and NPV of 100.0% (► **Table 5**).

Pooled analysis

Pooled analysis was performed to combine the overall accuracy of LSM and SSM-SR, LSM and SSM-SH; and the azygos vein parameters of diameter, mean velocity and BFVI for alcohol-related cirrhosis. Using the LSM-SR cutoff value >5.35 or the SSM-SR cutoff value >7.49 we predicted portal hypertension in



► **Fig. 4** Receiver operating characteristics (ROC) curves for the **a** liver stiffness measurement strain ratio, **b** histogram, **c** spleen stiffness measurement strain ratio, and **d** histogram.

our patients with 96.9% sensitivity and 94.7% NPV. Additionally, LSM-SH <7.49 or SSM-SH <39.85 predicted portal hypertension with a sensitivity and NPV of 93.8% and 90.0%, respectively. For those patients with alcohol-related cirrhosis, the combination of an azygos vein diameter >7.6 mm, mean velocity >5.8 cm/s or a BFVI >2.75 mm³/s predicted portal hypertension with a sensitivity and NPV of 100%. In general, the combination of EUS-elastography parameters and azygos vein evaluation improved the sensitivity and NPV for predicting portal hypertension (► **Supplementary Table 1**).

In our cohort of patients with cirrhosis, despite the presence of large esophageal varices detected during esophagogastroduodenoscopy, eight patients showed moderate and advanced fibrosis by transient elastography evaluation. However, after excluding these patients, significant difference from the controls were observed for liver and spleen stiffness measurements, as well as for azygos vein hemodynamic features (► **Supplementary Table 2**).

Discussion

In this study, we found that liver and spleen evaluation by EUS-elastography constitutes a useful diagnostic method for prediction of portal hypertension in patients with liver cirrhosis. These evaluations might be considered in the future for diagnostic workup of patients with cirrhosis because accurate differentiation of such patients with and without portal hypertension via a single diagnostic method may decrease the number of procedures that are required, and the duration of the diagnostic workup, considering that patients with chronic liver disease have significantly higher health care use and expenditure in comparison to patients without chronic liver disease [12].

Liver biopsy remains the gold standard for evaluation of fibrosis, but it has limited applicability in clinical practice because of its invasiveness and potential for procedure-related adverse events, thereby restricting its use for repetitive assessment in disease progression monitoring. In addition, the accuracy of liver biopsy may be affected by sampling errors, specimen size, and subjective histological interpretation, which may result in inconsistent identification of liver cirrhosis [13, 14].

► **Table 4** EUS-elastography cut-off parameters for the diagnosis of liver cirrhosis and alcohol-related cirrhosis, with respective area under the receiver operating characteristics (AUROC) curve.

	Cirrhosis (n = 32)		Alcohol-related cirrhosis (n = 10)	
	Cut-off	AUROC (95% CI)	Cut-off	AUROC (95% CI)
Liver stiffness measurement				
▪ Strain ratio	5.35	84.8 (74.8–94.7)	5.35	82.2 (66.2–98.3)
▪ Strain histogram	87.40	81.1 (70.2–92.0)	86.65	77.6 (61.0–94.2)
Spleen stiffness measurement				
▪ Strain ratio	7.49	81.5 (70.7–92.2)	8.05	77.9 (60.8–95.1)
▪ Strain histogram	39.85	80.0 (67.8–90.1)	39.70	77.2 (59.8–94.7)
Azygos-vein measurements				
▪ AzV diameter (mm)	6.60	74.4 (61.4–87.4)	7.60	91.5 (82.0–100.0)
▪ Mean velocity (cm/s)	4.90	65.7 (50.9–80.4)	5.80	80.1 (63.8–96.4)
▪ BFVI (cm ³ /s)	1.68	74.3 (61.0–87.6)	2.75	94.9 (88.2–100.0)

AUROC, area under the receiver operating characteristic; BFVI, blood-flow volume index

► **Table 5** Overall diagnostic accuracy of EUS elastography for the diagnosis of liver cirrhosis and portal hypertension [n/T; % (95% CI)].

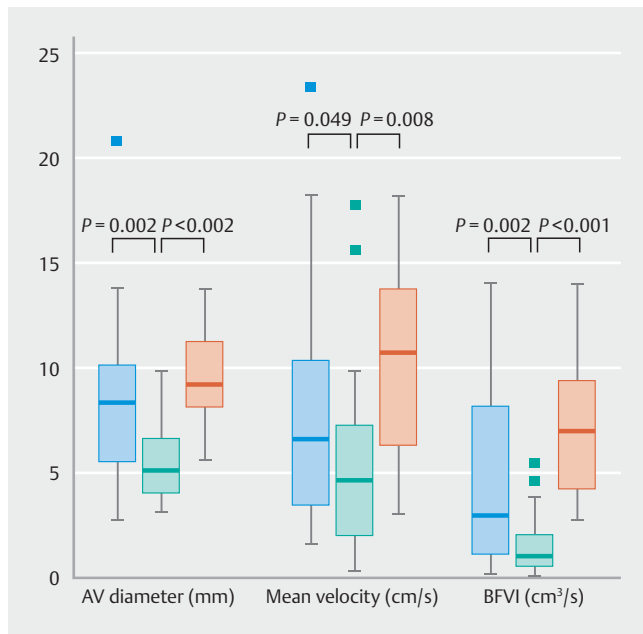
	Sensitivity	Specificity	PPV	NPV	Accuracy
Liver cirrhosis + portal hypertension (all etiologies) (n = 32) and controls (n = 29)					
▪ LSM-SR	84.3 (67.2–94.7)	82.8 (64.2–94.2)	84.4 (70.6–92.4)	82.8 (67.8–91.6)	83.6 (71.9–91.8)
▪ LSM-SH	87.5 (71.0–96.5)	69.0 (49.2–84.7)	75.7 (64.0–84.5)	83.3 (65.9–92.8)	78.7 (66.3–88.1)
▪ SSM-SR	87.5 (71.0–96.5)	69.0 (49.2–84.7)	75.7 (64.0–84.5)	83.3 (65.9–92.8)	78.7 (66.3–88.1)
▪ SSM-SH	56.3 (37.7–73.5)	89.7 (72.7–97.8)	85.7 (66.3–94.8)	65.0 (55.2–73.7)	72.1 (59.2–82.9)
Liver cirrhosis + portal hypertension related to alcohol (n = 10) and controls (n = 29)					
▪ AzV diameter (mm)	90.0 (55.5–99.7)	75.9 (56.5–89.7)	56.3 (29.9–80.2)	95.7 (78.0–99.9)	79.4 (63.5–90.7)
▪ Mean velocity (cm/s)	90.0 (55.5–99.7)	65.5 (45.7–82.1)	47.4 (24.4–71.1)	95.0 (75.1–99.9)	71.8 (55.1–85.0)
▪ BFVI (cm ³ /s)	100.0 (69.1–100.0)	79.3 (60.3–92.0)	62.5 (35.4–84.8)	100.0 (85.2–100.0)	84.6 (69.5–94.1)

AzV, azygos vein; BFVI, blood flow volume index; CI, confidence interval; LSM, liver stiffness measurement; n, number; NPV, negative predictive value; PPV, positive predictive value; SSM, spleen stiffness measurement; SH, strain histogram; SR, strain ratio; T, total.

Measurement of the hepatic venous pressure gradient via catheterization under radiological guidance is the gold standard for defining portal hypertension, but this procedure is invasive, and has limited applicability in clinical practice. Therefore, indirect parameters such as presence of esophageal varices are preferred as surrogate measures of portal hypertension.

Transient elastography of the liver has been shown to be a reliable method for the assessment of liver fibrosis and can ac-

curately rule out diagnoses of fibrosis and cirrhosis [15]. However, it is not accurate enough to differentiate between the various stages of fibrosis, and it correlates poorly with fibrosis severity in patients with higher hepatic venous-pressure-gradient values [16]. In addition, transient elastography measures shear-wave speed through the liver, which corresponds to liver stiffness and not to the actual amount of fibrosis in the liver. Conditions in which stiffness increases independently of fibrosis may



► **Fig. 5** Azygos vein (AZ) diameter (mm), mean velocity (cm/s) and blood flow volume index (BFVI; cm^3/s) among patients with liver cirrhosis (blue; $n=32$) patients with alcohol-related liver cirrhosis (red; $n=10/32$) and controls (green; $n=29$).

therefore lead to false-positive results, such as in acute hepatitis, hepatic congestion, and cholestasis [6].

Transient elastography of the spleen, as evaluated via abdominal ultrasonography, has also been used for diagnosis of portal hypertension in patients with cirrhosis and is superior to liver elastography for the identification of patients with esophageal varices [5]. In a meta-analysis comparing use of liver and spleen stiffness measured by abdominal ultrasonography for prediction of esophageal varices in patients with chronic liver disease, spleen stiffness had a pooled sensitivity of 88% and a pooled specificity of 78%, with a statistically significant superior diagnostic odds ratio compared with liver stiffness (25.73 versus 9.54, $P<0.05$) [4]. Nevertheless, in our study, EUS-elastography reached similar AUROC ranges in comparison to previous studies of transabdominal elastography [5], though a higher trend was noted for EUS-elastography in terms of AUROC and accuracy for predicting portal hypertension.

The gold standard for detection and grading of esophageal varices is esophagogastroduodenoscopy. However, EUS has been shown to be superior to esophagogastroduodenoscopy for detection of paraesophageal and periesophageal collateral veins, gastric varices, and portal hypertensive gastropathy [7]. Notably, EUS findings, such as the diameter of paraesophageal varices, can predict esophageal variceal recurrence after varix eradication with endoscopic band ligation, demonstrating its diagnostic applicability [17–19]. In addition, our study shows that EUS-elastography is able to predict portal hypertension, and in the future a single diagnostic method such as EUS might replace several methods for the evaluation of portal hypertension associated to liver cirrhosis in a single diagnostic step. Indeed, EUS allows evaluation of liver morphology, elastography

evaluation of liver and spleen, azygos vein flow index evaluation, measurement of portal pressure gradient, EUS-guided liver biopsy and EUS-guided therapy of gastric varices.

Overall, transabdominal transient elastography has limited applicability in patients with obesity and thick subcutaneous fat or restricted intercostal space, as well as in those with ascites; moreover, it is prone to variability related to probe compression during the evaluation [6]. These limitations can be overcome by the use of EUS-elastography. Despite the invasiveness of EUS, it can provide valuable information during the diagnostic workup of patients with cirrhosis, and it has the additional advantage of enabling liver tissue acquisition using a 19-G needle if needed, which is comparable in terms of total specimen-length acquisition to transjugular and percutaneous liver biopsies [20, 21]

By proposing cutoff values for liver and spleen SRs and SHs, we obtained AUC values $>80\%$. The proposed liver SR cutoff value was associated with a sensitivity of 84% and a higher specificity of 83% for the diagnosis of portal hypertension secondary to chronic liver cirrhosis in comparison to spleen stiffness measurement via transabdominal elastography [4], and the cutoff for spleen SH showed a specificity of 89.7% for detecting portal hypertension.

In addition, azygos vein hemodynamic features accurately predicted liver cirrhosis and portal hypertension in patients with alcoholic liver disease, with a high specificity and a high PPV. This may be beneficial considering the increasing disease burden of excessive alcohol consumption and subsequent chronic liver disease development [22], allowing the earliest detection of portal hypertension in patients with alcohol-related chronic liver disease.

In subanalysis between patients with alcohol-related cirrhosis and those with nonalcohol-related causes, we found a significantly superior mean velocity (10.7 vs 4.90 $P=0.03$) and blood flow volume index (6.96 vs 1.87, $P=0.007$), suggesting a potential role in chronic liver disease etiology and hemodynamic implications (► **Supplementary Table 3**). For diagnosis of portal hypertension in patients with alcoholic liver disease, we obtained high sensitivity for azygos vein diameter (90%) and BFVI (100%), supporting the benefit of implementing EUS elastography with evaluation of azygos vein hemodynamics in patients with chronic liver disease secondary to excessive alcohol consumption.

Furthermore, in pooled analysis we found that combining EUS elastography parameters for the liver and spleen predicts liver cirrhosis and portal hypertension, with high sensitivities and NPVs ($>90\%$); similar findings for azygos vein parameters were obtained for patients with alcohol-related chronic liver disease. These promising parameters should be considered in the diagnostic work-up evaluation of patients with chronic liver disease.

A cost-effectiveness analysis evaluating screening methods for alcohol-related liver fibrosis demonstrated that direct liver stiffness measurement via transient elastography is a highly cost-effective procedure, with 93% accuracy and incremental cost-effectiveness ratios of \$490 to \$1,037 per quality-adjusted life-year in high-prevalence populations [23]. Nonetheless,

there is a lack of studies evaluating the cost-effectiveness of EUS in the diagnostic workup of chronic liver disease, and its implications given the additional features found during EUS evaluation of patients with cirrhosis. In addition, a cost-effectiveness evaluation may be worth conducting, considering that EUS may detect the earliest structural and functional changes in the liver and spleen, and hemodynamic alterations in the portosystemic circulation.

In addition to being a single-center trial with a small number of operators and sample size, there are other limitations to our study. For example, liver biopsy was not used to define liver cirrhosis in our case cohort. Regardless, these data are promising and open a discussion regarding use of EUS for diagnostic workup of patients with suspected portal hypertension secondary to chronic liver disease. Prospective randomized controlled trials comparing esophagogastroduodenoscopy and EUS evaluation for early detection of portal hypertension may be of interest, particularly with reference to prediction of hepatic venous pressure gradient. In addition, larger studies comparing trans-abdominal versus EUS-elastography of the liver/spleen should be conducted in the near future to determine the most reliable diagnostic method for predicting portal hypertension.

Conclusion

In conclusion, implementation of EUS evaluation with elastography of the liver and spleen has diagnostic value for portal hypertension secondary to chronic liver disease, providing endoscopic, ultrasonographic, elastography, and Doppler evaluations in a single diagnostic test.

Competing interests

Carlos Robles-Medranda is a key opinion leader and consultant for Pentax Medical, Boston Scientific, G-Tech medical supply and MD consulting group. The other authors have no conflict of interest.

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► **Supplementary Table 1** Pooled analysis of overall diagnostic accuracy of EUS elastography for diagnosis of liver cirrhosis and portal hypertension [n/T; % (95% CI)].

	Sensitivity	Specificity	PPV	NPV	Accuracy
Liver cirrhosis + portal hypertension (all etiologies) (n = 32) and controls (n = 29)					
L/SSM-SR	96.9 (83.8–99.9)	62.1 (42.3–79.3)	73.8 (58.0–86.1)	94.7 (74.0–99.9)	80.3 (68.2–89.4)
L/SSM-SH	93.8 (79.2–99.2)	62.1 (42.3–79.3)	73.2 (57.1–85.8)	90.0 (68.3–98.8)	78.7 (66.3–88.1)
Liver cirrhosis + portal hypertension related to alcohol (n = 10) and controls (n = 29)					
D + mV + BFVI	100.0 (69.2–100.0)	55.1 (35.7–73.6)	43.5 (23.2–65.5)	100.0 (79.4–100.0)	66.7 (49.8–80.1)

CI, confidence interval; D, azygos vein diameter (mm); mV, mean Velocity (cm/s); BFVI, blood flow volume Index (cm³/s); L/SSM-SR, liver and spleen stiffness measurement; n, number; NPV, negative predictive value; PPV, positive predictive value; SR, strain ratio; SH, strain histogram; T, total.

► **Supplementary Table 2** Endoscopic ultrasonographic elastography results in cirrhotic (excluding moderate/advanced fibrosis, n = 8) and control patients.

	Cirrhosis (n = 24)	Controls (n = 29)	P value
Liver stiffness measurement			
▪ Strain ratio, median (range)	7.48 (3.10–16.2)	3.97 (2.01–8.85)	<0.001 ¹
▪ Strain histogram, median (range)	67.9 (31.8–121.0)	101.70 (53.75–156.10)	0.0002 ¹
Spleen stiffness measurement			
▪ Strain ratio, median (range)	12.7 (4.92–50.6)	6.50 (2.34–18.40)	<0.001 ¹
▪ Strain histogram, median (range)	37.0 (14.4–91.5)	65.45 (28.45–111.60)	<0.001 ¹
Azygos-vein measurements			
▪ Diameter (mm), median (range)	7.35 (2.62–20.7)	5.10 (3.10–9.80)	0.0104 ¹
▪ Mean velocity (cm/s), median (range)	6.80 (1.50–16.3)	4.60 (0.20–17.70)	0.0437 ¹
▪ Blood-flow-volume index (cm ³ /s), median (range)	2.94 (0.08–23.3)	0.94 (0.02–5.47)	0.0077 ¹

¹ Results of Mann-Whitney U test.

► **Supplementary Table 3** Endoscopic ultrasonographic elastography results in alcohol-related cirrhosis vs. non-alcohol related cirrhosis cases.

	Alcohol-related cirrhosis (n = 10)	Non-alcohol related cirrhosis (n = 22)	P value
Liver stiffness measurement			
▪ Strain ratio, median (range)	7.07 (3.55–11.1)	7.75 (3.10–16.2)	0.5419 ¹
▪ Strain histogram, median (range)	67.9 (46.6–109)	66.4 (30.3–121)	0.4832 ¹
Spleen stiffness measurement			
▪ Strain ratio, median (range)	12.1 (4.92–39.0)	12.1 (5.01–50.6)	0.7643 ¹
▪ Strain histogram, median (range)	39.2 (21.5–87.1)	39.7 (14.4–91.5)	0.6455 ¹
Azygos-vein measurements			
▪ Diameter (mm), median (range)	9.20 (5.60–13.8)	6.65 (2.62–20.7)	0.0556 ¹
▪ Mean velocity (cm/s), median (range)	10.7 (3.00–18.2)	4.90 (1.50–16.3)	0.0387 ¹
▪ Blood-flow-volume index (cm ³ /s), median (range)	6.96 (2.76–14.0)	1.87 (0.08–23.3)	0.0073 ¹

¹ Results of Mann-Whitney U test.