Prediction of the presence of esophageal varices using spleen stiffness measurement by transient elastography in cirrhotic patients

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Abstract

Upper gastrointestinal endoscopy (UGE) is currently recommended in cirrhotic patients to detect the presence of esophageal varices (EV). Spleen stiffness measurement (SSM) with FibroScan has been used for this purpose, showing variable sensitivity (S) and specificity (Sp).

The aim of this study was to evaluate the capability of SSM to detect the presence and size of EV in cirrhotic patients in comparison to other noninvasive modalities.

***Patients and methods :* Sixty-six patients with cirrhosis who had undergone UGE in the previous 6 months underwent SSM and liver stiffness measurement (LSM) using FibroScan. Biochemical parameters and ultrasonography data were also collected to calculate other noninvasive indexes.**

***Results :* Valid spleen stiffness measurements were obtained for 60 of the 66 patients initially included in the study (90.1%).**

In the multivariate analysis only splenomegaly and SSM were predictive of esophageal varices. SSM was the most accurate diagnostic tool, obtaining an area under the ROC curve of 0.8 for values below 48 KPascals, with S = 87%, Sp = 69%, and 76.7% of successfully diagnosed patients.

***Conclusions :* SSM with FibroScan was significantly higher for cirrhotic patients with EV. Our study suggests that spleen stiffness may be useful to identify cirrhotic patients at risk of having EV, although further studies are needed.** (Acta gastroenterol. belg., **2018,** 81, **496-502**).

Key words : Cirrhosis ; esophageal varices ; elastography.

Introduction

Liver cirrhosis is the final stage of most chronic liver diseases. Cirrhotic patients may develop portal hypertension (PHT) and esophageal varices (EV), which are one of the main complications during the course of this disease, occurring in approximately 50% of cases. Once EV have developed, the incidence of variceal bleeding is 35%, and mortality is reportedly as high as 10-20% (1).

Currently, the screening method recommended to detect EV is upper gastrointestinal endoscopy (UGE). Other noninvasive alternatives to detect these complications have been identified, but have unfortunately failed to show enough sensitivity (S) or specificity (Sp) (2,3).

Cirrhotic patients have increased liver stiffness (LS). Also splenomegaly is a common finding in these patients as a consequence of the development of portal hypertension. It is known that spleen stiffness (SS) may be modified by venous congestion, increased flow resistance, and increased fibrosis and angiogenesis, as in the context of portal hypertension (4)

Liver and spleen stiffness may be measured by transient elastography (FibroScan) (5,6). FibroScan is an elastography-based ultrasonography technique that measures stiffness in a tissue using an ultrasound wave and a low- frequency mechanical vibration pulse.

Several studies have described how liver FibroScan may be a reliable noninvasive method to predict the presence or absence of portal hypertension or EV in cirrhotic patients (7). However, it has not always shown a good correlation with EV size or severity of portal hypertension. Recently, Cholecchia, Stefanescu et al, and Sharma et al (5,6,8) proved that spleen FibroScan is a more reliable tool to predict the presence of portal hypertension or EV when compared to other noninvasive modalities, with some differences between studies (9).

The aim of this study was to evaluate the usefulness of spleen stiffness measurement (SSM) to detect the presence and size of EV when applied to cirrhotic patients, and to compare it with other noninvasive methods used with the same purpose.

Patients and Methods

This cross-sectional study was carried out at a tertiary hospital (Hospital Ramón y Cajal, Madrid, Spain) from April 2015 to March 2016.

Patients

Sixty-six patients with chronic liver disease of any etiology were consecutively included.

All patients had undergone UGE within 6 months before inclusion in the study.

Patient inclusion was carried out immediately after completion of a screening UGE procedure to rule out the presence of EV, or when prior to LSM a second observer

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detected liver cirrhosis with PHT in the US scan of a patient who had undergone a UGE procedure during the previous 6 months.

The diagnosis of cirrhosis and its etiology was based on clinical, biochemical and imaging data (abdominal ultrasound, computed axial tomography (CT), liver elastography by FibroScan), as well as liver biopsy when necessary. In no case was cirrhosis diagnosed using only LSM, but always with a combination of the above-mentioned modalities.

Exclusion criteria included use of propranolol or band ligation as primary or secondary prophylaxis for EV, portal vein thrombosis, moderate to severe ascites, acute or chronic liver failure according to the "EASL-CLIF Consortium" criteria (10), acute cholangitis, and focal lesions larger than 1 cm in the liver or spleen.

This study was carried out in accordance with the principles of the Declaration of Helsinki, and was approved by the Ethics Committee in our hospital.

Methods

An UGE procedure was performed by the endoscopists in our hospital within 6 months before enrollment in the study. The presence or absence of EV was documented. EV were then categorized into four groups, I to IV, according to Paquet's classification, and the presence of red spots as a risk factor was also recorded. EV were considered large when grade ≥ II, as proposed at the Baveno V Consensus Conference (1). The presence of gastric varices was included in the report but not taken into account for the analysis.

All patients underwent liver and spleen elastography using FibroScan (Echosens, Paris France, M Probe) with ultrasound control when needed (Toshiba, PowerVision 6000). These explorations were performed by a trained, experienced person (> 200 procedures) who was blinded to the results of the previous UGE procedure. Fasting was a requirement for all patients included. In all cases at least 10 LS and SS measures were obtained. The final results were drawn from an average value expressed in Kilopascals (KPa). Only results with more than 10 valid measurements, a success rate > 60%, and an interquartile range (IQR) < 30 were included.

The biochemical parameters collected were hemoglobin, platelet count (PC), INR (international normalized ratio), alanine and aspartate aminotransferases (ALT, AST), total bilirubin (TB), creatinine, and serum albumin. These parameters were obtained from routine blood tests carried out in the previous 6 months during regular patient care.

Baseline variables were recorded in every case, including age, sex, etiology of liver disease, presence of focal lesions or ascites, functional stage according to the Child-Pugh classification, and MELD (Model for End-stage Liver Disease) score.

Likewise, data were obtained from the abdominal ultrasounds performed during routine patient follow-up in the previous 6 months (Toshiba, Aplio XG). These data included morphology and appearance of liver parenchyma, anteroposterior diameter of the portal vein, spleen diameter between both poles (considering splenomegaly as a qualitative variable when spleen diameter was > 12 cm), and presence of ascites.

Other non invasive indexes calculated for the assessment of PHT included APRI, PC and P/SD, as well as Baveno VI criteria (LSM < 20 kPa and platelet count > 150,000). No follow- up data were collected.

Statistical analysis

We analyzed all collected variables and compared them between patients with and without EV.

The statistical analysis was performed using the Stata v.13.0 software package (Stata, College Station, Texas). Continuous variables were analyzed using mean ± standard deviation (SD) values, and qualitative variables were expressed as frequency and percentage.

For the univariate analysis data were compared using the Mann–Whitney U-test and the χ^2-test for continuous and categorical variables, respectively. Variables were considered statistically significant for $p < 0.05$.

A multivariate analysis was subsequently performed by binary logistic regression using the statistically significant variables obtained from the univariate analysis.

Odds ratios (OR) and 95% confidence intervals (CIs) were estimated for each variable.

Missing values were treated with data imputation.

To evaluate the diagnostic efficiency of LSM and SSM for the detection of EV, an analysis of the area under the ROC curve (AUROC) was performed. We used the value with the highest percentage of patients correctly classified as the cut-off point. Based on this cut-off point we calculated S and Sp, positive predictive value (PPV) and negative predictive value (NPV), and positive and negative likelihood ratios (LR+ and LR-). The same parameters were obtained for the previously reported tests (APRI, PD, P/ SD).

Finally, the diagnostic efficiency of LSM and SSM for the detection of large EV was calculated using the comparative analysis and ROC curve.

Results

In 60 patients (90.9 %), measurements were obtained according to the aforementioned quality criteria. Six (9.1%) of the 66 patients initially included in the study had an inconclusive result for SSM (IQR > 30% or success rate < 60%), and were henceforth excluded. Of the 6 patients who had an inconclusive SSM 3 had a small spleen diameter (< 9 cm) and the other 3 had a very high body mass index (BMI > 30), which made the technique unfeasible using the M probe".

Among the latter 60 patients, 3 (5%) had an invalid result for LSM. In 2 of them it was probably due to a high BMI, and in the remaining patient LSM failed because of the interposition of colonic gas.

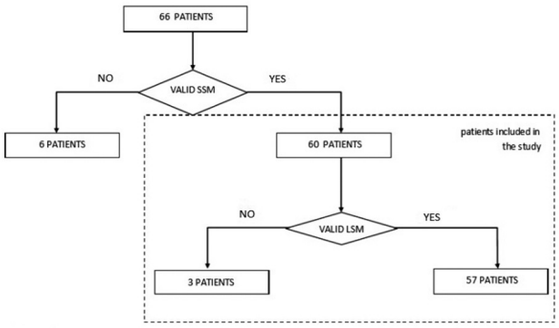

Fig. 1.

This information is summarized in Figure 1.

Baseline characteristics

Among the 60 patients analyzed, the etiology of chronic liver disease included hepatitis C virus (HCV) for 31 patients (51.6%), alcohol (OH) for 13 patients (21.7%), hepatitis B virus (HBV) for 6 patients (10%), nonalcoholic steatohepatitis (NASH) for 5 patients (8.3%), primary biliary cirrhosis (PBC) for 1 patient (1.7%), and cryptogenicity for one patient (1.7%); no etiology data were available for the 3 remaining subjects.

Table 1. — **Baseline characteristics, biochemical parameters and indirect measurements of portal hypertension**

	Patients included (n=60)	NO EV (n=32)	EV(n=28)
Age (years)	59,6±2,4	58,1 ± 2,0	61,4± 2,2
M:F	46:14	27:5	19:9
TB (mg/dL)	1,4±,09	1,1± 0,2	1,6± 0,2
AST	38,9±6,4	36,5± 3,6	41,8± 6,05
ALT	29,9±2,1	29,8± 3,0	29,9± 4,4
AST/ALT	1,4±0,2	1,3±0,1	1,5± 0,1
Albumin (g/L)	3,5±0,60	3,6± 0,1	3,4± 0,1
Cr	0,9±0,3	0,7± 0,04	0,9± 0,03
INR	1,2±0,2	1,1± 0,02	1,2± 0,03
Platelets(X10 9/l)	143±12,3	153± 15,7	132± 29,3
MELD	9,5±3,2	8,7 ±3,0	10,3±3,1
CHILD-PUGH	6.1 ± 1,3	5,9 ± 1,2	6,4±1,4
SS (Kpa)	51,2±6,1	40,2± 3,7	63,8± 2,7
LS(KPa)	27,7±3,9	21,1± 3,1	35,7± 4,0
Splenomegaly	44 (73%)	19/32 (59%)	25/28 (89%)
PD (mm)	12,1±0,7	12,1± 0,3	12,2± 0,3
APRI	0,92±0,1	0,8± 0,2	1,02± 0,1
P / SD	1114±214,2	1266± 131,3	963± 229,5

EV : esophageal varices M: Male, F : Female, TB : Total bilirrubin, Cr : Creatinine, AS : Spleen Stiffness, LS : Liver Stiffness, PD : Portal diameter, APRI : AST/platelet count, P/SD : Platelet count / Spleen diameter index.

Mean age was 59.6 (± 11.4) years, and 46 patients (76.7%) were male. Mean values included: TB 1.3 mg/dL (± 0.98), Cr 0.8 mg/dL (± 0.29), albumin 3.5 g/L (± 0.6), PC 143 x 10^9/L ± 123.8 x 10^9, and INR 1.2 (± 0.2).

Forty-six of 60 patients (76.7%) were Child-Pugh functional class A, 12 patients (20%) were class B, and 2 patients (3.3%) were class C, with an overall mean Child-Pugh score of 6.15 ± 1.3 points. Mean score on the MELD scale was 9.5 ± 3.2. This information is summarized in Table 1.

Twenty-eight patients (46%) had EV in the UGE procedure performed. Sixteen patients (26.7%) had grade-I varices, 7 patients (11.7%) had grade-II/ III, and 5 (8.3%) had grade-IV varices. EV were considered large when above grade I, which represents 20% of the total.

Transient elastography and indirect asessment of PHT

Ultrasound parameters and SSM were analyzed for all patients. Three of them had no reliable LS measurements as previously mentioned. The basal ultrasound, biochemistry, and elastography parameters are shown in Table 1.

Regarding elastography measurements, these ranged from 13.7 to 75 KPa for SS, and from 9 to 75 KPa for LS. SS was significantly higher in patients with EV as compared to patients without EV (63.8 vs 40.2; p=0.00). These differences were also found in LS (35.7 vs 21.2; p=0.0) (Figure 2). Amongst the 57 patients with valid LSM, 8 patients (14%) fulfilled the Baveno VI criteria, all of them with compensated cirrhosis. Of these 8 patients, 7 (87.5%) had no EV in the UGE procedure performed, and 1 (12.5%) did have EV.

For the multivariate analysis we took into account all variables that were associated with the presence of EV in the univariate analysis (TB, platelet count, SS, LS, SD, APRI, P/SD, MELD). Among these variables, only SS and splenomegaly were predictive of EV (Table 2).

The AUROC calculated for SS and LS measurements was 0.80 and 0.74, respectively (Figures 3 and 4). A

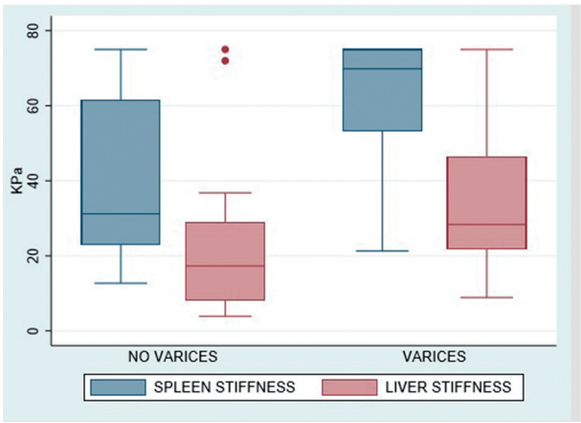

Fig. 2.

Table 2. — **Univariate and multivariate analysis by logistic regression for prediction of presence of EV**

	Univariate analysis			Multivariate analysis		
	OR (95%CI)		P value	OR (95%CI)		P value
Age (years)	1,02	(0,98-1,07)	0,20			
M:F	2,55	(0,73-8,84)	0,13			
TB (mg/dL)	**4,08 (1,50-11,07)**		**0,01**	1,30	(0,50-2,60)	0,57
AST	1,00	(0,97-1,02)	0,80			
ALT	1,00	(0,98-1,02)	0,50			
AST/ALT	1,60	(0,67-3,85)	0,06			
Albumin (g/L)	0,59	(0,24-1,42)	0,19			
Cr	0,90	(0,16-5,10)	0, 52			
INR	11,27 (0,37-34,3)		0,37			
Platelets(X10 9/l)	**0,90**	(0,91-0,97)	**0,02**	1,00	(0,90-1,01)	0,70
MELD	1,24	(1.01-1.52)	**0,02**	0,27	(0,90-1,01)	0, 80
CHILD-PUGH	1,40	(0,54-4,04)	0,08			
SS (Kpa)	**1,03**	**(1.01-1.10)**	**0,00**	**1,05**	**(1,04-1,10)**	**0,004**
LS(KPa)	**1,04**	**(1,01-1,07)**	**0,01**	1,01	(0,90-1,10)	0,70
Splenomegaly	**12,10 (3,03-48,89)**		**0,00**	**6,10 (1,4-29,5)**		**0,017**
PD (mm)	0,96	(0,70-1,30)	0,80			
APRI	**4,40 (1,30-14,80)**		**0,03**	1,30 (0,30-4,1)		0,67
P / SD	**0,90**	**(0,94-0,99)**	**0,009**	1,01 (0,90-1,0)		0,20

EV : Esophageal varices, M : Male, F : Female, TB : Total bilirrubin, Cr : Creatinine, SS : Spleen Stiffness, LS : Liver Stiffness, PD : Portal diameter. APRI : AST/platelet count, P/SD : Platelet count / Spleen diameter index, OR : Odds ratio, CI (Confidence interval).

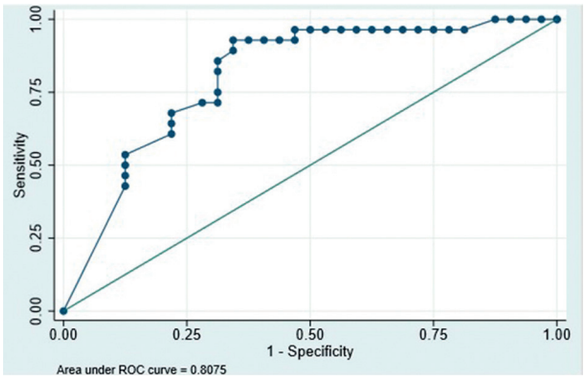

Fig. 3.

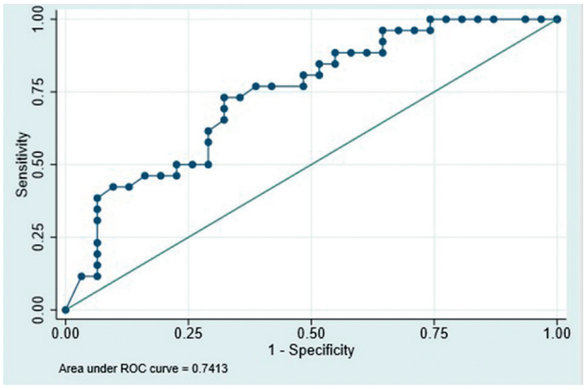

Fig. 4.

Table 3. — **Differences in diagnostic performance to identify EV. AUROC: Under the ROC curve**

	Cut-off	AUROC	S (%)	Sp(%)	LR+	LR-	PPV(%)	NPV(%)	% Correctly classified
SS (kPa)	48	0,80	85,7	68,7	2,7	0,2	70,5	84,6	76,7%
LS(kPa)	23,3	0,74	73,0	67,7	2,3	0,4	65,5	75,0	70,1%
PD (cm)	12,5	0,51	42,3	65,6	1,2	0,9	45,4	56,0	55,2%
APRI	0,63	0,65	64,2	59,3	1,5	0,6	56,2	64,2	61,7%
P/SD	794	0,70	75	75	3	0,3	72,4	77,4	75%

Prevalence EV : 46%. S : Sensibility, Sp : Specificity, LR : Likelihood ratio PPV : Positive predictive value, NPV : Negative predictive value.

cut-off point of 48 KPa in the SS curve had S=85.7%, Sp=68.7%, LR+=2.7, and LR-=0.2. In the LS curve, a cut-off point of 23.3 KPa had S=73%, Sp=67.7%, LR+=2.3, and LR-=0.4.

The AUROC for the APRI and P/SD indexes was 0.65 and 0.7, respectively. All values estimated using ROC curves are shown in Table 3.

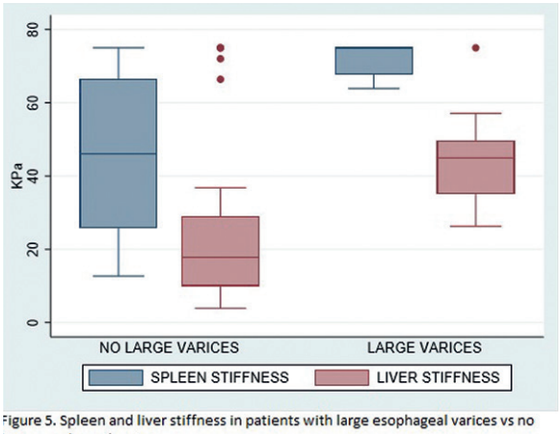

Figure 5. Spleen and liver stiffness in patients with large esophageal varices vs no large esophageal varices

Fig. 5.

As for the effectiveness of elastography in detecting large EV, SS was significantly higher among patients with large VE (71.6 ± 1.32 KPa) than in those with non- large EV (57.9 ± 4.1 KPa) ; p=0.02. The same thing occurred for LS, which was higher in patients with large EV (44.7 ± 4.4 KPa vs 30.0 ± 5.5 KPa) ; p=0.01 (Figure 5).

The AUROC of SS for the detection of large EV was calculated as 0.84, with the best cut-off being obtained at 63.9 KPa (S=100% and Sp=70.7%, LR+ of 3.4, LR- of 0.0). For LS, the AUROC was 0.86. With a cut-off point of 35.3 KPa, S was 80% and Sp was 80.6%, with LR+ of 4.1 and LR- of 0.2. All these results are shown in Table 4.

Discussion

Development of PHT in liver cirrhosis may lead to the development of EV, whose prevalence in such cases is around 50%. UGE is currently the preferred screening method to detect EV (1). Several noninvasive methods have been identified to detect the development of PHT or EV, but so far have failed to show enough reliability in this role (11).

Our data support the hypothesis that SSM may be a useful noninvasive tool for the identification of cirrhotic patients at risk of having EV at UGE, showing a good S with moderate Sp.

In contrast to LSM, SSM-related quality parameters remain to be standardized (12, 13). Of all 66 patients initially included in the study, we managed to perform SSM consistently on 60 (90.1%). Only 73.3% of them showed splenomegaly, which indicates that SSM can be performed in a reliable way, even in patients without an enlarged spleen. This success rate is possibly related to the use of ultrasound control in most cases. Only 3 of all failed cases were due to an excessively small spleen diameter. In the other 3 patients SSM failed because of obesity or intestinal gas interposition, which suggests that SSM is likely to have the same limitations as LSM in this setting (14,15) In clinical practice FibroScan cannot currently perform measurements above 75 KPa. Whether this cut-off value is enough for SSM remains to be established.

In recent years, the usefulness of noninvasive parameters (initially used to estimate the severity of hepatic fibrosis) to detect PHT or EV has drawn increasing attention. Biochemical parameters such as platelet count or the APRI index have been used, among others (16,17,18). In our data, when the APRI index was used to calculate an AUROC in order to predict the presence of EV the result was 0,63, having 61,7% of patients correctly classified. These results are similar to those found in previous publications (19,20,21)

Ultrasound parameters have also been used for this purpose (22). Splenomegaly is a common finding in patients with cirrhosis and PHT, but its relationship with EV has been controversial in previous studies (23,24). In our data, splenomegaly was significantly more common in the group of patients with EV (89% vs 59%). Despite this, a high number of patients with splenomegaly had no EV in the UGE procedure performed. This indicates that while a certain relationship between presence of splenomegaly and EV seems plausible, the former is not enough to predict the presence of the latter.

The combination of biochemistry and ultrasonography parameters improves their diagnostic performance in order to detect PHT or EV. The P/SD index was initially reported in 2003 by Giannini (25,26). In that study this index showed an AUROC of 0.86 to detect the presence of EV. With a cut-off of 909, S was 92% and Sp was 67%. In our study, the AUROC for P/SD was 0.7. With a cut-off point of 909, S was 75% and Sp was 63%.

A relationship between LSM by FibroScan and PHT gradient in cirrhotic patients has been reported (27). To evaluate the relationship between LS and presence of EV, Casterá et al reported a cut-off of 21.5 KPa with a S of 76% and a Sp of 78% (21).

Moreover, the Baveno VI criteria were recently published (7), pointing out that compensated patients with liver stiffness < 20 kPa and platelet count > 150,000 have a very low risk of having varices requiring treatment, and may thus avoid screening endoscopy. In our study 8 patients fulfilled the Baveno VI criteria. Of these, 7 had no EV and could have safely avoided a screening UGE procedure. Only one patient fulfilled the criteria and had

Table 4. — **Diagnostic efficacy of elastography for detection of large EV**

	Cut-off	AUROC	S(%)	Sp(%)	LR+	LR-	PPV(%)	NPV(%)	% Correctly classified
SS (KPa)	63,9	0,84	100	70,7	3,4	0,0	46,1	100	76,7
LS (KPa)	35,3	0,86	80,0	80,6	4,1	0,2	47,0	95,0	80,7

large EV in the UGE procedure performed. These figures support its use in clinical practice to identify patients who can safely avoid screening endoscopy, although in our study only a small number of patients had a platelet count > 150,000 and met these criteria.

The usefulness of the SSM has also been studied against the aforementioned hypothesis that the development of PHT leads to an increase in portal flow and vascular resistance, as well as an increase in angiogenesis and splenic fibrosis (5).

A study previously published by Stefanescu *et al.* (5) proved, with figures that were very similar to ours, that in a group of 135 cirrhotic patients LS and SS measurements were significantly different between patients with and without EV.

A recent meta-analysis addressing the accuracy of SSM have showed that SSM is significantly better than LSM for identifying the presence of EV (28).

According to what has been published so far (28,29,30), SS showed in our analysis the best results for the detection of EV. LS obtained an AUROC of 0.7 using a cut-off point of 23.3 KPa, and SS obtained an AUROC of 0.8 using a cut-off point > 48 KPa.

Our study also showed that only SSM and splenomegaly were considered predictive of EV after the multivariate analysis.

Sharma *et al*. (8) carried out a study in 174 patients with chronic liver disease of any etiology, in whom they also identified SS (with a cut-off of 40.8 KPa) as the best noninvasive test for the screening of EV. This study also showed differences in SS values between patients with large EV and those without EV (56 vs 49 KPa).

When our elastography data were analyzed for the identification of large EV, LS and SS had AUROC values above 0.8. A relevant finding in our study is that, with an SSM greater than 63.3 KPa, all patients had large EV with a S and NPV of 100%.

Despite the fact that in our data the Baveno VI criteria showed very good results, this was limited by the small number of patients that fulfilled said criteria, as it is only applicable to patients with a platelet count > 150,000. In contrast, SSM does not have these limitations, and therefore could be of help in these cases.

As in the aforementioned publications (28,30,31), when we compared the different noninvasive parameters to evaluate the presence of EV, SS came first and LS came second in terms of diagnostic performance. These data suggest that SSM may be a suitable and applicable tool for the screening of EV with high sensitivity but lower specificity, thus performing better to rule out the presence of EV. The lower sensitivity obtained in our study could be related to the smaller number of patients included, and a population of patients with liver disease of different etiologies.

The strengths of this research include a representative cohort of patients with cirrhosis with different etiologies, comparable in age and sex in both groups, with a rate of patients with EV of almost 50%. SSM was performed blindly by someone skilled in the technique, thus reducing any possible biases, and the high success rate (90.2%) likely was closely related to the use of ultrasound in choosing the site for the FibroScan test.

The limitations of our study are the smaller sample size in comparison with other published studies, the use of some retrospective data for the analysis, potential interobserver variability in estimating the size of EV, and finally the absence of direct PHT gradient measurements to be added to the comparison between groups. While it is true that including patients with different etiologies may lead to heterogeneous results, we aimed to perform a study in patients resembling those who are usually seen in routine clinical practice.

In conclusion, the results of this study show that SSM appears to be a useful tool to rule out the presence of EV and large EV, and which will likely complement other noninvasive methods, having a role in the screening of EV in cirrhotic patients. In spite of this, further studies are needed to strengthen its role in clinical practice.

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