DIAGNOSIS OF CIRRHOSIS BY TRANSIENT ELASTOGRAPHY (FIBROSCAN®): A PROSPECTIVE STUDY.

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Running title: Transient elastography and cirrhosis.
Key words: liver stiffness, portal hypertension, fibrosis, oesophageal varices, liver biopsy, hepatocellular carcinoma, ascites.
Words: 3433

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Competing interest: none declared.
Abstract

Background. Transient elastography (FibroScan®) is a new non-invasive rapid and reproducible method, allowing evaluating liver fibrosis by measurement of liver stiffness. In cirrhotic patients, liver stiffness measurements range from 12.5 to 75.5 kPa. However, the clinical relevance of these values is unknown. The aim of this prospective study was to evaluate the accuracy of liver stiffness measurement for the detection of cirrhosis in patients with chronic liver disease. Methods. 711 patients with chronic liver disease were studied. Aetiologies of chronic liver diseases were HCV or HBV infection, alcohol, NASH, other or combination of above aetiologies. Liver fibrosis was evaluated according to METAVIR. Results. Stiffness was significantly correlated to the fibrosis stage (r=0.73, p < 0.0001). The areas under the ROC curve (95% CI) were 0.80 (0.75-0.84) for patients with significant fibrosis (F>2), 0.90 (0.86-0.93) for patients with severe fibrosis (F3) and 0.96 (0.94-0.98) for patients with cirrhosis. Using a cut-off value of 17.6 kPa, patients with cirrhosis were detected with both PPV and NPV of 90%. Liver stiffness was significantly correlated with clinical, biological, and morphological parameters of liver disease. With a NPV > 90%, the cut-off for the presence of oesophageal varices stage 2/3, cirrhosis Child-Pugh B or C, past history of ascites, hepatocellular carcinoma, and oesophageal bleeding were 27.5 kPa, 37.5 kPa, 49.1 kPa, 53.7 kPa, and 62.7 kPa, respectively. Conclusion. Transient elastography is a promising non invasive method for the detection of cirrhosis in patients with chronic liver disease. Its use for the follow-up and management of these patients could be of great interest and should be further evaluated.
Introduction

Progressive hepatic fibrosis with the development of cirrhosis is a feature of almost all chronic liver diseases. Approximately 10-20% of patients with chronic hepatitis C virus infection have cirrhosis at first clinical presentation, and as many 20-30% of those who do not have cirrhosis will eventually develop this condition and its complications within one or more decades (1-3). These complications are liver failure, ascites, variceal bleeding, portal-systemic encephalopathy, and hepatocellular carcinoma (3).

Liver biopsy is currently considered the gold standard for assessing hepatic fibrosis. However, it is an invasive and painful procedure (4), with rare but potential life-threatening complications (5), limiting its acceptance and repetition in usually asymptomatic patients. In addition, the accuracy of liver biopsy in assessing fibrosis may be questioned because of sampling error and interobserver variability that may lead to understaging of cirrhosis (6-9). Thus, there is a need to develop and validate non-invasive tests that can accurately reflect the full spectrum of hepatic fibrosis, cirrhosis, and its severity in liver diseases.

Transient elastography (FibroScan®, Echosens®, Paris, France) is a novel rapid and non-invasive technique which measures liver stiffness (10). Briefly, this system is equipped with a probe consisting in an ultrasonic transducer mounted on the axis of a vibrator. A vibration of mild amplitude and low frequency is transmitted from the vibrator to the tissue by the transducer itself. This vibration induces an elastic shear wave which propagates through the tissue. In the meantime, pulse-echo ultrasonic acquisitions are performed to follow the propagation of the shear wave and measure its velocity which is directly related to the tissue stiffness (or elastic modulus). The harder the tissue, the faster the shear wave propagates. Recent reports have shown that liver stiffness measurement using FibroScan® allowed accurate prediction of hepatic fibrosis in patient with chronic hepatitis C virus infection (11-14). In patients with chronic hepatitis C, we have shown that liver stiffness measurements ranged from 2.4 to 75 kPa with a median value of 7.4 kPa (14). Based on the stiffness measurement distribution according to fibrosis stage and the ROC curves, we found that the cut-off value for cirrhosis was 12.5 kPa. However, the clinical relevance of these values (from 12.5 to 75 kPa) in cirrhotic patients is unknown.

The aim of this prospective study was to assess the accuracy of transient elastography for the detection of cirrhosis in clinical practice in a large cohort of consecutive patients with chronic liver disease.

Patients and methods

Patients

Between June 2003 and September 2004, all consecutive patients with chronic liver diseases seen at the Hepatology Unit of Haut-Lévêque Hospital (University Hospital of Bordeaux, Pessac, France) were prospectively included. The determination of aetiology of chronic liver disease was made using standard diagnostic criteria. Hepatitis C virus (HCV) or hepatitis B virus (HBV) was diagnosed by serological detection of hepatitis C antibodies (with positive serum HCV-RNA by PCR) and hepatitis B surface antigen, respectively. Alcoholic liver disease was diagnosed in those with consumption of at least 40 g of alcohol daily for 5 years or more. All other diseases were diagnosed as usually. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki. Patients were enrolled after written informed consent was obtained. All patients consented to the study.

Characteristics of patients

For all patients, the following parameters were determined at the time of liver stiffness measurement. Clinical parameters included weight, height, past history of ascites or bleeding varices and hepatocellular carcinoma. Biological parameters included aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl-transpeptidase (GGT), total bilirubin, platelet count,
prothrombin time (PT), V factor, albumin, and alpha-foetoprotein. Morphological parameters included oesophageal varices (after upper gastrointestinal endoscopy), and ultrasonographic splenomegaly. Since ascites is a physical limitation to the technique because elastic waves do not propagate through liquids, patients with ascites were excluded.

Liver stiffness measurement

Details of the technical background and examination procedure have been previously described (11, 12). Measurements were performed on the right lobe of the liver through intercostal spaces on patients lying in dorsal decubitus with the right arm in maximal abduction. The tip of the probe transducer was covered with coupling gel and placed on the skin, between the rib bones at the level of the right lobe of the liver. The operator, assisted by an ultrasonic time-motion image, located a liver portion of at least 6-cm thick free of large vascular structures. Once the measurement area had been located, the operator pressed the probe button to start an acquisition. The measurement depth was between 25 mm and 65 mm below the skin surface. Measurement which did not had a correct vibration shape or a correct follow up of the vibration propagation were automatically rejected by the software. Up to ten successful measurements were performed on each patient. The success rate was calculated as the ratio of the number of successful measurements over the total number of acquisitions. The results are expressed in kilopascal (kPa). The median value of the successful measurements was kept as representative of the liver stiffness. The whole examination duration was less than 5 minutes. Only liver stiffness measurements obtained with at least 5 successful measurements and a success rate of at least 30% were considered reliable.

Liver histology and quantification of liver fibrosis

For patients who had liver biopsy at the time of liver stiffness measurement (usual indications of liver biopsy), liver biopsy was fixed in formalin and paraffin-embedded. Liver stiffness measurement was performed just before liver biopsy. All biopsy specimens were analyzed independently by an experienced pathologist blinded to the clinical data and the results of liver stiffness measurement. Liver biopsies that contained less than 10 portal tracts (except for cirrhosis) were excluded from the histological analysis. The length of each liver biopsy specimen was also established in millimetres. Fibrosis was staged according to METAVIR scoring system as follows: no or mild fibrosis (no fibrosis or portal fibrosis without septa, F0F1), moderate fibrosis (portal fibrosis and few septa, F2), severe fibrosis (numerous septa without cirrhosis, F3) and cirrhosis F4 (15).

Statistical analysis

The Kruskall-Wallis non parametric analysis of variance was used to compare the liver stiffness among the different METAVIR fibrosis stages. For fibrosis and complications of cirrhosis, the diagnostic performance of liver stiffness measurement was assessed by using receiver operating characteristics (ROC) curves. A subject is assessed as positive or negative according to whether the non-invasive marker value is greater than or less than or equal to a given cut-off value. Connected with any cut-off value is the probability of a true positive (sensitivity) and the probability of a true negative (specificity). The ROC curve is a plot of sensitivity versus 1- specificity for all possible cut-off values. The most commonly used index of accuracy is the area under the ROC curve (AUROC), values close to 1.0 indicating high diagnostic accuracy. ROC curves were thus built for the detection of patients with METAVIR fibrosis stage of 2 or more (F ≥ 2), for the detection of patients with METAVIR fibrosis stage of 3 or more (F ≥ 3) and for the detection of patients with cirrhosis (F = 4).

Spearman coefficient of correlation and their associated probability (p) were used to evaluate the relationship between parameters. As some data were missing for some patients, the number of patients (N) included in the calculation of each correlation coefficient was specified.

Optimal cut-off values for liver stiffness were chosen to optimize the predictive value according to the diagnostic question. Statistical analyses were performed with NCSS 2004 software (Statistical Systems, Kayville, UT).
Results

Patients

A total of 758 patients were enrolled. Forty-seven patients (6.2%) were excluded because of unsuccessful liver stiffness measurement mostly due to overweight (31 patients had less than 5 valid measurements and 16 had a success rate lower than 30%). Thus, 711 patients were analyzed. Their characteristics at the time of FibroScan® examination are summarized in Table 1.

Table 1. Characteristics of patients at the time of FibroScan® examination

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Patients with liver biopsy</th>
<th>F3F4 fibrosis patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=711 (%)</td>
<td>n=354 (%)</td>
<td>n=144 (%)</td>
</tr>
<tr>
<td>Males (%)</td>
<td>403 (57)</td>
<td>206 (58)</td>
<td>102 (71)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>52 ± 13</td>
<td>50 ± 13</td>
<td>53 ± 12</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.2 ± 4.2</td>
<td>24.5 ± 4.3</td>
<td>25.2 ± 4.3</td>
</tr>
<tr>
<td>AST (UI/l)</td>
<td>59.5 ± 86.1</td>
<td>71.3 ± 110.5</td>
<td>94.7 ± 138.7</td>
</tr>
<tr>
<td>ALT (UI/l)</td>
<td>79.2 ± 108.3</td>
<td>82.7 ± 106.6</td>
<td>108.1 ± 119.1</td>
</tr>
<tr>
<td>GGT (UI/l)</td>
<td>136 ± 245</td>
<td>159 ± 229</td>
<td>206 ± 272</td>
</tr>
<tr>
<td>Total bilirubin (µmol/L)</td>
<td>16.9 ± 31.5</td>
<td>19.7 ± 37.3</td>
<td>27.3 ± 44</td>
</tr>
<tr>
<td>Platelet count (G/l)</td>
<td>209 ± 87</td>
<td>213 ± 91</td>
<td>165 ± 83</td>
</tr>
<tr>
<td>Prothrombin Time (%)</td>
<td>90 ± 14</td>
<td>89 ± 15</td>
<td>82 ± 17</td>
</tr>
<tr>
<td>V Factor (%)</td>
<td>88.6 ± 18.5</td>
<td>92.5 ± 15</td>
<td>80.5 ± 20.5</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>38.5 ± 5.6</td>
<td>38.5 ± 5.2</td>
<td>36.1 ± 6.3</td>
</tr>
<tr>
<td>Alpha-foetoprotein (ng/ml)</td>
<td>49 ± 456</td>
<td>31 ± 105</td>
<td>54 ± 270</td>
</tr>
<tr>
<td>Fibrosis score (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No or mild fibrosis</td>
<td>111 (31)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate fibrosis</td>
<td>99 (28)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe fibrosis</td>
<td>49 (14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>95 (27)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Past history of ascites</td>
<td>18 (13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Past history of bleeding varices</td>
<td>14 (10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>19 (13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oesophageal varices stage 2/3</td>
<td>42 (29)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>US splenomegaly</td>
<td>48 (33)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Results are given as mean ± standard deviation or n (%).

BMI = body-mass index, ALT = alanine aminotransferase, AST = aspartate aminotransferase, GGT = γ-glutamyl-transpeptidase, US ultrasonographic.

They were 403 males, with a mean age of 52 ± 13 years. Aetiologies of chronic liver diseases were: HCV (n=398) or HBV infection (n=43), alcoholic liver disease (n=89), HCV infection and alcoholic liver disease (n=26), HCV and HIV infection (n=24), Non-Alcoholic Steato-Hepatitis (n=26), hemochromatosis (n=17), cholestatic liver disease (n=13), and others (n=75).
Three hundred fifty-four patients (49.8%) had undergone a liver biopsy at the time of liver stiffness measurement. Fibrosis stage distribution was as follows: 111 patients (31.4%) with no or mild fibrosis (F0F1), 99 patients (28.0%) with moderate fibrosis (F2), 49 patients (13.8%) with severe fibrosis (F3) and 95 patients (26.8%) with cirrhosis (F4). The median biopsy length was 16.5 mm.

For cirrhotic patients, Child-Pugh score was A in 70 (73.7%) cases, Child B in 15 cases (15.8%), and Child C in 10 (10.5%) cases.

Relationship between liver stiffness and histological parameters

Liver stiffness measurements ranged from 2.4 to 75.4 kPa (median: 6.8 kPa). The mean number of measurement per patient was 12.6 ± 4.1 (range: 7 - 33). Six hundred ninety six out of 711 patients had 10 valid measurements. The other patients had between 5 and 9 valid measurements. Therefore, the success rate was 84.7 ± 18.3 % (range: 30 - 100%).

Figure 1 shows box-plots of liver stiffness for each fibrosis stage. For patients with severe fibrosis (F3 and F4), the median liver stiffness was 18.7 kPa (range: 3.3 - 75.4 kPa). For patients with cirrhosis, median liver stiffness was 31.1 kPa (range: 5.5 - 75.4 kPa). Liver stiffness was significantly different between patients according to their fibrosis stage (p < 0.001) and significantly correlated to the fibrosis stage (r=0.73, p < 0.0001). Figure 2 shows the diagnostic value (ROC curves) of liver stiffness measurement for different degrees of fibrosis: moderate fibrosis or more (F ≥ F2), severe fibrosis or more (F ≥ F3) and cirrhosis (F = 4). The corresponding AUROCs (95% CI) were 0.80 (0.75 – 0.84) for F ≥ F2, 0.90 (0.86 – 0.93) for F ≥ F3, and 0.96 (0.94 – 0.98) for F = 4. Based on the stiffness measurement distribution according to fibrosis stage and the ROC curves, the best discriminant cut-off levels were determined (positive predictive value of at least 90%). These cut-off levels were 7.2 kPa for moderate fibrosis or more, 12.5 kPa for severe fibrosis or more and 17.6 kPa for cirrhosis (Table 2).

Table 2. Cut-off values of liver stiffness according to fibrosis stage for a positive predictive value of at least 90%.

<table>
<thead>
<tr>
<th>Cut-off</th>
<th>F≥2</th>
<th>F≥3</th>
<th>F=cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPV</td>
<td>90</td>
<td>90</td>
<td>91</td>
</tr>
<tr>
<td>NPV</td>
<td>52</td>
<td>80</td>
<td>92</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>64</td>
<td>65</td>
<td>77</td>
</tr>
<tr>
<td>Specificity</td>
<td>85</td>
<td>95</td>
<td>97</td>
</tr>
<tr>
<td>PLR</td>
<td>4.2</td>
<td>13.7</td>
<td>28.4</td>
</tr>
</tbody>
</table>

PPV: Positive Predictive Value; NPV: Negative Predictive Value; PLR: Positive Likelihood Ratio.

Twenty out of 95 cirrhotic patients (21%) had liver stiffness measurement less than 17.6 kPa. For patients with viral and alcohol-related cirrhosis, median liver stiffness values were 23 kPa and 52.4 kPa, respectively (p<0.001).

Correlation between elastography measurement and parameters of severity of cirrhosis

For all included patients as well as for the subgroup of F3F4 patients, as indicated in Table 3, liver stiffness was significantly (p < 0.05) correlated with clinical parameters (past history of bleeding varices, hepatocellular carcinoma, or ascites), biological parameters (platelet count, prothrombin time, factor V, albumin, and total bilirubin) and morphological parameters (oesophageal varices stage 2/3, US splenomegaly). In cirrhotic patients, liver stiffness was significantly (p<0.0001) correlated with Child-Pugh score (r=0.517).
Table 3. Correlations between transient elastography and biochemical, clinical and ultrasonographic features of the patients.

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>F3F4 fibrosis patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>r</td>
</tr>
<tr>
<td>AST</td>
<td>678</td>
<td>0.480</td>
</tr>
<tr>
<td>ALT</td>
<td>698</td>
<td>0.216</td>
</tr>
<tr>
<td>GGT</td>
<td>688</td>
<td>0.426</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>666</td>
<td>0.448</td>
</tr>
<tr>
<td>Platelet count</td>
<td>686</td>
<td>-0.427</td>
</tr>
<tr>
<td>Prothrombin time</td>
<td>617</td>
<td>-0.500</td>
</tr>
<tr>
<td>V Factor</td>
<td>222</td>
<td>-0.516</td>
</tr>
<tr>
<td>Albumin</td>
<td>481</td>
<td>-0.370</td>
</tr>
<tr>
<td>Alpha-foetoprotein</td>
<td>355</td>
<td>0.451</td>
</tr>
<tr>
<td>Child-Pugh score</td>
<td>144</td>
<td>0.590</td>
</tr>
<tr>
<td>Past history of ascites</td>
<td>144</td>
<td>0.447</td>
</tr>
<tr>
<td>Oesophageal varices</td>
<td>85</td>
<td>0.492</td>
</tr>
<tr>
<td>Oesophageal varices stage 2 or 3</td>
<td>85</td>
<td>0.370</td>
</tr>
<tr>
<td>Past history of bleeding varices</td>
<td>144</td>
<td>0.387</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>144</td>
<td>0.252</td>
</tr>
<tr>
<td>US splenomegaly</td>
<td>133</td>
<td>0.493</td>
</tr>
</tbody>
</table>

ALT=alanine aminotransferase, AST=aspartate aminotransferase, GGT=γ-glutamyl-transpeptidase, US=ultrasonographic, NS : not significant, N=number of patients with a correct value.

Diagnosis accuracy of liver stiffness measurement in clinical practice

For patients with severe fibrosis or more (F ≥ F3), the AUROCs giving the performances of liver stiffness measurement to detect complications of cirrhosis are given in Table 4.

Table 4. Diagnostic accuracy of liver stiffness for complications of cirrhosis (144 patients with F3F4 fibrosis)

<table>
<thead>
<tr>
<th></th>
<th>AUROC (95%CI)</th>
<th>Cut-off (kPa)</th>
<th>PPV</th>
<th>NPV</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oesophageal varices stage 2 or 3</td>
<td>0.73 (0.60-0.82)</td>
<td>27.5</td>
<td>45</td>
<td>90</td>
<td>88</td>
<td>53</td>
</tr>
<tr>
<td>Child-Pugh A versus Child-Pugh BC *</td>
<td>0.90 (0.82-0.93)</td>
<td>37.5</td>
<td>48</td>
<td>95</td>
<td>79</td>
<td>82</td>
</tr>
<tr>
<td>Past history of ascites</td>
<td>0.89 (0.81-0.94)</td>
<td>49.1</td>
<td>43</td>
<td>95</td>
<td>67</td>
<td>87</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>0.71 (0.58-0.81)</td>
<td>53.7</td>
<td>30</td>
<td>90</td>
<td>37</td>
<td>87</td>
</tr>
<tr>
<td>Past history of variceal bleeding</td>
<td>0.88 (0.77-0.94)</td>
<td>62.7</td>
<td>47</td>
<td>95</td>
<td>57</td>
<td>93</td>
</tr>
</tbody>
</table>

CI: Confidence Interval - PPV: Positive Predictive Value – NPV: Negative Predictive Value
* F3 patients were classified as Child-Pugh A.

With a negative predictive value > 90%, the cut-off for the presence of oesophageal varices stage 2/3 was 27.5 kPa, for cirrhosis Child BC was 37.5 kPa, for a past history of ascites was 49.1 kPa, for hepatocellular carcinoma was 53.7 kPa, and for oesophageal bleeding was 62.7 kPa. According to these negative predictive values, the usefulness of liver stiffness measurement with FibroScan® in clinical practice is indicated in Figure 4.
Discussion

The results of the present study conducted prospectively in a large cohort of patients with chronic liver disease show that transient elastography is an efficient technique for the diagnosis of cirrhosis and its severity. With a cut-off value of 17.6 kPa, negative and positive predictive values for the diagnosis of cirrhosis are 92% and 91%, respectively. We established the cut-off for the complications of cirrhosis with negative predictive value of more than 90%. These cut-off values are 27.5 kPa for the presence of oesophageal varices stage 2/3, 37.5 kPa for cirrhosis Child BC, 49.1 kPa for a past history of ascites, 53.7 kPa for hepatocellular carcinoma, and 62.7 kPa for oesophageal bleeding. In clinical practice, such results could be of major relevance for the follow-up of patients with severe fibrosis or cirrhosis.

In the present study, cut-off values for the diagnosis of fibrosis were slightly different from those previously published (13, 14). In published studies, for the diagnosis of fibrosis \( \geq F_2 \), cut-off values ranged from 7.1 to 8.8 kPa (13, 14). In our study, this cut-off is 7.2 kPa. For the diagnosis of fibrosis \( \geq F_3 \), cut-off values ranged from 9.5 to 9.6 kPa (13, 14). In our study, this cut-off is 12.5 kPa. Finally, for the diagnosis of cirrhosis, cut-off values ranged from 12.5 to 14.6 kPa (13, 14). In our study, the cut-off for the diagnosis of cirrhosis was 17.6 kPa. These differences could be due to the population of this study which was composed of patients with chronic liver diseases of various aetiologies. In the two previous studies, only patients with chronic HCV infection were included. Secondly, in the two previously published studies, cut-off values were chosen to maximise the sum of sensitivity and specificity whereas in this study, we chose cut-off values to have a positive predictive value of more than 90% which favours specificity.

Cirrhotic patients with alcoholic liver disease had higher liver stiffness values than cirrhotic patients with chronic hepatitis C. Indeed, patients with chronic hepatitis C are diagnosed at an early stage than alcoholic patients, with an histological diagnosis without clinical complications of cirrhosis. On the opposite side, patients with alcoholic disease are diagnosed later, when clinical complications of cirrhosis occur.

To our knowledge, this study is also the first one comparing liver stiffness measurement and fibrosis stage assessed on liver biopsies in a large population of patients with chronic liver disease of various aetiologies. The diagnostic performances for \( F \geq F_2 \), \( F \geq F_3 \) and \( F = F_4 \) obtained on these various aetiological populations are similar to those obtained on the previously published studies conducted only on HCV patients (13, 14). In our study, the proportion of patients with advanced fibrosis stages (\( F \geq 3 \)) was higher than in the general population so the diagnosis performance might be lower in the general population. However, these results indicate that liver stiffness measurement could be used to evaluate liver fibrosis in chronic liver diseases whatever the aetiology was. A liver biopsy was not performed in all patients. However, no statistical significance was observed between the characteristics of patients with or without liver biopsy.

Needle liver biopsy has been used as the “gold standard” for the assessment of liver fibrosis. Usually, the diagnosis of cirrhosis is based on a biopsy specimen that only represents 1/50,000 of the total liver mass (5). Furthermore, inter- and intra-observer discrepancies of 10% to 20% in assessing hepatic fibrosis have been reported, which may lead to understaging of cirrhosis (7, 15, 16). Therefore, while liver biopsy remains the “gold standard”, both the clinician and the researcher should view the results of a liver biopsy with some reservation and should interpret the findings in the broader clinical context. Although risks of liver biopsy can be possibly reduced by operator experience and using an ultrasound guidance, several known risks of obtaining the tissue, such as pain, bleeding, pneumothorax, hemothorax, bile peritonitis, hemobilia, puncture of kidney and intestine, infections, anxiety, and even death do not seem to be entirely avoidable (4, 5, 17, 18).

Liver stiffness measurement using FibroScan® is reproducible and independent of the operator (12) and explores a volume of liver parenchyma which can be approximated by a cylinder of 1-cm diameter and 4-cm length. This volume is 100 times bigger than the biopsy specimen volume and is
thus much more representative of the entire hepatic parenchyma. The correlation of between liver stiffness and fibrosis stage is not affected by steatosis and activity grade (13).

A variety of indirect markers of cirrhosis have been evaluated including variables such as the AST/ALT ratio (17, 19, 20), platelet count (21), prothrombin index (22), APRI (23), and Fibrosure® (24). All these methods have been evaluated in HCV patients. Our study shows that liver stiffness measurement using transient elastography is a new non-invasive method for the diagnosis of cirrhosis either in HCV-infected patients or in all other patients with chronic liver disease. With FibroScan®, AUROC for the diagnosis of cirrhosis is 0.96. None of the other non-invasive methods have such an accurate value.

Ultrasonographic or radiological evaluation of the liver to assess fibrosis has been limited to the identification of individuals with cirrhosis and its complications. In a study of 243 patients, the diagnosis of cirrhosis could be made by ultrasound with an accuracy of 82-88% (25). However, significant interobserver variability and inability to gather all of the required measurements, due to technical problems, limit the value of ultrasonography. Using pulsed Doppler ultrasonography, Chawla et al showed that there was a significant decrease in the portal flow velocity in patients with Child’s C cirrhosis as compared to controls and patients with Child’s A and Child’s B cirrhosis (26). With liver stiffness measurement using FibroScan®, there is no intra- or inter-observer variability and this technique is strongly reproducible (12). With only five successful acquisitions and only a 30% success rate of liver stiffness measurement, the result of liver stiffness measurement correlated to fibrosis stage.

Cirrhosis places the patient at risk of clinical complications such as portal hypertension, and variceal rupture is the second cause of death in cirrhosis justifying early screening for oesophageal varices. The usual means of diagnosing oesophageal varices is upper gastro-intestinal endoscopy. However, endoscopy can be considered invasive due to the technique and level of discomfort. Non-invasive methods of diagnosis of considerable interest have to be developed. In a study of cirrhotic patients, diagnosis accuracy of oesophageal varices was 72% with 2 variables: platelet count and prothrombin index (21). In another study, positive predictive value of platelet count for the presence of oesophageal varices was 67% (27). In our study, 20 patients did not undergo an endoscopy because of refusal or because an endoscopy had been performed between one and two years before this study. With a negative predictive value of 95%, liver stiffness measurement value > 27.5 kPa was associated with the presence of oesophageal varices stage 2 or 3, independently of the cause of cirrhosis. Thus, in clinical practice, a prospective study should be done evaluating the relevance of oesophageal varices screening in patients with liver stiffness value more than 27.5 kPa.

Maharaj et al, by performing 3 transcutaneous biopsies in the same patients using different entry points, reported that, in proven cirrhotic patients, a histopathologic feature of cirrhosis was present in all 3 biopsy specimens of only 50% of the patients (6). Similarly, Abdi et al (28) performed several post mortem biopsies and showed that the diagnosis of cirrhosis could be obtained from one biopsy specimen in only 16 of 20 cases. According to Bedossa et al, sampling variation of liver fibrosis is a significant limitation in the assessment of fibrosis with liver biopsy (8). Thus, some cirrhotic patients are misclassified as F3 patients. For the usefulness of liver stiffness measurement with FibroScan® in clinical practice, in order to include all patients with cirrhosis, even real cirrhotic patients with wrong F3 fibrosis at liver biopsy examination, we evaluated the diagnostic accuracy of liver stiffness for complications of cirrhosis in F3F4 patients.

In patients with hepatocellular carcinoma, ultrasonography was performed before FibroScan® in order to evaluate liver stiffness in a part of the liver without hepatocellular carcinoma. Therefore, tumour stiffness could not influence the result of FibroScan®. In this study, only a small number a patients had an hepatocellular carcinoma. Thus, the role of FibroScan® in assessing the risk of hepatocellular carcinoma needs further investigations. At last, in clinical practice (need for surgery, medical treatments…), the risk of cirrhosis decompensation could be excluded in patients with liver stiffness measurement < 27 kPa (cut-off value for Child A stage).

In conclusion, liver stiffness measurement is a good method for the diagnosis of fibrosis and cirrhosis, whatever the cause of liver disease. Values in cirrhotic patients ranged from 17.6 kPa
through 75.4 kPa. Liver stiffness measurement could be accurate for assessing the severity of cirrhosis. However, a longitudinal cohort study has to be performed in order to predict complications of cirrhosis using FibroScan®. In the latter, screening for complications of cirrhosis, and close follow-up could be performed.
References


Figure 1
Liver stiffness values for each fibrosis stage. The vertical axis is in logarithmic scale. The top and bottom of boxes are the 1st and 3rd quartiles. The length of the box represents the interquartile ranges within which are located 50% of the values. The lines through the middle of the boxes represent the median.

Figure 2
Receiver operator characteristics (ROC) curves for liver stiffness measurement for different fibrosis thresholds: F0-1 versus F2-3-4 (F≥2), F0-1-2 versus F3-4 (F≥3), and F0-1-2-3 versus F4 (F=4).

Figure 3
Receiver operator characteristics (ROC) curves for liver stiffness measurement for the detection of oesophageal varices of grade 2 or 3 (N=85)

Figure 4.
Usefulness of liver stiffness measurement with FibroScan® in clinical practice.
Figure 1

Elasticity (kPa)

Fibrosis stage

1

0

1

10

100

2

3

4
Figure 2

Sensitivity vs. 1 - Specificity for different liver disease stages:
- Blue line: moderate fibrosis or more
- Pink line: severe fibrosis or more
- Green line: cirrhosis
Figure 3

AUROC: 0.73 (0.6-0.82)
Figure 4

Liver stiffness value

27.5  37.5  49.1  53.7  62.7 kPa

- No oesophageal varices
  - stage 2 or 3

- No Child-Pugh B or C

- No past history of ascites

- No hepatocellular carcinoma

- No past history of variceal bleeding