

What to expect from FibroScan (transient elastography) for the evaluation of chronic hepatopathies?

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Abstract

Currently, liver biopsy is considered to be the gold-standard method for the evaluation of fibrosis in chronic liver disease, but other, non-invasive methods are being developed, among them, liver stiffness (LS) evaluation by means of the FibroScan device.

We will present our department's experience regarding the use of FibroScan in a 10 month period:

A. The rate of valid measurements (VM) by FibroScan. Failure to obtain VM of the liver stiffness was observed in 6.9% of the 1461 patients we investigated. Female gender, older age and higher Body Mass Index were statistically significant associated with failure to obtain VM.

B. A study comparing the FibroScan results to liver biopsy in patients with chronic hepatitis C showed that for a cut-off value of 6.8 kPa, the LS measurement had a PPV of 97.2%, a NPV of 34.2%, a sensitivity of 59.2%, a specificity of 92.6% for the presence of significant fibrosis (at least F2 Metavir), with a diagnostic performance of 76.1% (AUROC 0,761).

C. The FibroScan evaluation of patients with liver cirrhosis proved that LS is a good predictive factor for the presence of cirrhosis, with a sensitivity of approximately 88% for a cut-off value of 14 kPa. Also, we found that the LS was significantly higher in patients with grade II and III EV (that have to be treated with beta-blockers) than in patients without EV or grade I EV (32.9 ± 17.8 kPa vs. 44.4 ± 24.2 kPa, $p = 0.0009$).

In conclusion, transient elastography is a promising method for the evaluation of patients with chronic C viral hepatopathies, enabling an accurate enough staging of liver cirrhosis and the differentiation of mild and no fibrosis (F01) from significant fibrosis (F2-4), important for the decision of antiviral treatment.

Key words: fibrosis, hepatitis C, liver stiffness, transient elastography

In the evolution of chronic viral (B, C or B+D) and non-viral hepatitis (nonalcoholic steatohepatitis - NASH or alcoholic steatohepatitis - ASH), liver fibrosis is a very

important factor associated with prognosis. Hence, the necessity of a precise evaluation of the severity of fibrosis in those patients, in order to perform a correct staging and, eventually, to take a decision regarding the treatment.

Currently, the biopsy examination of the liver would seem to be the optimal method to evaluate changes in fibrosis over time [1]. Nevertheless, the liver biopsy (LB)

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has its shortcomings: the intra- and interobserver variability [2, 3]; the sampling variability (as proven in a study by Ratziu et al) [4]; and, last, but not least, the fact that LB is an invasive method, with morbidity and mortality greater than zero.

Considering all these facts, non invasive methods for the evaluation of liver fibrosis have been developed in the last few years, in order to replace the LB, among them the FibroScan evaluation of liver stiffness (transient elastography) [5, 6], an ultrasound-based method reported to be useful for identification of hepatic fibrosis, especially for patients with C chronic hepatopathies.

Transient elastography is based on the principle of Hooke's law, which characterizes a material's strain response to external stress [7]. This method uses an ultrasound transducer probe mounted on the axis of a vibrator. Low-frequency vibrations are transmitted into the liver, through an intercostal space, which creates an elastic shear wave. A pulse-echo ultrasound acquisition is used to detect the velocity of wave propagation, and the velocity is proportional to tissue stiffness, with faster wave progression occurring through stiffer tissue [7]. With this method we can detect and measure the liver stiffness (in normal and pathological individuals), with the results in kiloPascals (values between 2.5 and 75 kPa).

At the beginning of 2008, more than 250 FibroScan devices (Echosens, France) were in use throughout the world. Even if the first results of liver fibrosis evaluation by FibroScan came from France [8], several studies from different parts of the world have been recently published [7, 9, 10].

In order to be able to use transient elastography in clinical practice, valid measurements have to be obtained in the majority of evaluated cases. The method has to be reproducible (small inter- and intra-observer variability) and also to establish in which domains it has the most reliable results.

We will present our department's experience regarding the use of FibroScan in a 10 months period, specifically:

- A. The rate of valid measurements by FibroScan;
- B. A study comparing the FibroScan results to liver biopsy in patients with chronic hepatitis C;
- C. The FibroScan evaluation of patients with liver cirrhosis (the rate of correct evaluation and the relation between the liver stiffness and portal hypertension)

Results

A. Valid measurements in FibroScan: from the 1461 patients evaluated, failure to obtain a valid measurement (VM) was observed in 101 cases (6.9%), so that valid measurements were obtained in 93.1% of cases (1360 patients).

The proportion of failure among females was significantly higher (64/704 – 9.1%) than in males (37/757 – 4.9%) ($p = 0.0019$, $RR = 0.9558$). The mean age in the failure group was 54.2 ± 10.1 , significantly higher than in the VM group (50.6 ± 14.1) ($p < 0.0001$).

The mean body mass index in the failure group was 30.9 ± 5.4 , extremely significant higher than in the VM group (26.1 ± 4.6) ($p < 0.0001$). We did not find significant differences between the mean height in the failure group (166.5 ± 9.3 cm) vs. the VM group (168.6 ± 19.1 cm), $p = 0.0745$ (fig.1).

The presence of steatosis on ultrasound examination did not influence the chance to obtain valid measurements (15.5% of the patients in the VM group had steatosis, vs. 15.8% in the failure group, $p = 0.8874$).

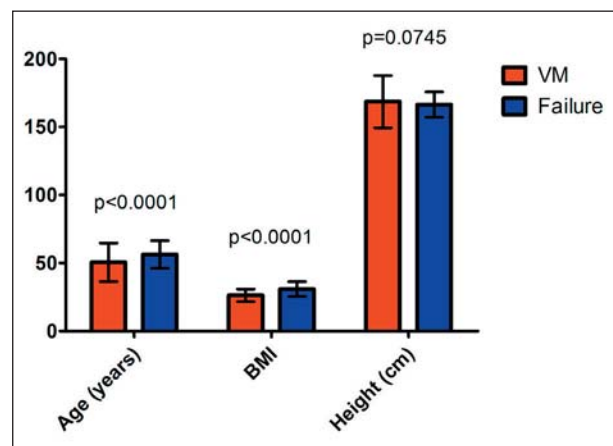


Fig.1. Factors that influenced the rate of valid measurements of liver stiffness by means of FibroScan.

B. FibroScan vs. liver biopsy in the evaluation of patients with C chronic hepatitis.

We analyzed a group of 150 patients (98 women and 52 men, mean age 48.15 ± 12 years) with chronic C hepatitis in which liver biopsy and liver stiffness (LS) evaluation by FibroScan were performed in the same session. The liver biopsies were evaluated according to the METAVIR score. In 5 cases we could not obtain valid measurements of LS. In the 145 cases in which FibroScan evaluation was possible, the **mean value of LS was 8.4 ± 5.1 kPa**, ranging from 2.3 to 38 kPa.

The mean values of LS in various subgroups of HCV patients, according to fibrosis were (fig.2):

- 5.3 ± 0.8 kPa in patients with $F = 0$ (4 cases);
- 5.4 ± 2 kPa in patients with $F = 1$ (23 cases);
- 7.1 ± 2.7 kPa in patients with $F = 2$ (71 cases);

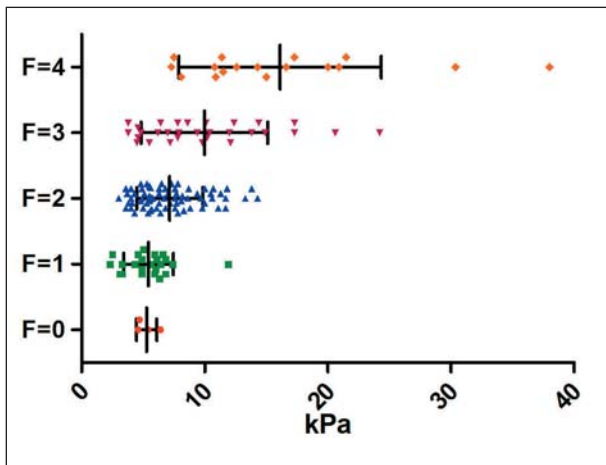


Fig.2. The mean values of LS in various subgroups of HCV patients, according to fibrosis (F0-F4 METAVIR).

- 9.9 ± 5.1 kPa in patients with F = 3 (30 cases);
- 16.1 ± 8.2 kPa in patients with F = 4 (17 cases).

The statistical significance of the differences between the LS in these subgroups was: F0 vs. F1 p = 0.8035 (NS), F0 vs. F2 p = 0.1225 (NS); F0 vs. F3 p < 0.0001 (S); F0 vs. F4 p < 0.0001 (S); F1 vs. F2 p = 0.0083 (S); F1 vs. F3 = 0.0002 (S); F1 vs. F4 p < 0.0001 (ES); F2 vs. F3 p = 0.0102 (S); F2 vs. F4 p < 0.0001 (ES); F3 vs. F4 p = 0.003 (S).

The mean value of LS in *patients with significant fibrosis* (118 patients with $F \geq 2$ Metavir) was 9.2 ± 5.4 kPa, significantly higher than in *patients without fibrosis or with minimal fibrosis* (27 patients with $F < 2$ Metavir) - 5.4 ± 1.9 kPa (p=0.0012) (it is considered that patients with significant fibrosis $F \geq 2$, should receive antiviral therapy) (fig.3).

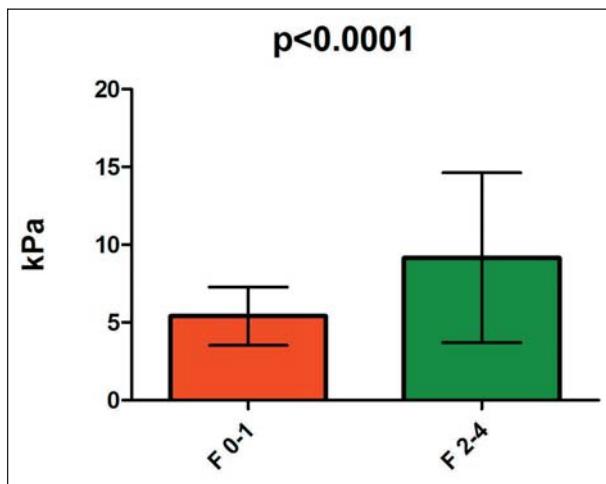


Fig.3. The mean value of LS in patients with significant fibrosis ($F \geq 2$) as compared to the patients with no or minimal fibrosis (F0-F1).

For a *cut-off value of 6.8 kPa*, the LS measurement had a PPV of 97.2%, a NPV of 34.2%, a *sensitivity of 59.2%*, a *specificity of 92.6% for the presence of significant fibrosis (at least F2 Metavir - patients that should receive antiviral treatment)*, with a *diagnostic performance of 76.1%* (AUROC 0.761) (fig.4). For the cut-off value of 6.8 kPa, we had the highest sum of sensibility and specificity.

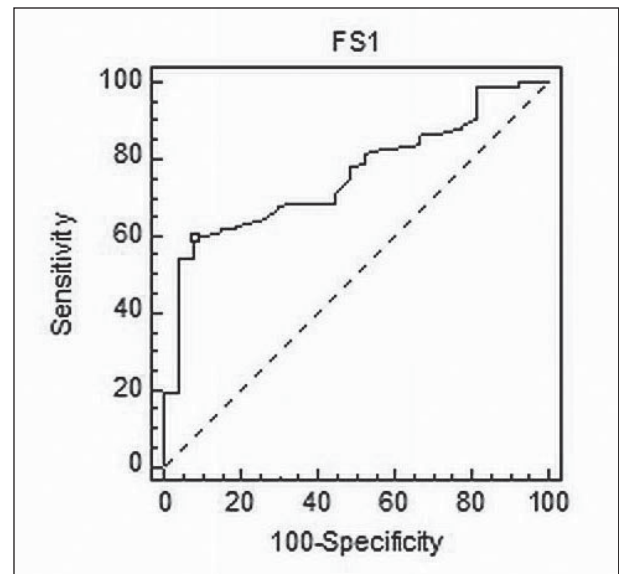


Fig.4. The AUROC of the predictive value of FS for the presence of significant fibrosis ($F \geq 2$ Metavir).

C. FibroScan evaluation of the patients with known liver cirrhosis (proven by clinical, biological, ultrasound, endoscopic or morphological evaluation). 277 patients were evaluated, 58.8% (163) male, 41.2% (114) female, mean age 56.6 ± 8.5 years old. In 13 cases (4.7%) we could not obtain 10 valid measurements, than 264 (95.3%) patients were classified. The FibroScan measurements ranged from 7.2 to 75 kPa, with a *mean value of 36.8 ± 21 kPa*.

Using a cut-off value of 14 kPa, 89% of patients (235/264 subjects) have been correctly classified. If a cut-off value of 13 kPa was used, 92% of patients (243/264 subjects) have been correctly classified.

The value of FibroScan in the evaluation of portal hypertension

189 cirrhotics with a recent gastroscopy and no history of band ligation or hepatocarcinoma were evaluated. The mean value of the liver stiffness was:

- 32.9 ± 17.9 kPa in the group of patients who did not have esophageal varices (EV) (62 patients);
- 32.9 ± 17.9 kPa in the group of patients with grade I EV (58 patients);

- 41.9 ± 21.5 kPa in the group of patients with grade II EV (56 patients);
- 55.2 ± 22.7 kPa in the group of patients with grade III EV (13 patients) (fig.5).

We found a statistically significant weak correlation between the grade of EV and the value of liver stiffness, with Spearman's correlation index $r = 0.2322$, $p = 0.0013$.

Also, we found that there was a statistically significant difference between the mean value of liver stiffness in patients with no EV and grade I EV as compared with patients with grade II and III EV, known to have a higher risk of bleeding (32.9 ± 17.8 kPa vs. 44.4 ± 24.2 kPa, $p = 0.0009$) and must have a prophylactic treatment with beta blockers (fig.6).

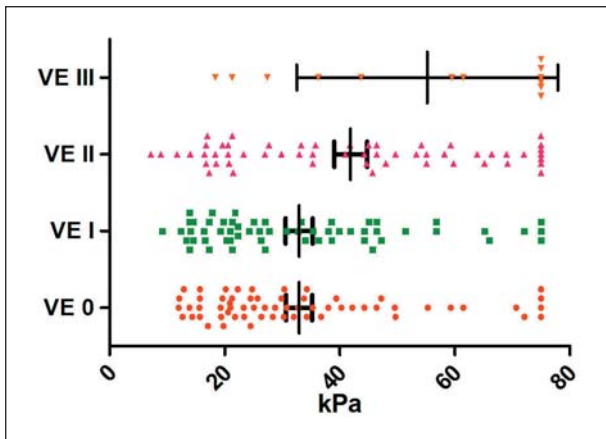


Fig.5. The mean value of FibroScan in cirrhotics with different grades of esophageal varices (EV).

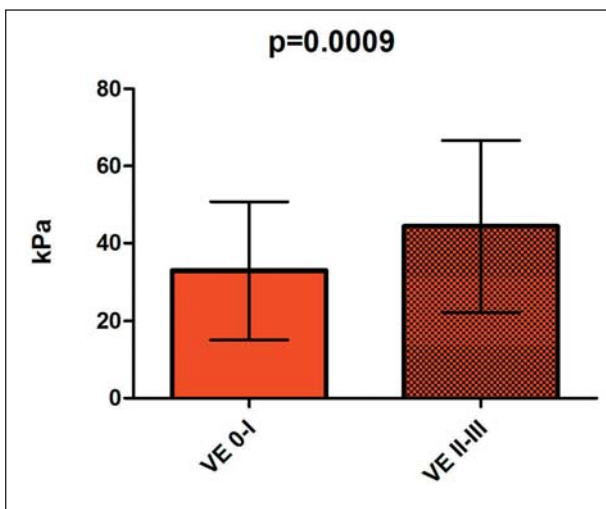


Fig.6. The mean value of FibroScan in patients with EV grade 0 and I vs. EV grade II or III.

Discussion

The majority of published studies regarding the FibroScan evaluation of LS were performed on patients with C viral hepatitis. Lately, the FibroScan device was successfully used for the assessment of fibrosis in other chronic liver diseases: chronic B viral hepatitis, primary biliary cirrhosis, post transplant evaluation or NASH [11, 12, 13].

The FibroScan evaluation of LS is considered to be a reproducible method, with low inter- and intraobserver variability [14, 15] and with a rate of successful measurements of 94-97% [14], thus making it useful for daily practice.

Based on the studies presented above we would suggest the use of FibroScan measurement of LS in two situations:

1. When liver cirrhosis is suspected (based on anamnestic, clinical and biological data); however, the evaluation is not possible when ascites is present. The LS measurement by means of FibroScan is a reliable method for the diagnosis of cirrhosis, with a sensitivity of 87% (95% CI, 84%-90%), a specificity of 91% (95% CI, 89%-92%), with positive likelihood ratio 11.7 (95% CI, 7.9-17.1) and negative likelihood ratio of 0.14 (95% CI 0.10-0.20), as shown in a meta-analysis performed by Talwalkar et al. [7]. The advantage of FibroScan evaluation of liver fibrosis on other non-invasive methods is that the transient elastography can also assess the severity of fibrosis (values up to 75 kPa), as shown in some studies, that suggest cut-off values of LS that predict the apparition of cirrhosis complications (esophageal varices, variceal bleeding, vascular decompensation or hepatocarcinoma) [16, 17].

2. The second clinical application of FibroScan is the evaluation of patients with chronic C viral hepatitis. In viremic patients, if the LS is greater than 6.8 kPa (according to the results of our study), there is a great probability of finding significant fibrosis on a liver biopsy (F2-F4), thus the patient requires antiviral therapy. Probably, in these cases a liver biopsy should not be needed for treatment.

In a multicentric French study coordinated by Beaugrand [18], performed on 494 HCV patients who were evaluated by means of percutaneous liver biopsy (with a significant fragment) and valid FibroScan examination, a significant correlation was found ($p < 0.001$) between the fibrosis and the values of LS measured through transient elastography ($r = 0.57$). This study tried to establish cut-off values for the LS that could differentiate between various stages of fibrosis. Thus, the cut-off value of 7.5 kPa differentiates F0-1 from F2-4 with a sensitivity of 67%, specificity of 87%, PPV 86% and NPV of 68%, with a diagnostic accuracy of 76%.

Other studies [10, 16] established cut-off values that differentiate F0-1 from F2-4, ranging from 7.2-7.3 kPa. As a practical approach, patients with LS lower than 7 kPa should undergo liver biopsy in order to discover viremic patients underestimated by FibroScan and who, otherwise, would not receive antiviral therapy. This strategy is already used in France, a country in which non-invasive evaluation of chronic C viral hepatitis is used more and more frequently.

Conclusion

Transient elastography is a promising method for the evaluation of patients with chronic C viral hepatopathies, enabling an accurate enough staging of liver cirrhosis and the differentiation of mild and no fibrosis (F01) from significant fibrosis (F2-4), this last evaluation for the decision of antiviral treatment.

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