Liste des abréviations

LSM	Liver stiffness measurement
Doppler-US	Doppler-ultrasound
VTQ	Virtual Touch Quantification (Siemens Medical Solutions, Mountain View, CA)
SSI	Supersonic Shear Imaging (Supersonic Imagine, Aix-en-Provence, France)
Rs	Spearman's rank correlation coefficient
AUROC	Area under Receiver Operating Characteristic
kPa	kilo Pascal
m/s	meter/second

Plan

Doppler ultrasonography devices, including elastography, allow for accurate screening for severe liver fibrosis.

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ABSTRACT

Objectives:

Advanced chronic liver disease is frequent yet largely underdiagnosed. Doppler-US is a common examination and we recently identified three simple Doppler-US signs associated with severe liver fibrosis. Recent Doppler-US devices include elastography modules, allowing for liver stiffness measurement (LSM). Our aim was to assess whether the use of elastography following positive simple Doppler-US signs improves the detection of severe liver fibrosis in a single Doppler-US examination.

Methods:

514 patients with chronic liver disease who consecutively underwent percutaneous liver biopsy were included in the study. All patients had a Doppler-US examination and LSM with Virtual Touch Quantification (VTQ) on the same day as a liver biopsy. A subset of 326 patients also had LSM with 2D shear wave elastography (SSI). Severe fibrosis was defined as Metavir F≥3 on liver biopsy.

Results:

Multivariate analysis confirmed our three simple Doppler-US signs (liver surface irregularity, splenomegaly ≥110mm, and demodulation of hepatic veins) as independently associated with severe fibrosis. The presence of at least one of these three signs showed 85.6% sensitivity and 36.1% specificity for the diagnosis of severe liver fibrosis. Using VTQ (≥1.59m/s) where there was a positive Doppler-US sign increased the specificity to 80.8%,

at the cost of a decrease in sensitivity (73.7%). Similar results were obtained with SSI (≥9.5kPa), with 73.3% specificity and 81.5% sensitivity.

Conclusions:

Elastography improves the accuracy of Doppler-US in the detection of severe fibrosis. This two-step procedure will help radiologists to accurately identify patients who need to be referred to specialist hepatologists during routine Doppler-US examinations.

Highlights:

- Three simple Doppler-US signs are associated with severe liver fibrosis.
- Combined together, these simple signs are sensitive but they lack specificity.
- Doppler-US devices now include elastography modules allowing liver stiffness measurement.
- Using elastography when the simple Doppler-US signs are present improves the diagnostic accuracy.
- This approach represents an attractive procedure for the diagnostic of advanced liver diseases.

Keywords:

Liver; Cirrhosis; Diagnostic; Ultrasonography; Elastography.

INTRODUCTION

Chronic liver disease usually remains asymptomatic for many years and advanced stages are only diagnosed late, when life-threatening complications occur. Early diagnosis of liver fibrosis is therefore important for identifying patients with severe hepatic disease and for delaying its development by introducing specific treatments. Liver biopsy remains the basis for the diagnosis and staging of liver fibrosis **[1]**. However, due to the high burden of chronic liver diseases, this invasive method cannot be used as a first-line procedure. Non-invasive tests of liver fibrosis have recently been developed. Blood tests (FibroMeter, Fibrotest, CirrhoMeter) **[2-4]** and liver stiffness measurement (LSM) with Fibroscan (Echosens, Paris, France) using Vibration Controlled Transient Elastography **[5, 6]** produce good results. Unfortunately, these tools are usually employed after the patient has been referred to a hepatologist for a biological abnormality or a symptom suggestive of chronic liver disease. Therefore, the bulk of the population with asymptomatic chronic liver disease does not derive any benefit from these diagnostic tools.

Before the rise of blood tests and LSM, ultrasound (B-mode and Doppler) parameters were shown in numerous studies to be able to diagnose liver fibrosis. Similarly, we have recently shown that severe liver fibrosis is associated with the presence of three simple Doppler-ultrasound (Doppler-US) signs: irregularity of liver surface, spleen diameter ≥110 mm, and demodulation of hepatic veins flow **[7]**. Since abdominal ultrasound is widely used to investigate numerous symptoms, it would appear to be an excellent tool for the detection of severe liver fibrosis. However, despite the fact that our three Doppler-US signs can diagnose

severe liver fibrosis with high sensitivity, they still lack specificity, and would cause a high rate of unnecessary referrals to specialists.

In recent years, most manufacturers have developed shear wave elastography modules in their Doppler-US devices. Specifically, Siemens have developed a point shear wave elastography using Acoustic Radiation Force Impulse (VTQ: Virtual Touch Quantification, Siemens Medical Solutions, Mountain View, CA) **[8]**, and Aixplorer have developed two-dimensional shear wave elastography (SSI: Supersonic Shear Imaging, Supersonic Imaging, Aix-en-Provence, France) **[9]**. These two elastography methods have previously shown very good diagnostic accuracy in the assessment of liver fibrosis in chronic liver disease **[10, 11]**. Therefore, VTQ and SSI would appear promising in terms of improving the specificity of the Doppler-US signs within the same examination, which would finally open up the possibility of more accurate detection of severe liver fibrosis.

The aim of our study was twofold: first, to validate the three Doppler-US signs for the diagnosis of severe liver fibrosis in a large cohort of patients; second, to assess whether the addition of elastography improves the specificity of Doppler-US diagnosis of severe liver fibrosis.

PATIENTS AND METHODS

Patients

All patients with chronic liver disease who consecutively underwent a liver biopsy in the Hepato-Gastroenterology Department of our institution from December 2009 to October 2016 were eligible for inclusion in the study. Exclusion criteria were: decompensated liver disease (jaundice, ascites, encephalopathy, variceal bleeding) and suspected or confirmed hepatocellular carcinoma. All patients gave written informed consent for the prospective cohort study and Institutional Review Board approval was obtained.

Liver histology

Liver biopsies were performed using Menghini's technique with a 1.4-1.6mm diameter needle. Biopsy specimens were fixed in a formalin-alcohol-acetic solution and embedded in paraffin; 5 µm- thick sections were then cut and stained with haematoxylin-eosin-saffron. Pathological examinations were performed by a senior specialist in hepatology (SM) and blinded for patient data. Liver fibrosis was staged from F0 to F4 according to the METAVIR scoring system: F0 = no fibrosis; F1 = portal fibrosis without septa; F2 = portal fibrosis and few septa; F3 = numerous septa without cirrhosis; F4 = cirrhosis. "Significant liver fibrosis" was defined as F ≥2 stages and "severe liver fibrosis" as F ≥3 stages. Liver biopsy was taken as the reference for the assessment of liver fibrosis and severe liver fibrosis was the primary diagnostic target of the study.

Ultrasound-Doppler and shear wave elastography examinations

Doppler-US examination and VTQ and SSI measurements were performed under fasting conditions on the day of the liver biopsy by a radiologist with more than 2 years in elastography practice, who was blinded to clinical and biological patient data.

Ultrasound-Doppler examination – A S2000 device (Siemens, Erlangen - Germany) or an Aixplorer (Supersonic imagine – Aix en Provence – France) were used for Abdominal examination. A 1-4 MHZ (S2000) and a 1-6 MHZ (Aixplorer) curved probe were used for abdominal examination and a 4-9 MHZ (S2000) and 2-10 MHZ (Aixplorer) linear probe for liver surface examination. The following parameters were recorded as described in a previous study **[7]**: a) *Liver surface irregularity* recorded on the anterior surface of the left lobe (Figure 1); b) *Maximum and mean portal flow velocity* taking care to obtain an angle between the Doppler beam and the long axis of the vessel below 60°; c) *Hepatic vein Doppler* was performed in the middle or the right hepatic vein at least 3cm from the inferior vena cava (Figure 1). Measurements were performed in normal breathing, with no deep end-inspiratory breath holding, which could result in a demodulation of the hepatic vein waveform. According to the classification of Bolondi *et al.,* hepatic vein waveforms were classified in 3 patterns: normal triphasic waveform, biphasic oscillation with disappearance of the reversed flow, and flat monophasic waveform **[12]**. Demodulation of hepatic vein flow has defined as to bi- or monophasic waveform; d) *Spleen length* was measured as the larger diameter in a cranio-caudal axis (Figure 1); e) *Collateral circulation* was defined as any patent umbilical vein or a left gastric vein with a reverse flow **[12]** or any abnormal vein; f) *Ascites*.

SSI – Only a subgroup of the patients included in the study have SSI measurement since this elastography technique has been available in our center only since May 2012. LSM with

SSI was performed on patients lying in dorsal or lateral decubitus with the right arm in abduction. The site of measurement was chosen, in the right lobe of the liver in a zone free of large vascular structures and at least 15mm below the capsule. An apnoea was mandatory. A homogeneous colour mapping of the stiffness was obtained. Liver stiffness measurement was calculated in a region of interest of at least 15mm in diameter positioned in this colour map (Figure 2). Ten measurements were obtained for each patient. Measurements were judged as failed when no or little signal was obtained in the SSI box for all acquisitions. Number of valid measurements was recorded. The result expressed in kilo Pascal (kPa) was the median of these valid measurements.

VTQ – LSM with VTQ was performed under the same conditions as SSI but apnoea requested for the measurement was shorter and a measurement in a quiet breathing was also possible. The examination was performed in the right lobe of the liver. Distance between capsule and measurement windows was at least 3cm. The region of interest where the measurement was performed was free of large vascular structures (Figure 2). Ten valid measurements were recorded and the result given in m/s was expressed as the median of these valid measurements.

FibroScan

LSM with FibroScan was performed using the standard M probe by a specialist nurse with an experience of more than 500 procedures, who was blinded to patient data. LSM was performed under fasting conditions on the day of VTQ and SSI measurements and of the liver biopsy. Examinations were conducted as recommended by the manufacturer (Figure 2) **[13]**. The result (kPa) was the median of 10 valid measurements.

Statistical analysis

Quantitative variables were expressed as mean ± standard deviation and compared using the Mann-Whitney test. Qualitative variables were expressed as percentages and compared using the Fisher's Exact Test. Correlations between quantitative variables were assessed using the Spearman's rank correlation coefficient (Rs). Diagnostic accuracy of elastography devices for binary diagnostic targets (significant F ≥2 fibrosis, severe F ≥3 fibrosis, or cirrhosis) was assessed using the Area under Receiver Operating Characteristic (AUROC) and the rate of correctly classified patients according to the highest Youden index that maximises sensitivity and specificity. We also used the new Obuchowski index which is a multinomial version of the AUROC adapted to ordinal references such as pathological fibrosis staging **[14, 15]**. The Obuchowski index ranges from 0 to 1 and the result can be interpreted as the probability that the non-invasive test will correctly rank two randomly chosen patients with different fibrosis stages. A p value <0.05 was considered as statistically significant. Statistical analyses were performed using SPSS version 18.0 software (IBM, Armonk, NY, USA). Results were reported in accordance with the recently published LiverFibroSTARD statements **[16]**.

RESULTS

Patients

A total of 514 patients referred to our institution for suspicion of liver disease were included in the study. Their characteristics at the time of inclusion are summarised in Table 1: 62.5% were male, mean age was 53.8±13.7 years, and mean body mass index was 29.8±6.3 kg/m2. Non-alcoholic fatty liver disease was the main cause of chronic liver disease (54.3%), followed by viral hepatitis (16.0%) and alcohol abuse (15.0%). Mean biopsy length was 32±11mm, 89.2% had ≥20 mm length and 95.7% had ≥15mm. The prevalence of significant fibrosis, severe fibrosis, and cirrhosis was 44.2%, 23.0%, and 7.8%, respectively. Failure of LSM occurred in 47 patients with Fibroscan (9.1%) and in only one patient with VTQ (0.2%, p <0.001 vs Fibroscan). As it has only been available since May 2012, SSI was performed in 326 patients of whom 3 had measurement failure (0.9%). None of the patients who experienced LSM failure with Fibroscan also experienced LSM failure with VTQ (and with SSI when available). An LSM result was available for all three devices in 292 patients (core group).

Validation of the three Doppler-ultrasound signs

The population in the present study did not overlap with the population in our previous work, in which we identified the three Doppler-US signs associated with severe liver fibrosis [7]. Among the seven Doppler-US signs evaluated in the 514 patients included in the study, three were independently associated with severe fibrosis (stepwise forward multivariate binary logistic regression): liver surface irregularity (1st step, p <0.001, Odd Ratio: 2.6 [1.7-4.1]), spleen length ≥110mm (2nd step, p <0001, Odd Ratio: 2.4 [1.6-3.8]), and demodulation of

hepatic vein flow (3rd step, p=0.004, Odd Ratio: 1.9 [1.2-3.1]). Table 2 shows the accuracy of the three Doppler-US signs, alone or in combination, in the diagnosis of severe fibrosis. As expected, the presence of at least one of the three signs provided the highest sensitivity (85.6%) but also the lowest specificity (36.1%).

Diagnostic accuracy of elastography devices

Fibroscan, VTQ and SSI results were well correlated (Figure 3): Fibroscan vs VTQ: Rs=0.588 (p <0.001); Fibroscan vs SSI: Rs=0.633 (p <0.001); VTQ vs SSI: Rs=0.539 (p <0.001). For each device, AUROCs and Obuchowski index in the core group were similar than those observed in the maximum population (Table 3). Direct comparison of AUROCs and Obuchowski index in the core group showed that Fibroscan was significantly more accurate than VTQ and SSI. There was no significant difference between the diagnostic accuracy of VTQ and SSI.

The best diagnostic cut-offs for significant fibrosis, severe fibrosis, and cirrhosis were determined for each device according to the highest Youden index in their maximum population. Diagnostic accuracy using these cut-offs is presented in Table 4 (core population) and in Table s1 (maximum population for each device). VTQ and SSI showed excellent >90% negative predictive value and very good >80% sensitivity for the diagnosis of severe fibrosis, making them of significant interest as second-line procedures to increase the specificity of the three simple Doppler-US signs.

Combination of Doppler-ultrasound with elastography

Table 5 shows the diagnostic accuracy of several strategies using the simple Doppler-US signs followed, if positive, by second-line elastography. Two strategies emerged as the most

suitable for clinical practice: LSM if ≥1 of the three Doppler-US signs was present, or LSM if liver surface irregularity was present or if spleen length was ≥110mm. These two strategies provided the highest sensitivity (75-80% according to both VTQ and the SSI population) and the highest negative predictive value (90-95%). Interestingly, compared to Doppler-US alone (Table 2), these strategies halved the rate of positive result and increased the positive predictive value from 30% to 45-55% while maintaining an excellent >90% negative predictive value, all of this coming at the cost of a 5-10% decrease in sensitivity. In other words, the addition of LSM to Doppler-US signs was of great interest from the point of view of decreasing the need for specialist referral (less positive result of the procedure) and decreasing unnecessary referrals (better positive predictive value). Interestingly, the two Doppler-US + LSM strategies led to very close results. Indeed, the strategy "LSM if liver surface irregularity present or spleen length ≥110mm" (Figure 4) appeared the most attractive clinical practice: it uses only simple ultrasound signs with no need for Doppler examination, which will greatly facilitate its everyday use.

DISCUSSION

Elastography is a non-invasive technique which shows good performance in the diagnosis of hepatic fibrosis. However, it is not possible perform elastography in the entire population, or even in all patients undergoing an abdominal ultrasound examination. Our strategy of concentrating on simple ultrasound signs and, if some of them are present, performing elastography measurements secondarily, has the advantage of avoiding the extension of elastography to all patients, retaining a simple initial test before carrying out more time-consuming measurements on a smaller number of subjects.

The multivariate analysis identified three simple Doppler-US signs as independently associated with severe liver fibrosis: liver surface irregularity, spleen length ≥110 mm, and demodulation of hepatic veins flow. This result confirms the finding of our previous study performed in a different set of patients [7]. These signs are among the most often reported in the literature for the diagnosis of severe fibrosis **[17, 18]**. Interestingly the addition of acoustic elastography after detection of these ultrasound signs dramatically improved the diagnostic performance, and especially specificity (36% to 81 %,) for a moderate cost in terms of sensitivity (86% to 74%).

The objective of a screening test for severe asymptomatic liver fibrosis is to find the largest amount of disease, which requires high sensitivity. However, on the other hand, it is important not to overestimate the diagnosis (low specificity), to prevent too many healthy people being referred to the hepatologist. In improving the PPV by 25%, elastography allows an acceptable PPV (45-55% depending on the strategy employed) for referring the patient to a hepatologist. In other words, one out of every two patients who are referred to a hepatologist has severe liver fibrosis. The selected elements must be chosen carefully

because they influence the number of diseases finally diagnosed but also the number of patients wrongly referred to a hepatologist. Finally, it is interesting to note that among the three selected ultrasound signs, demodulation of the hepatic veins is the one with the lowest performance. Therefore, the presence of one of the other two signs (irregularity of liver surface or spleen diameter ≥ 110 mm) leads to quite close results when followed by elastography, compared to taking into account one of the three signs (specificity 82% against 81% and sensitivity 72% against 74%). As Doppler measurements are a little bit more time consuming to perform than morphological examination, and because hepatic vein spectrum is highly sensible to breath, we suggested an alternative diagnostic strategy retaining only the two morphological signs (liver surface irregularity and splenomegaly) without the Doppler sign. This could be done easily and would facilitate the application of diagnostic procedure in daily practice, thus opening it up to tertiary centres as well as first-line general practitioners.

Even if we know that different cut-offs depending on the aetiology of hepatopathy can be suggested in the literature, we have voluntarily selected a single cut-off without regard to the probable subjacent aetiology for many reasons. First to allow its simple application by everyone without needing hepatological expertise. Secondly, being in a global diagnostic logic, we don't know if the patient examined has viral hepatitis, heavy alcohol consumption or liver steatosis. It isn't therefore appropriate to use variable cut-offs in our model. Finally, the cut-offs suggested in our study are in accordance with generally accepted cut-offs **[19, 20]**.

Our study has been performed on a pre-selected population with chronic liver disease. This is a limitation, because the high prevalence of severe hepatic fibrosis in our study population (23%) probably exaggerated the accuracy of our model. Indeed, the prevalence of severe fibrosis in the general population is estimated to be approximately 2-5% **[21]**. It will

therefore be necessary to confirm our results in a non-pre-selected population. Sensitivity and specificity are not influenced by the prevalence of the disease, so the same results are expected in the general population. However, due to lower prevalence, a better NPV should be obtained, albeit with a poorer PPV.

As limitation we have also to notice that SSI measurements were available only in a subgroup of the study population, since the technique was available in our centre only since May 2012. However, the number of measurements was important, in 326 of the 514 included patients, and the results of SSI technique are in the same range than other elastography technique.

Based on our study results, we suggest to systematically examine the liver (irregular surface) and the spleen (length ≥110 mm) during ultrasound examination of the abdomen and/or the pelvis. Then, if either of these two signs is positive, a liver stiffness measurement using elastography should be performed. Finally, patients with elevated value of elastography should be referred to a specialized hepatologist. In addition to patients who undergo ultrasound in a context of a suspected chronic liver disease, we propose to extend this procedure to patient undergoing imaging for a non-liver-related condition. The cost in time is probably acceptable for the physician, but implementing this procedure will lead to further review and consultations. It will be necessary to assess whether this is cost-effective, both in terms of complications avoided and extension of lifespan.

In conclusion, performing liver elastography after checking simple morphological ultrasound signs allows to efficiently identify asymptomatic patients with severe liver fibrosis. Since abdominal ultrasound is widely used in a variety of situations and in connection with various symptoms, it could present an opportunity to diagnose asymptomatic liver disease more efficiently.

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TABLES

Table I : Patient characteristics at inclusion

	All (n=514)	Core group (n=292)	Others (n=222)	p
Age (years)	53.8 ± 13.7	53.6 ± 13.9	54.2 ± 13.5	0.625
Male sex (%)	62.5	66.8	56.8	0.022
BMI (kg/m^2)	29.8 ± 6.3	29.8 ± 6.1	29.8 ± 6.6	0.914
Cause of CLD (%):				0.326
- NAFLD	54.3	55.8	52.3	
- Viral hepatitis	16.0	13.4	19.4	
- Alcohol	15.0	15.8	14.0	
- Others	14.8	15.1	14.4	
Biopsy length (mm)	32 ± 11	29 ± 9	35 ± 14	<0.001
Fibrosis stage (%):				0.028
- 0	21.8	19.5	24.8	
- 1	34.0	39.4	27.0	
- 2	21.2	21.6	20.7	
- 3	15.2	12.7	18.5	
- 4	7.8	6.8	9.0	
AST (IU/l)	55 ± 45	56 ± 51	52 ± 36	0.676
ALT (IU/l)	71 ± 64	73 ± 67	69 ± 60	0.299
GammaGT (IU/l)	160 ± 261	150 ± 237	172 ± 290	0.187
Alkaline Phophatases (IU/l)	91 ± 76	92 ± 84	89 ± 64	0.683
Bilirubin (µmol/l)	12 ± 7	13 ± 7	10 ± 7	<0.001
Prothrombin time (%)	97 ± 12	97 ± 13	98 ± 12	0.024
Platelets (G/l)	218 ± 68	217 ± 64	219 ± 72	0.744
Albumin (g/l)	41.5 ± 4.2	41.1 ± 4.2	42.0 ± 4.2	0.036

BMI: body mass index; CLD: cause of chronic liver disease; NAFLD: non-alcoholic fatty liver disease; AST: aspartate aminotransferase; ALT: alanine aminotransferase

Table II : Accuracy of the three Doppler-ultrasound signs for the diagnosis of severe liver fibrosis in the 514 included patients

Doppler-ultrasound criterion	DA	Se	Spe	NPV	PPV	-LR	+LR	OR	Positive rate [a]
Liver surface irregularity	68.3	55.1	72.2	84.4	37.1	0.62	2.0	3.2	34.0
Spleen length >110 mm	60.1	65.3	58.6	85.0	32.0	0.59	1.6	2.7	46.9
Demodulation of HVF	68.7	44.9	75.8	82.2	35.6	0.73	1.9	2.5	29.0
Liver surface irregularity or spleen length >110 mm	53.1	83.9	43.9	90.2	30.8	0.37	1.5	4.1	62.5
Liver surface irregularity or demodulation of HVF	59.9	66.9	57.8	85.4	32.1	0.57	1.6	2.8	47.9
Spleen length >110 mm or demodulation of HVF	53.9	80.5	46.0	88.8	30.7	0.42	1.5	3.5	60.1
≥1 of the 3 signs	47.5	85.6	36.1	89.4	28.5	0.40	1.3	3.4	68.9
≥2 of the 3 signs	72.0	60.2	75.5	86.4	42.3	0.53	2.5	4.7	32.7
All 3 signs	77.6	19.5	94.9	79.8	53.5	0.85	3.9	4.6	8.4

[a] Rate of positive Doppler-ultrasound criterion in patients (i.e. rate of patients requiring referral to specialist for further investigations)

DA: diagnostic accuracy (i.e. rate of correctly classified patients, %); Se: sensitivity (%); Spe: specificity (%); NPV: negative predictive value (%); PPV: positive predictive value (%), -LR: negative likelihood ratio; +LR: positive likelihood ratio; OR: Odd Ratio; HVF: hepatic vein flow

Table III : AUROC and Obuchowski index of Fibroscan, VTQ, and SSI in their maximum population and in the core group, the latter allowing for direct comparison between the three elastography devices

Population	Device		AUROC			Obuchowski index
			F ≥2	F ≥3	F 4	
Maximal population for each device	Fibroscan	(n=467)	0.826 ± 0.019	0.890 ± 0.016	0.949 ± 0.014	0.839 ± 0.013
	VTQ	(n=513)	0.755 ± 0.021	0.812 ± 0.021	0.884 ± 0.021	0.774 ± 0.015
	SSI	(n=323)	0.747 ± 0.027	0.795 ± 0.025	0.834 ± 0.027	0.757 ± 0.021
Core group (n=292)	Fibroscan		0.849 ± 0.022	0.918 ± 0.018	0.934 ± 0.021	0.856 ± 0.014
	VTQ		0.755 ± 0.029	0.838 ± 0.026	0.896 ± 0.028	0.775 ± 0.021
	SSI		0.787 ± 0.027	0.826 ± 0.024	0.862 ± 0.025	0.792 ± 0.020
	Comparison (p):					
	Fibroscan vs VTQ		<0.001	0.002	0.020	<0.001
	Fibroscan vs SSI		0.015	<0.001	0.006	0.003
	VTQ vs SSI		0.293	0.604	0.257	0.482

Table IV : Accuracy of Fibroscan, VTQ and SSI for the binary diagnosis of significant fibrosis, severe fibrosis, and cirrhosis in the core population (n=292)

Diagnostic target	Device	Cut-off	DA	Se	Spe	NPV	PPV	-LR	+LR	OR
F ≥2	FS	9.9	76.0	73.3	77.9	80.7	69.8	0.34	3.3	9.7
	VTQ	1.29	71.2	78.3	66.3	81.4	61.8	0.33	2.3	7.1
	SSI	8.3	72.9	84.2	65.1	85.5	62.7	0.24	2.4	9.9
F ≥3	FS	10.4	79.8	93.0	76.6	97.8	49.1	0.09	4.0	43.4
	VTQ	1.59	76.4	80.7	75.3	94.1	44.2	0.26	3.3	12.8
	SSI	9.5	72.3	91.2	67.7	97.0	40.6	0.13	2.8	21.8
F4	FS	16.0	88.7	90.0	88.6	99.2	36.7	0.11	7.9	70.0
	VTQ	2.19	86.0	85.0	86.0	98.7	30.9	0.17	6.1	34.9
	SSI	10.3	68.2	100.0	65.8	100.0	17.7	0.00	2.9	NA

DA: diagnostic accuracy (i.e. rate of correctly classified patients, %); Se: sensitivity (%); Spe: specificity (%); NPV: negative predictive value (%); PPV: positive predictive value (%), -LR: negative likelihood ratio; +LR: positive likelihood ratio; OR: Odd Ratio

Table V : Accuracy for the diagnostic of severe liver fibrosis of strategies using Doppler-US signs followed, if positive, by liver elastography

Population	First-line Doppler-US criterion	Second-line elastography	DA	Se	Spe	NPV	PPV	-LR	+LR	OR	Positive rate [a]
VTQ	Liver surface irregularity	VTQ ≥1.59 m/s	79.9	50.8	88.6	85.8	57.1	0.55	4.5	8.0	20.5
available	Spleen length >110 mm	VTQ ≥1.59 m/s	79.5	54.2	87.1	86.4	55.7	0.53	4.2	8.0	22.4
(n=513)	Demodulation of HVF	VTQ ≥1.59 m/s	80.1	41.5	91.6	84.0	59.8	0.64	5.0	7.8	16.0
	Liver surface irregularity or spleen length >110 mm	***VTQ ≥1.59 m/s***	***79.9***	***72.0***	***82.3***	***90.8***	***54.8***	***0.34***	***4.1***	***12.0***	***30.2***
	Liver surface irregularity or demodulation of HVF	VTQ ≥1.59 m/s	79.3	61.0	84.8	87.9	54.5	0.46	4.0	8.7	25.7
	Spleen length >110 mm or demodulation of HVF	VTQ ≥1.59 m/s	79.9	68.6	83.3	89.9	55.1	0.38	4.1	10.9	28.7
	≥1 of the 3 signs	***VTQ ≥1.59 m/s***	***79.1***	***73.7***	***80.8***	***91.1***	***53.4***	***0.33***	***3.8***	***11.8***	***31.8***
	≥2 of the 3 signs	VTQ ≥1.59 m/s	80.9	54.2	88.9	86.7	59.3	0.51	4.9	9.5	21.1
	All 3 signs	VTQ ≥1.59 m/s	79.5	18.6	97.7	80.1	71.0	0.83	8.2	9.8	6.0
SSI	Liver surface irregularity	SSI ≥9.5 kPa	79.9	55.4	86.0	88.4	50.0	0.52	4.0	7.7	22.3
available	Spleen length >110 mm	SSI ≥9.5 kPa	76.8	64.6	79.8	90.0	44.7	0.44	3.2	7.2	29.1
(n=323)	Demodulation of HVF	SSI ≥9.5 kPa	80.2	41.5	89.9	85.9	50.9	0.65	4.1	6.3	16.4
	Liver surface irregularity or spleen length >110 mm	***SSI ≥9.5 kPa***	***76.5***	***80.0***	***75.6***	***93.8***	***45.2***	***0.26***	***3.3***	***12.4***	***35.6***
	Liver surface irregularity or demodulation of HVF	SSI ≥9.5 kPa	78.3	69.2	80.6	91.2	47.4	0.38	3.6	9.4	29.4
	Spleen length >110 mm or demodulation of HVF	SSI ≥9.5 kPa	75.9	73.8	76.4	92.1	44.0	0.34	3.1	9.1	33.7
	≥1 of the 3 signs	***SSI ≥9.5 kPa***	***74.9***	***81.5***	***73.3***	***94.0***	***43.4***	***0.25***	***3.0***	***12.1***	***37.8***
	≥2 of the 3 signs	SSI ≥9.5 kPa	80.8	60.0	86.0	89.5	52.0	0.46	4.3	9.3	23.2
	All 3 signs	SSI ≥9.5 kPa	81.1	20.0	96.5	82.7	59.1	0.83	5.7	6.9	6.8

[a] Rate of positive result for the procedure in patients, (i.e., rate of patients requiring referral to specialist for further investigations)

DA: diagnostic accuracy (i.e. rate of correctly classified patients, %); Se: sensitivity (%); Spe: specificity (%); NPV: negative predictive value (%); PPV: positive predictive value (%), -LR: negative likelihood ratio; +LR: positive likelihood ratio; OR: Odd Ratio

FIGURES

Figure 1 : Illustration of the 3 selected sonographic signs:
A) Liver surface irregularity (white arrowheads), B) Demodulation of hepatic vein flow (biphasic oscillation), C) Spleen length >110 mm

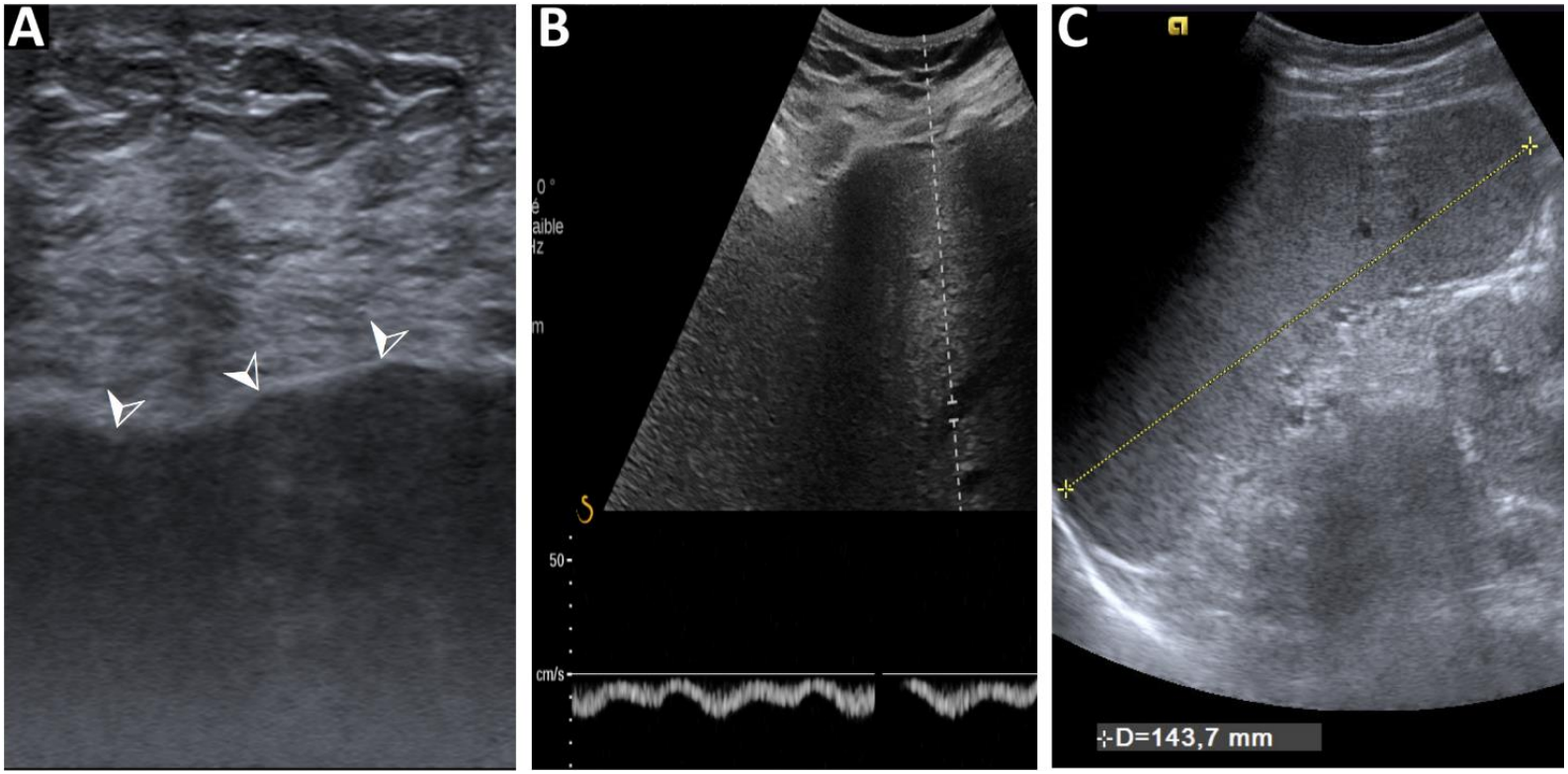


Figure 2: Illustration of the 3 techniques of elastography used: A) Fibroscan (Echosens), B), VTQ (Siemens), C) SSI (Aixplorer)

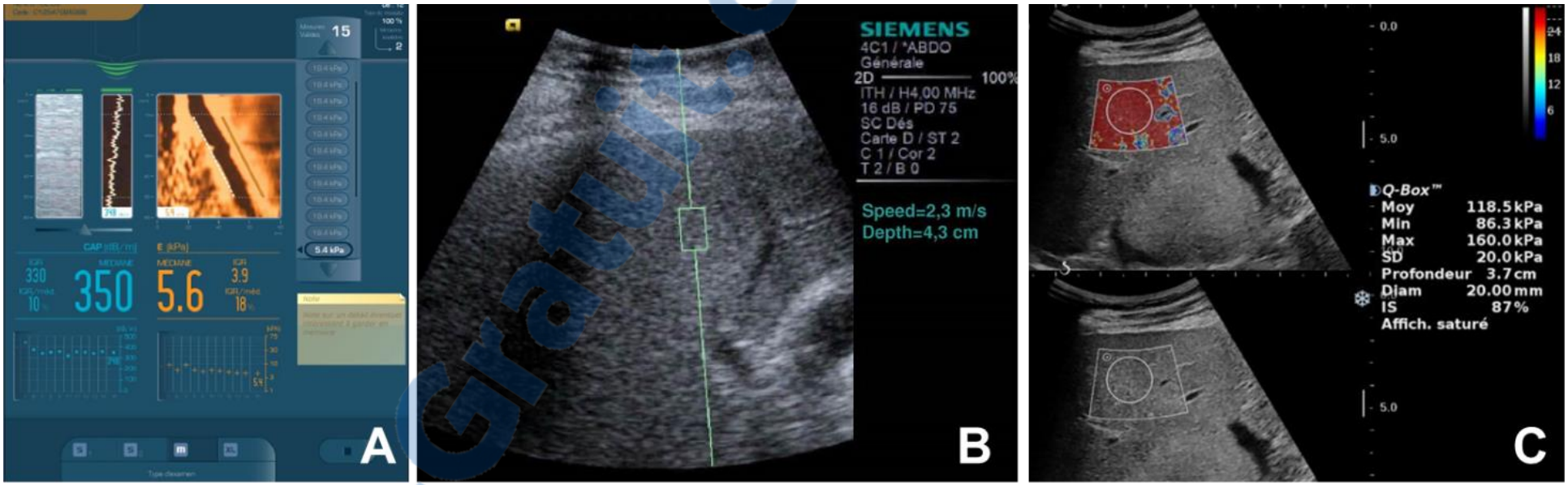
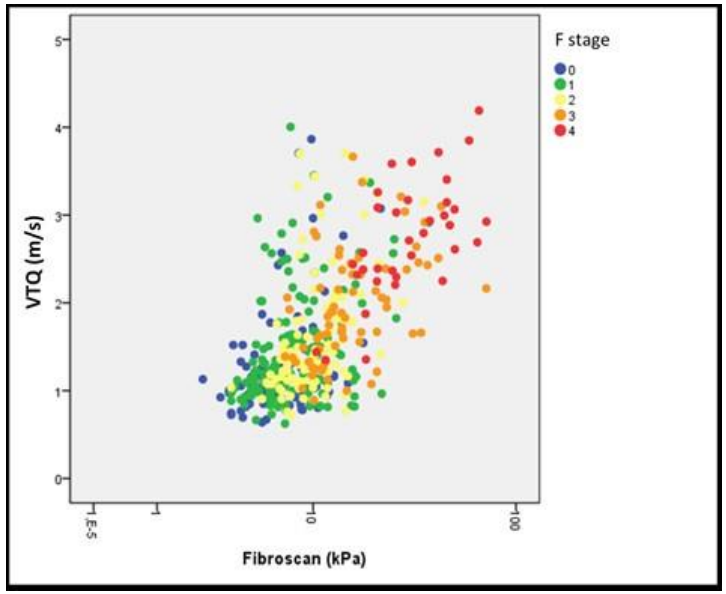
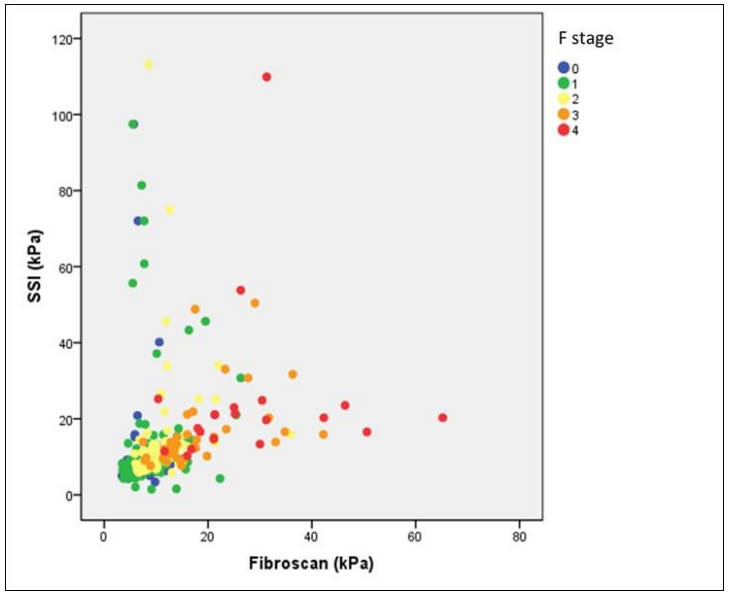


Figure 3 : Correlation between Fibroscan, VTQ, and SSI results





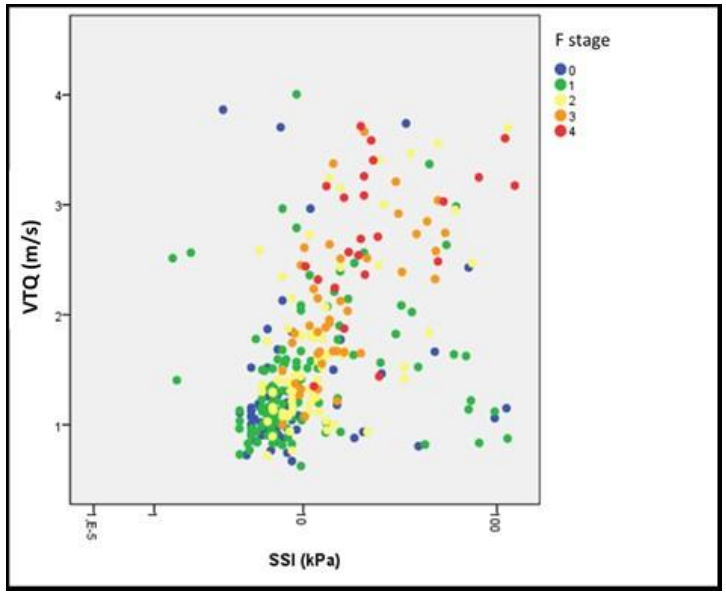
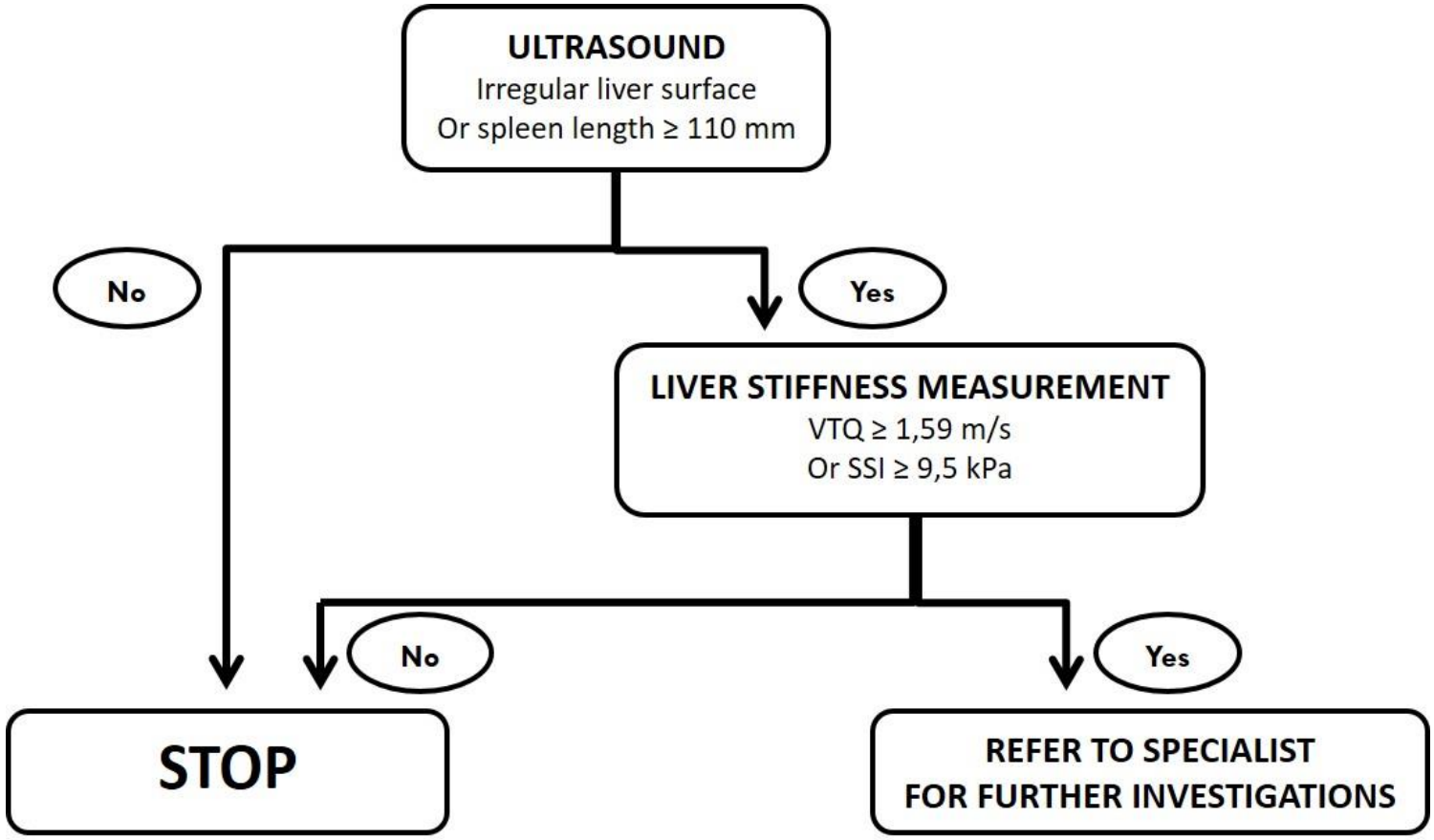


Figure 4 : Practical algorithm for the detection of severe liver fibrosis with the new ultrasound devices including an elastography module



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SUPPLEMENTARY MATERIAL

Table s1 : Accuracy of Fibroscan, VTQ and SSI for the binary diagnosis of significant fibrosis, severe fibrosis, and cirrhosis in the maximum population for each device

Diagnostic target	Device	Patients (n)	Cut-off	DA	Se	Spe	NPV	PPV	-LR	+LR	OR
F ≥2	FS	467	9.9	75.2	73.4	76.5	78.3	71.4	0.35	3.1	9.0
	VTQ	513	1.29	69.6	78.9	62.2	78.8	62.4	0.34	2.1	6.1
	SSI	323	8.3	70.0	85.0	59.5	85.0	59.5	0.25	2.1	8.3
F ≥3	FS	467	10.4	77.7	87.6	74.9	95.4	50.3	0.17	3.5	21.1
	VTQ	513	1.59	73.7	80.5	71.6	92.5	45.9	0.27	2.8	10.4
	SSI	323	9.5	68.7	92.3	62.8	97.0	38.5	0.12	2.5	20.3
F4	FS	467	16.0	88.2	94.3	87.7	99.5	38.4	0.07	7.7	118.0
	VTQ	513	2.19	82.8	90.0	82.2	99.0	30.0	0.12	5.1	41.7
	SSI	323	10.3	63.8	100.0	61.0	100.0	16.4	0.00	2.6	NA

DA: diagnostic accuracy (i.e. rate of correctly classified patients, %); Se: sensitivity (%); Spe: specificity (%); NPV: negative predictive value (%); PPV: positive predictive value (%), -LR: negative likelihood ratio; +LR: positive likelihood ratio; OR: Odd Ratio

DELAHAYE Jean

Les appareils d'échographie Doppler, incluant l'élastographie, permettent un dépistage précis de la fibrose hépatique sévère.

RÉSUMÉ

Introduction :
Les maladies chroniques du foie à un stade avancé sont fréquentes mais largement sous-diagnostiquées. L'échographie-doppler est un examen courant et nous avons récemment identifié trois signes échographiques simples associés à une fibrose hépatique sévère. Les appareils récents d'échographie-doppler comprennent des modules d'élastographie, ce qui permet de mesurer la dureté du foie (LSM). Notre objectif est d'évaluer si l'utilisation de l'élastographie après mise en évidence de ces signes échographiques simples améliore la détection de la fibrose hépatique sévère lors d'un seul examen échographique.
Méthodes :
514 patients consécutifs atteints d'une maladie hépatique chronique ayant subi une biopsie hépatique percutanée ont été inclus dans l'étude. Tous les patients ont subi un examen d'échographie-doppler et une élastometrie par la méthode VTQ (Virtual Touch Quantification) le même jour qu'une biopsie du foie. Un sous-ensemble de 326 patients ont également bénéficié d'une élastometrie avec la méthode SSI (2D shear wave elastography). La fibrose sévère a été définie pour les scores Metavir F≥ 3 sur la biopsie du foie.
Résultats :
L'analyse multivariée a confirmé que nos trois signes échographiques simples (irrégularité de la surface du foie, splénomégalie ≥ 110 mm, et démodulation des veines hépatiques) sont indépendamment associés à une fibrose sévère. La présence d'au moins un de ces trois signes a montré une sensibilité de 85,6 % et une spécificité de 36,1 % pour le diagnostic de fibrose hépatique sévère. L'utilisation de VTQ (≥ 1.59 m/s) lorsqu'un signe échographique était positif a augmenté la spécificité à 80,8 %, au prix d'une diminution de la sensibilité (73,7 %). Des résultats similaires ont été obtenus avec SSI (≥ 9.5 kPa), avec une spécificité de 73,3 % et une sensibilité de 81,5 %.
Conclusion :
L'élastographie améliore la précision de l'échographie-doppler dans la détection de la fibrose hépatique sévère. Cette procédure en deux étapes aidera les radiologues à identifier avec précision les patients qui doivent être référés à des hépatologues spécialisés lors des examens échographiques de routine.

Mots-clés : Foie ; Cirrhose ; Diagnostic ; Echographie ; Elastographie.

Doppler ultrasonography devices, including elastography, allow for accurate screening for severe liver fibrosis.

ABSTRACT

Introduction:
Advanced chronic liver disease is frequent yet largely underdiagnosed. Doppler-US is a common examination and we recently identified three simple Doppler-US signs associated with severe liver fibrosis. Recent Doppler-US devices include elastography modules, allowing for liver stiffness measurement (LSM). Our aim was to assess whether the use of elastography following positive simple Doppler-US signs improves the detection of severe liver fibrosis in a single Doppler-US examination.
Methods:
514 patients with chronic liver disease who consecutively underwent percutaneous liver biopsy were included in the study. All patients had a Doppler-US examination and LSM with Virtual Touch Quantification (VTQ) on the same day as a liver biopsy. A subset of 326 patients also had LSM with 2D shear wave elastography (SSI). Severe fibrosis was defined as Metavir F≥3 on liver biopsy.
Results:
Multivariate analysis confirmed our three simple Doppler-US signs (liver surface irregularity, splenomegaly ≥110mm, and demodulation of hepatic veins) as independently associated with severe fibrosis. The presence of at least one of these three signs showed 85.6 % sensitivity and 36.1% specificity for the diagnosis of severe liver fibrosis. Using VTQ (≥1.59m/s) where there was a positive Doppler-US sign increased the specificity to 80.8%, at the cost of a decrease in sensitivity (73.7 %). Similar results were obtained with SSI (≥9.5kPa), with 73.3% specificity and 81.5% sensitivity.
Conclusion:
Elastography improves the accuracy of Doppler-US in the detection of severe liver fibrosis. This two-step procedure will help radiologists to accurately identify patients who need to be referred to specialist hepatologists during routine Doppler-US examinations.

Keywords : Liver ; Cirrhosis ; Diagnostic ; Ultrasonography ; Elastography.

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