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Fibroscan® and Shear Wave correlated well in hepatic fibrosis evaluation of patients with chronic liver diseases "in real life situation"

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Abstract

Background: A new noninvasive medical device based on ultrasound elastography such as the Shear Wave Elastography (SWE) was designed in order to measure the liver hardness. The purpose of this work was to evaluate the correlation of the results of the liver elasticity measurements obtained by Fibroscan® (FS) and SWE for patients with chronic liver diseases.

Methods: Between January and October 2017, the patients who were followed during this period of time underwent noninvasive assessments of liver fibrosis by SWE in the intercostal spaces during abdominal ultrasound procedures and/or FS. The correlation between FS and SWE was estimated and tested at a 0.05 significance level.

Results: Four hundred and seventy-six patients were included in this study. The main etiologies of chronic liver disease were non alcoholic fatty disease (NAFLD), chronic viral hepatitis B (HBV) and chronic viral hepatitis C (HCV). All patients underwent a SWE and 167 among them underwent a FS procedure. The patients who were followed revealed a median FS measurement of 5.80 kpa (Q25 = 4.90 kPa; Q75 = 8 kPa) and a median SWE measurement of 7.00 kPa (Q25 = 6.10 kPa; Q75 = 8.10 kPa). We could observe a significant correlation between the FS and SWE measurements (0.49; P = .001) in the total cohort. The average absolute difference between the measurements of these 2 methods was of 2.54 kPa (sd = 3.39). There was no significant correlation for patients with NAFLD no matter whether they presented with signs of suspected non alcoholic steatohepatitis (NASH) or not (R = 0.20; P = .108). All patients intending to perform the examination were able to undergo the SWE, allowing 33.3% of the patients who failed the FS to have a noninvasive evaluation of their fibrosis.

Conclusion: The SWE technique proved to be as efficient as the FS one for the evaluation of the liver fibrosis in real life situation.

Abbreviations: 2D-SWE = two-dimensional Shear Wave elastography, ALAT = alanine aminotransferase, AP = alkaline phosphatases, ASAT = aspartate aminotransferase, AUROC = area under the receiver operating characteristic curve, BMI = body mass index, FS = fibroscan®, GGT = gamma-glutamyl transpeptidase, GHPSO = groupe hospitalier public du sud de l'oise, HBV = hepatitis B, HCV = hepatitis C, IQR = interquartile range, kPa = kilopascals, LSM = liver stiffness measurement, NAFLD = non alcoholic fatty liver disease, NASH = non alcoholic steatohepatitis, ROI = region of interest, SWE = shear wave elastography, TE = transient elastography.

Keywords: chronic liver diseases, elastography Shear Wave®, Fibroscan®, real life

1. Introduction

The chronic liver disease is a major public health problem with an estimated 1.5 million deaths per year worldwide due to a cirrhosis and its complications.[1] Indeed, chronic inflammation of the liver, whatever the cause, can lead to the formation of fibrosis, the ultimate stage of which is cirrhosis. Cirrhosis, a true precancerous state, provides the basis for hepatocellular carcinoma, even though it may occur in a noncirrhotic liver. Therefore, an accurate assessment of the degree of hepatic fibrosis is essential for a long-term follow-up and a treatment when there is a chronic liver disease.[2] The liver biopsy remains the gold standard for in order to evaluate a liver fibrosis.[3] It has largely been replaced because of its invasiveness by non -invasive evaluations of the liver fibrosis, first

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for patients suffering from chronic hepatitis C (HCV). Several composite biological scores have been developed, the most widely used of which is Fibrotest®.[4] Then, the impulse elastometry or Fibroscan® (FS) was developed. This technique allows an evaluation of the liver elasticity through a mechanical vibration. The development of an XL probe has made it possible to reduce the failure rate for obese patients, but this technique remains limited in cases when there is ascites.. Thus, in order to overcome this shortcoming, the Shear Wave Elastography (SWE) which is also known as supersonic or 2-dimensional (2D) shear imaging, was developed by the Aixplorer unit.[5] The SWE has the advantage of providing images of the liver stiffness in real time because the shear waves are generated by ultrasound pushes. The SWE is providing a real time quantitative map of the liver stiffness.[6–8] The aim of our study was to analyse the correlation of liver stiffness measurements (LSM) through FS and SWE procedures in real life situations where a large population of patients with chronic liver diseases triggered by different causes was followed in a non academic hospital in real life situations.

2. Patients and Methods

2.1. Patients

Our prospective study lasted 10 months. From January to October 2017, 476 consecutive patients followed in the Hepatology and Gastroenterology department were included in the study after giving their consent to take part in it and if they met the following criteria: 1) at least be 18 years old; 2) presenting with chronic liver disease due to various causes; 3) underwent SWE and/or FS. For each patient, the following demographic and clinico-biological data were reported: the age, gender, cause of liver diseases, body mass index (BMI), existence or not of cirrhosis, prothrombin time, transaminases, alkaline phosphatases (AP) and gamma-glutamyl transpeptidase activities (GGT) the platelet count and the total bilirubin concentration. In contrast, the patients with an obvious cirrhosis, decompensated cirrhosis (Child-Pugh B or C), acute liver disease and the ones who refused to take part in the study were excluded.

3. Methods

3.1. Liver stiffness measurement

The SWE and FS tests were performed after at least 6 hours of fasting with a less- than- 6 months interval between the 2 examinations. A Transient Elastography (TE) was performed by a FS 502 Touch model (Echosens, Paris, France) according to the previously described methods.[9] The examinations were performed by 3 board certified hepatologists using the M probe. The TE was performed in the right lobe of the liver through the intercostal space. Once the measurement area was located, the examiner pressed the probe button to start the acquisition. The measurement depth was calculated to be between 25 and 65 mm. A total of 10 valid measurements were performed with each patient. The results were expressed in kilopascals (kPa). We resorted to only the successful LSM defined by an interquartile range (IQR)/median ratio < 0.3.[10–12] The failure rate was defined with the acquisition of <10 valid measurements.

3.2. Two dimensional-Shear Wave Elastography (2D-SWE)

The 2D-SWE was performed using the SuperSonic Imagine Aixplorer Ultimate ultrasound system and the Xc6-1 transducer (Aixplorer, Aix-en-Provence, France). Three to five measurements were performed on each patient, and the average value expressed in kPa was used as the representative measurement.[13] The patient was positioned flat on his back with his right arm under his head if possible to clear the right hypochondrium. The measurements were performed at the level of the right hepatic lobe using an approach from the right anterior axillary line. The region of acquisition interest (ROI) was selected at least 1 cm below the liver capsule, without significant vessels if possible. The measurements were performed under gentle breath-holds without deep inspirations. Almost all the 5 examinations were performed by an experienced radiologist, previously trained in the use of the Shear Wave technique. A SWE measurement was considered valid if the IQR was estimated to be <30% of the median value. A technical failure was defined as the inability to obtain at least 3 valid measurements.[14]

4. Operational definitions

A chronic liver disease was defined by persistent liver test abnormalities associated with an identified cause (alcohol, virus...) for at least six months.

A significant fibrosis corresponded to $F \geq 2$ fibrosis. The threshold values of 7.7 kPa and 13 kPa had been retained at the FS to define a significant fibrosis and cirrhosis respectively in the absence of sufficient liver biopsy data which is the "gold standard".[15]

5. Ethical considerations

All patients gave their consent to participate in the study. The examinations were performed blinded to the outcome of other examinations. These examinations were performed as parts of the patients' usual care. The protocol was in accordance with the Helsinki Declaration and approved by the ethics committee of groupe hospitalier public du sud de l'oise (GHPSO).

6. Data analysis

A data analysis was performed with the R software and the R Studio interface.[16] Some differences between quantitative variables were estimated with Student t-test with Welch correlation at the 0.05 significance level. The Bland Altman analysis was used to assess the degree of agreement between the 2 methods (SWE and FS) with a 95% confidence interval.

7. Results

7.1. Characteristic of patients

During the study period, 834 patients had consulted in the hospital in the hepatology and gastroenterology Department as outpatients and 476 patients with chronic liver diseases were included (Fig. 1). The average age of the patients was 60 years and 56% of patients were men. The demographic, clinical and laboratory parameters of 476 patients in this study was summarised in Table 1.

7.2. Liver stiffness measurements and their correlation

A SWE was performed on all patients. The median LSM by 2D-SWE was of 7.00 kPa (Q25 = 6.10 kPa; Q75 = 8.10 kPa).

This median LSM was of 7.1 kPa and of 13.3 kPa in cirrhotic and noncirrhotic patients respectively ($P = .0085$).

A FS was performed on 167 patients. The median LSM by FS was of 5.80 kpa (Q25 = 4.90 kPa; Q75 = 8 kPa.). A FS had been performed in patients with viral hepatitis B (HBV), HCV and NAFLD respectively in 52.1%, 37.4% and 26.6% of the cases.

The LSM by TE with M probe was not technically feasible for 78 (33.3%) NAFLD patients. In the total patient cohort, the correlation of LSM between TE and SWE (Fig. 2) showed a significant association ($R = 0.47$; $P < .001$).

In addition, Bland and Altman analysis showed a degree of agreement or concordance of the results (95% of liver elasticity values were within ± 2 standard deviations of the average difference) between the 2 methods SWE and FS with a 95% confidence interval. This method of analysis is reported in Figure 3.

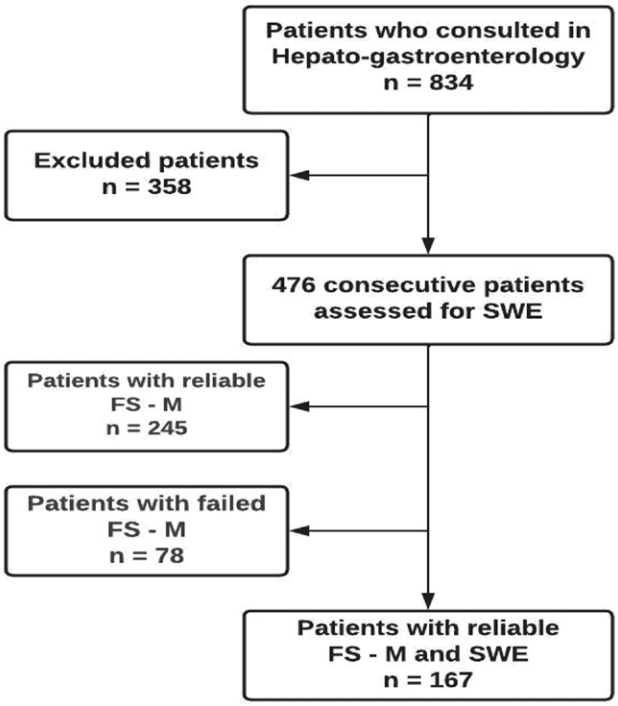

Figure 1. Flow chart of included patients.

Table 1

Characteristics of included patients and etiologies of liver disease.

Men	276 (56.1%)
Mean age	60 ± 13.8
Cirrhotic patients	43 (9%)
Body mass index (kg/m2)	31.42 (26–42.3)
Median prothrombin time (% of normal)	93.9 (32–142)
Median platelets (G/L)	221 (27–929)
Median ASAT	32.1 (5–158)
Median ALAT	33 (5–185)
Median total bilirubin (μM/L)	9.9 (2.5–66)
Median glutamyl transpeptidase (IU/L)	56.9 (5.2–644)
Median Alkalin phosphatase (IU/L)	73.3 (8.1–249)
NAFLD	235 (49.4%)
Chronic hepatitis B	94 (19.7%)
Chronic hepatitis C	91 (19.1%)

ASAT = aspartate aminotransferase, ALAT = alanine aminotransferase, NAFLD = non alcoholic fatty liver disease.

7.3. Liver stiffness measurements in relationship with the cause of chronic disease

The median LSM by 2D-SWE and TE was respectively 6.1 ± 1.3 and 5.9 ± 2.2 for patients with chronic HBV; 7.8 ± 3 and 10.9 ± 12.9 in patients with chronic HCV; 7.6 ± 2.6 and 7 ± 4.2 for patients with NAFLD.There was a significant correlation of LSM by TE and 2D-SWE for patients with chronic HBV (R = 0.49; P < .001; Fig. 4) and chronic HCV (R = 0.50; P < .001; Fig. 5).

However, there was no significant correlation for patients with NAFLD no matter whether they presented with signs of suspected NASH or not (R = 0.20; P = .108; Fig. 6).

8. Discussion

The Liver biopsy remains the gold standard for the evaluation of the liver fibrosis. It has been replaced because of its numerous limitations, first in chronic HCV and then in other diseases.[3] This costly invasive procedure with rare but sometimes severe complications is difficult to repeat in order to regularly follow the evolution of fibrosis in patients.[17,18] Moreover, the histological analysis is not the best option due to its high inter- and intraobserver variability and sampling fluctuations inherent to its technique. Given all these limitations, a few reliable and reproducible noninvasive tests especially the LSM by elastography- have been developed to assess a liver fibrosis. The diagnostic performance of the FS has been compared in the literature to the liver biopsy.

Several studies reported an excellent diagnostic performance of the TE for the detection of advanced fibrosis and cirrhosis in chronic HCV infection, with areas under the receiver operating characteristic curve (AUROCs) of 0.88–0.99.[9,19,20] Some similar results were subsequently reported by other studies in chronic HCV and HBV infections.[21–28]

Several meta analyses have confirmed the excellent diagnostic accuracy of the TE for diagnosing cirrhosis (AUROC, 0.93–0.96), even better for detecting moderate fibrosis (F2–F4) (AUROC, 0.83–0.88), with cutoffs ranging from 7.0–7.9 kPa for the diagnosis of moderate fibrosis (F2–F4) and 11.3–15.6 kPa for the diagnosis of cirrhosis (F4).[15,29–31]

A meta-analysis of the TE performance using the M probe in NAFLD (n = 854) reported a pooled sensitivity and specificity of 79% and 75% for F2–F4, 85% and 82% for F3–F4, and 92% and 92% for stage F4.[32] The pooled AUROC was not reported, though AUROC ranges for the included studies were 0.79–0.87 for F2–F4, 0.76–0.98 for F3–F4, and 0.91–0.99 for stage F4. The introduction of the XL probe has led to more reliable results than with the M probe in the cases of overweight or obese patients.[33]

In our « real life situation study » we found a fairly good correlation between the liver stiffness measurement performed with FS and share wave techniques. One limitation of our study relies on the fact that we were not equipped with the "XL" probe which contrasted with a population presenting a chronic hepatopathy due to NAFLD with or without NASH in 50% of the cases. The factors associated with stiffness measurement failures by FS in our study could be explained by a high BMI (average BMI at 31.42 kg/m2), and the unavailability of the "XL" probe which was recently developed and dedicated to overweight patients. Our results were superior to those reported by Foucher et al who had a 5% measurement failure rate and 15% of cases of noninterpretable results, with obesity as the main limiting factor.[34]

All patients intending to perform the examination were able to undergo a SWE elastography,allowing 33.3% of patients with a failed FS to have a noninvasive evaluation of fibrosis in our study.

The average SWE values in noncirrhotic and cirrhotic patients were 7.1 kPa and 13.3 kPa, respectively (P = .0085). These results corroborate those of the meta-analysis by Hermann et al who found an optimal threshold of 13.5 kPa for the diagnosis of cirrhosis.[35]The results obtained confirm that SWE allowed the diagnosis of cirrhosis and, therefore, the identification of patients who should be monitored for the development of different complications and treated.

In chronic liver diseases, the evaluation of hepatic fibrosis is an important parameter in the treatment and monitoring decisions of patients suffering from a chronic liver disease.

In our study, the use of the SWE method for the elasticity assessment was compared to the FS validated for this purpose. The use of the SWE method offers the advantage of being integrated into a conventional ultrasound system. It can be performed during a standard B-mode liver ultrasound, which is commonly used for the follow-ups of patients suffering from a chronic liver disease. In addition, the advantages offered by the SWE include the ability to choose the positioning of the ROI in the liver, thus avoiding interfering structures such as large blood

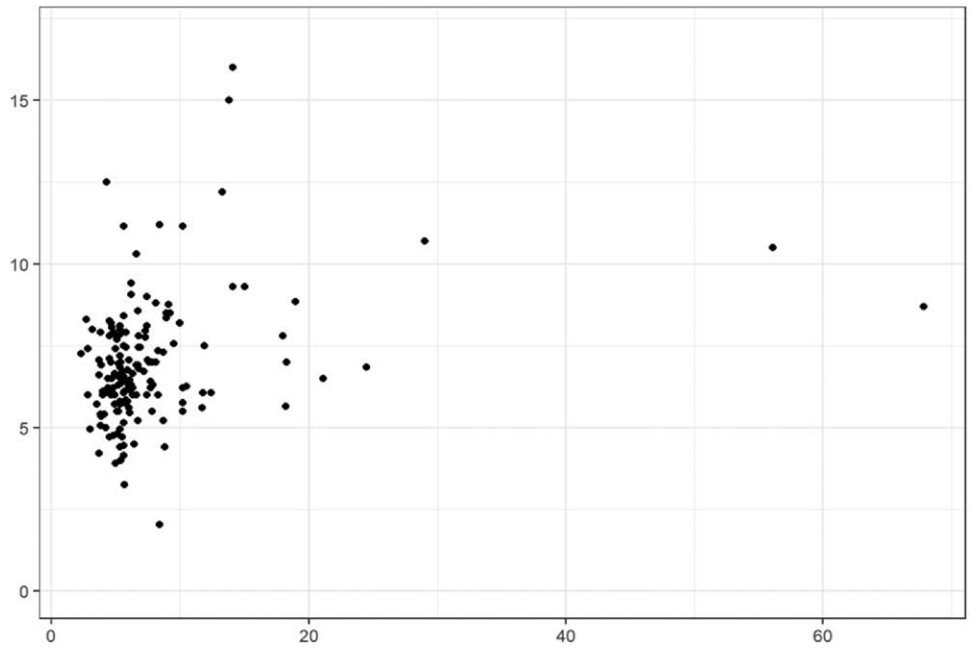

Figure 2. correlation of FS and SWE measurement values in the total cohort.

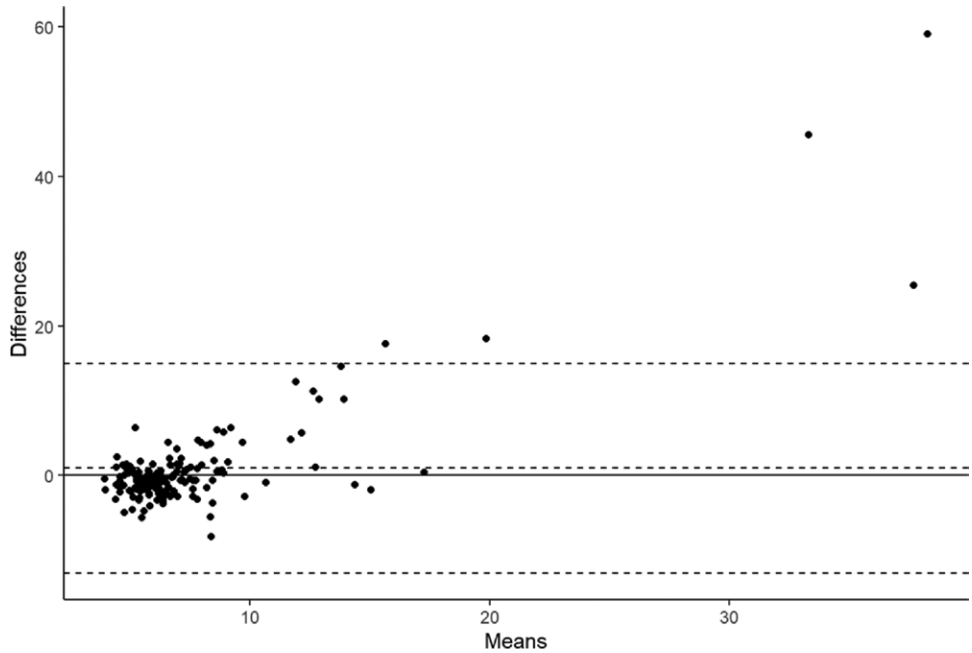

Figure 3. Blant and Altman analysis of FS and SWE methods.

vessels and bile ducts. In addition, the SWE method is not influenced by obesity or ascites.

Our study, conducted in real life situations, showing patients suffering from a chronic liver disease and consecutively followed up in medical consultation, allowed us to evaluate the correlation of the elasticity measurements obtained between the FS and the SWE methods on the one hand and the level of agreement between these 2 methods on the other hand.

A significant linear correlation (R = 0.47; P < .001) was observed between the LSM obtained by FS and SWE techniques regardless of the cause of the liver disease.

This Pearson correlation had been strengthened in our study by Blant Altman analysis, which enhanced the concordance between the FS and SWE methods. Therefore, the SWE in the light of the data in the literature constitutes a new physical method tool for the evaluation of the fibrosis.[35,36]

In the subgroup of HBV-infected patients, there was a significant correlation (R = 0.486; P < .001), as well as in the subgroup of HCV-infected patients (R = 0.501 P = .003).

These "real life situation " results confirmed the data of the literature.[35,36]

More recent studies have evaluated the SWE method in patients with a chronic HBV infection and found diagnostic accuracies at AUROC levels of 88–92%, 93–95% and 95–98% for the diagnosis of significant fibrosis, severe fibrosis and cirrhosis respectively.[37,38] In the meta-analysis by Hermannet al.,

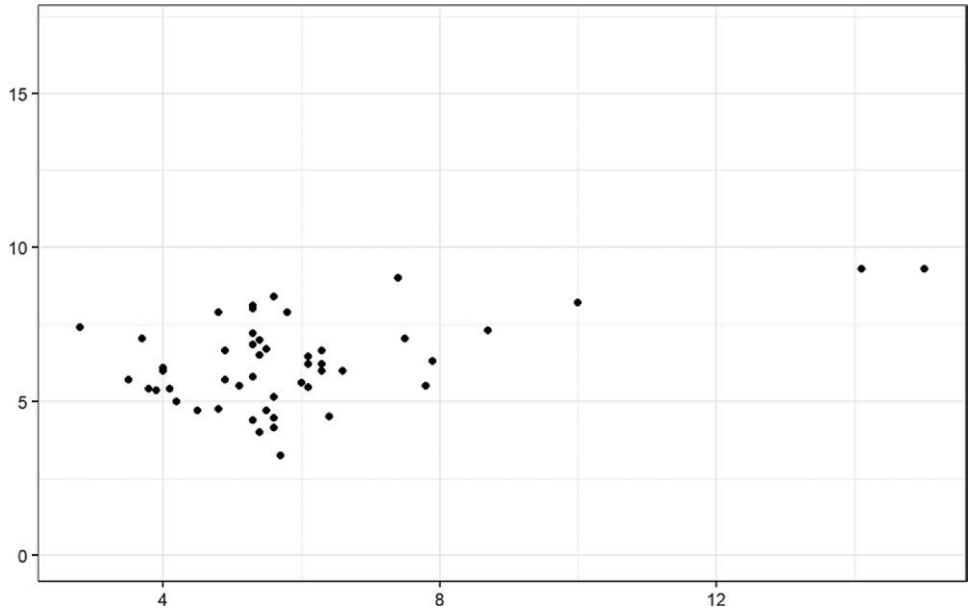

Figure 4. Correlation median LSM by FS and SWE in chronic HBV patients.

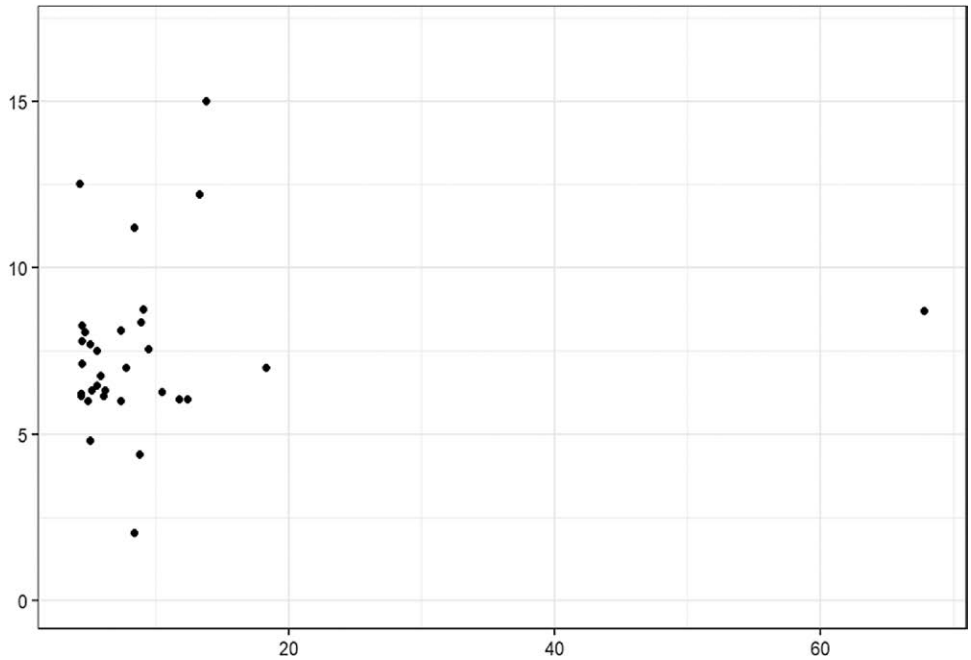

Figure 5. Correlation median LSM by FS and SWE in chronic HCV patients.

the AUROCs were 91%, 93%, and 96% for the diagnosis of significant fibrosis, severe fibrosis, and cirrhosis, respectively.[35]

In addition, the SWE method was better than the FS one for the diagnosis of all stages of the fibrosis and significantly better for the diagnosis of significant fibrosis and cirrhosis ($P < .001$ and $P = .007$, respectively).

Zeng et al also showed that the diagnostic performance of the SWE method was significantly better than the FS one.[38]

One explanation could be the increased ROI of the SWE method which allows the examination of a larger area of the liver than the FS method.

In a study of 121 HCV patients comparing the SWE method to the FS one with histology as the reference method, an excellent diagnostic accuracy of the SWE was found for all stages of fibrosis (AUROC: 92%, 98% and 98% for the diagnosis of significant fibrosis, severe fibrosis and cirrhosis). This diagnostic performance of the SWE was significantly superior to the one of the FS.[8] This corroborates quite well the results of Hermann et al with AUROCs of 86%, 92% and 93% for the diagnosis of significant fibrosis, severe fibrosis and cirrhosis respectively.[35]

The AUROC of 0.022–0.084 (95% confidence interval) of the SWE was greater than the AUROC of the FS for diagnosing a significant fibrosis ($P = .001$) and 0.003–0.034 for diagnosing a cirrhosis ($P = .022$)for the whole patients in the meta-analysis by Hermann et al.[35]

This difference was more significant for patients suffering from HBV. The optimal thresholds were 7.1, 9.2, and 13.5 kPa, respectively. When comparing the SWE to elastography in this

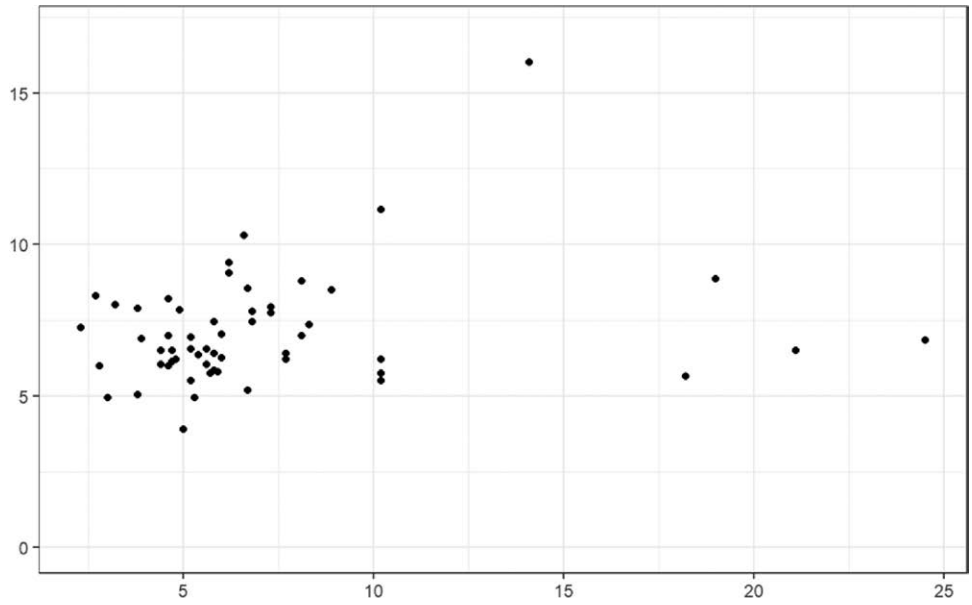

Figure 6. Correlation median LSM by FS and SWE in NAFLD patients.

meta-analysis, no significant difference was found between the 2 methods if the FS quality criteria were met.[39] The SWE has the advantage of being simple to use, and with a good clinical application. The SWE proved to be less expensive (<15.000 euros) than the FS and could be a good alternative for assessing the liver elasticity in developing countries with a very high HBV endemicity.

In the subpopulation of patients with NAFLD with or without NASH, our study did not find a significant correlation between the SWE and FS methods (R = 0.20; P = .108). This could be explained on the one hand by the small number of patients who benefited from a FS in this subpopulation (26.6%), and on the other hand by hepatic steatosis and hepatic inflammation in NAFLD patients with NASH which would influence the result in the direction of an increase in the liver hardness. For de Ledinghen et al, several factors other than a fibrosis influence the result of the FS in the sense of an increase in the liver hardness which favours false positive results: hepatic inflammation, steatosis, cholestasis, heart failure, postprandial condition. These factors must therefore be taken into account when interpreting the results.[40] For Olteanu et al, the BMI, the level of necrotic-inflammatory activity and hepatic steatosis, significantly influence the correlation between the FS and SWE values (p respectively at 0.0020; 0.001; 0.004).[41]

Conversely, Herman et al reported a good significant correlation with the FS and SWE values in the assessment of a liver fibrosis in NAFLD patients.[35]

Our study has several limitations. The "real life" data were generated during routine patient care.

First, it was not possible to assess the liver elasticity through FS and SWE techniques on the same day for each patient.

Then, the unavailability of the XL probe did not allow the assessment of the liver elasticity in the cases of overweight patients.

Finally, the small number of patients who underwent a liver biopsy was also a limitation in the absence of comparison to a reference examination.

9. Conclusions

In our study performed in « real life situations », it appears clearly that the SWE is as powerful as the FS in order to evaluate the hepatic elasticity. This new technique has the advantage of being integrated in a conventional ultrasound system. It can be performed during a standard liver ultrasound in B mode.

It could be an alternative for hepatology departments which are not equipped with a FS with an XL probe for the examination of patients with a high BMI.

In the light of the results of this work, studies become therefore a necessity and will have to bededicated to explore factors that could influence the results of the SWE.

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Author contributions

HT.Z: design of the study, collecting the data, writing of the manuscript.
JFD.C: design of the study, writing of the manuscript, practicing Fibroscan®.
G.F: care of patients ,relecture of the manuscript.
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M.M: care of patients, relecture of the manuscipt.
F.K: design of the study, practicing Shear Wave, relecture of the manuscript.
T.LM: design of the study, data collection, statistical analysis.

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