Liver stiffness assessment by means of transient elastography (FibroScan®) in patients with liver cirrhosis – a predictor of portal hypertension?

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Abstract

The aim of our paper was to assess the value of liver stiffness (LS) measurement by means of Transient Elastography (TE), for the diagnosis of cirrhosis and for the prediction of portal hypertension.

Patients and methods. Our study included 596 successive patients with proven liver cirrhosis, in which LS measurement and upper digestive endoscopy were performed.

Results. For a cut-off values of 12.5kPa and 14.6kPa for the diagnosis of cirrhosis, 96.8% and 85.1% of the patients, respectively, were correctly classified. We found a strong, direct, statistically significant correlation between the value of LS and the severity of EV: Spearman correlation index r=0.703, (p<0.0001). For a cut-off value of 23.3kPa, LS had 72.1% sensitivity, 87.8% specificity, 71% PPV and 87.3% NPV for predicting the presence of large EV, AUROC=0.8811 (p<0.0001). For a cut-off value of 41.3kPa, LS had 54.7% sensitivity, 80.0% specificity, 85% PPV and 45.9% NPV for predicting variceal rupture in patients with large EV (grade II and III), AUROC=0.6816 (p<0.0001).

Conclusion. LS measurement is a reliable tool for predicting the presence of cirrhosis and of large EV. However, in patients with high values of LS, endoscopy should be performed in order to accurately assess their presence and severity.

Key words: liver cirrhosis, esophageal varices, liver stiffness, transient elastography

Introduction

Chronic liver diseases are frequent among the general population, especially in areas with a high incidence of infection with hepatitis viruses. According to the WHO data, in Romania approximately 5% of the population are infected with hepatitis B virus (HBV) and 4-5% with hepatitis C virus (HCV) [1]. Also, one must not forget the rising incidence of alcoholic steato-hepatitis (ASH) and non-alcoholic steato-hepatitis (NASH) [2].

Progressive hepatic fibrosis with the development of cirrhosis is a feature of almost all chronic liver diseases. It is characterized by a profound derangement of liver architecture caused by fibrosis and nodule formation. Approximately 20–30% of the patients with chronic C hepatitis will eventually develop cirrhosis and its complications within one or more decades after diagnosis [3]. These complications are liver failure, ascites, variceal bleeding, portal-systemic encephalopathy, and hepatocellular carcinoma (HCC) [3].

If in advanced cirrhosis the clinical signs are diagnostic, compensated liver cirrhosis is not always easy to diagnose. Currently, the biopsy examination of the liver would seem to be the optimal method to evaluate changes in fibrosis over time [4]. Nevertheless, liver biopsy (LB) has its shortcomings: the intra- and interobserver variability [5, 6]; the sampling variability [7]; and, last, but not least, the fact that LB is an invasive method, with morbidity
and mortality greater than 0. Furthermore, LB can miss the diagnosis of cirrhosis in up to 20% of the cases [5], and diagnostic laparoscopy is a rather invasive method.

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. The most promising non-invasive methods are the FibroTest – ActiTest [8] and transient elastography (TE) [9, 10].

The aim of our paper was to assess the value of liver stiffness (LS) measurement by means of Transient Elastography (TE) for the diagnosis of cirrhosis and for the prediction of portal hypertension in patients from the Department of Gastroenterology and Hepatology of Timișoara.

Patients and methods

Patients

Our study included 596 successive patients with proven liver cirrhosis (LC) admitted to the Department of Gastroenterology and Hepatology of Timișoara. LC was diagnosed based on clinical, biological, ultrasound, endoscopic criteria and/or liver biopsy. As recommended in the literature [10], we did not perform LS measurements in patients with ascites, so we began the evaluation with abdominal ultrasound, in order to exclude the presence of fluid in the abdominal cavity. We also excluded patients with HCC.

Upper digestive endoscopy was performed on all the patients. Esophageal varices (EV) were classified as: small (grade I) - small straight varices; medium (grade II) - enlarged tortuous varices occupying less than one third of the lumen; large (grade III) - large coil-shaped varices occupying more than one third of the lumen.

Liver Stiffness measurement by means of Transient Elastography

In all the patients we performed LS measurement (LSM) by TE, using a FibroScan® device (EchoSens - Paris, France) [11, 12]. The system consists of a probe with an ultrasonic transducer mounted on the axis of a vibrator. This vibrator induces a wave of mild amplitude and low frequency to the tissue. Thus, an elastic shear wave is created that propagates in the tissue and, in the meantime, a pulse-echo ultrasound is performed to follow the shear wave and measure its velocity. The propagation velocity is directly related to the tissue stiffness. The harder the tissue, the faster the shear waves propagates [13]. With this method LS can be measured in normal and pathological individuals, the results being measured in kiloPascals (values between 2.5 and 75 kPa).

LSM was performed according to the classical methodology [10, 14] by three physicians who had previously performed at least 50 examinations, considered to be sufficient for a proper training [15]. The measurements were made on patients lying in dorsal decubitus with the right arm in maximal abduction. The right lobe of the liver was aimed at, through the intercostal spaces. The tip of the probe transducer was covered with coupling gel and placed on the skin, between the ribs at the level of the right lobe of the liver. The operator, assisted by ultrasound time-motion and A-mode images provided by the system, located a portion of the liver free of large vascular structures that was at least 6 cm thick. Once the measurement area was located, the operator pressed the probe button to begin an acquisition. Ten successful acquisitions were performed in each patient.

The success rate was calculated as the ratio of the number of successful acquisitions over the total number of acquisitions. In each patient 10 VM were performed, after which a median value of the LS was obtained, measured in kPa. Only in patients in which LSM had a success rate of at least 60%, with IQR<30%, the measurements were considered reliable (IQR = interquartile range, which is the difference between the 75th percentile and the 25th percentile, essentially the range of the middle 50% of the data). Failure was defined if 10 VM could not be obtained with a success rate of at least 60%, with IQR<30%, otherwise the result would not be reliable, according to the latest published data [16].

Statistical analysis

The data we obtained from our patients were collected in a Microsoft Excel file. The statistical analysis was performed using Microsoft Excel and GraphPad Prism programs. For the statistical study of quantitative variables, the mean and standard deviation were calculated. Unpaired t-test was used to compare means. The diagnostic performance of LS measurements was assessed by using receiver operating characteristics (ROC) curves. Optimal cutoff values for LS measurements were chosen to maximize the sum of Sensitivity (Se) and Specificity (Sp). Sensitivities and specificities were calculated according to standard methods.

Results:

Our group of 596 patients included 276 women and 320 men, mean age 63.5±2.1 years. The etiology of liver cirrhosis was: HCV infection in 307 (51.5%) cases, HBV infection in 74 (12.4%) cases, biviral infection (HBV+HDV, HCV+HBV, HBV+HIV) in 23 (3.9%) cases, alcoholic in 146 (24.5%) cases, viral + alcoholic in 15 (2.5%) cases, autoimmune in 4 (0.7%) cases, primary biliary cirrhosis in 14 (2.3%) cases, haemochromatosis in 1 (0.2%) case and cryptogenic in 12 cases (2%) (Fig.1).
The LS measurements ranged from 11.1 to 75 kPa. By using a cut-off value of 12.5 kPa for the diagnosis of cirrhosis 577 of the 596 patients were correctly classified (96.8%). If a cut-off value of 14.6 kPa was used 507 of the 596 patients were correctly classified (85.1%).

The mean LS values in various subgroups of patients, according to the degree of EV are presented in Table 1 and Fig. 2.

<table>
<thead>
<tr>
<th>Esophageal varices</th>
<th>Number of cases</th>
<th>Mean value of LS (kPa)</th>
<th>Standard deviation (kPa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No EV</td>
<td>253</td>
<td>20.04</td>
<td>9.95</td>
</tr>
<tr>
<td>Grade I EV</td>
<td>107</td>
<td>26.29</td>
<td>12.12</td>
</tr>
<tr>
<td>Grade II EV</td>
<td>155</td>
<td>39.78</td>
<td>16.66</td>
</tr>
<tr>
<td>Grade III EV</td>
<td>80</td>
<td>60.38</td>
<td>17.17</td>
</tr>
</tbody>
</table>

We found a strong, direct, statistically significant correlation between the value of LS measurements and the severity of EV: Spearman correlation index $r=0.703$, ($p<0.0001$).

The mean value of LS measurements in patients with large varices (grade II and III - N=238) was 46.9±19.5 kPa, statistically significant higher than in patients with no or small varices - N=358 (21.7±10.6 kPa), $p<0.0001$.

We tried to establish the value of LS which best predicts the presence of significant varices (at least grade II, considered to have a high risk of bleeding). For a cut-off value of 23.3 kPa, LS measurement by means of FibroScan had 72.1% sensitivity and 87.8% specificity for predicting the presence of large EV, with 71% PPV and 87.3% NPV, AUROC=0.8811 ($p<0.0001$) (Fig. 3).

In subjects with large EV, we found out that the mean value of LS in the subgroup with a history of variceal bleeding (N=80) was statistically significant higher than in patients with no history of bleeding (N=158): 55.2±19.4 kPa vs. 28.1±16.4 kPa, $p<0.001$.

We tried to establish the value of LS that best predicts the risk of bleeding. For a cut-off value of 41.3 kPa, LS measurement had 54.7% sensitivity and 80.0% specificity for predicting variceal rupture, with 85% PPV and 45.9% NPV, AUROC=0.6816 ($p<0.0001$) (Fig. 4).
Discussions

As we mentioned above, advanced cirrhosis can be diagnosed sometimes based only on clinical signs, but compensated LC is not always easy to diagnose. LB also has its shortcomings, one of the most important, the fact that it is an invasive method. There were some studies that investigated the utility of abdominal ultrasound for the diagnosis of liver cirrhosis: the one performed by Zheng demonstrated an accuracy of 80.7% [17] and the one performed by Gaiani, an accuracy of 80.7% [18].

Until the development of LS assessment by means of TE, we did not have a very accurate method for the diagnosis of liver cirrhosis. TE had been proven a reliable tool for assessing hepatic fibrosis in patients with chronic C hepatitis [11, 19] with achieving the greatest accuracy for detecting severe fibrosis and cirrhosis [20, 21]. In addition, in patients with cirrhosis, TE may be of prognostic value in predicting OV [22, 23].

The optimal TE cut-off for the diagnosis of cirrhosis has not been decided upon yet, since reported cut-offs for cirrhosis range from 10.3 kPa in chronic hepatitis B to 17.3 kPa in chronic cholestatic diseases [24]. In a large series of patients with chronic liver diseases of various etiologies (approximately 35% of them with chronic C hepatitis), Ganne-Carrié et al. proposed a cut-off of 14.6 kPa [21] and suggested that TE cut-off values could be optimized if specifically defined for each etiology. In another study a cut-off value of 12.5 kPa was proposed for cirrhosis in chronic C hepatitis [11].

In our study, in which more than 50% of the patients were chronically infected with C hepatitis virus, by using a cut-off value of 12.5 kPa for the diagnosis of cirrhosis, 96.8% (577/596) of the patients were correctly classified. If a cut-off value of 14.6 kPa was used, 85.1% (507/596) of the patients were correctly classified. These data confirm those we obtained in a previous, smaller study, in which, using a cut-off value of 14 kPa, 89.6% of patients (155/173 subjects) have been correctly classified. If a cut-off value of 13 kPa was used, 92.5% of patients (160/173 subjects) have been correctly classified [25].

It is a well known fact that cirrhosis places the patient at risk of clinical complications, such as portal hypertension, and that variceal bleeding is the second cause of death in cirrhosis, justifying early screening for EV. The usual means of diagnosing EV is upper gastrointestinal endoscopy. However, endoscopy can be considered invasive due to the technique and to the level of discomfort of the patient.

Data regarding the value of LS for predicting the presence and severity of EV are contradictory. In some previous studies, LS values smaller than 19 kPa were highly predictive for the absence of large EV (grade II and III), and the proposed cut-off values for the presence of grade II and III EV ranged from 27.5 to 35 kPa and the one for esophageal bleeding was 62.7 kPa [22-24]. Other studies concluded that TE was not accurate in the prediction of EV, with an AUROC ranging from 0.76 to 0.84 [26, 27]. Although sensitivity was good (71%-96%), specificity and PPV were low (60%-80% and 48%-54%) and overall accuracy was inferior as compared to simple tests like platelet count/spleen diameter ratio [26, 27].

In our study, for a cut-off value of 23.3 kPa, LS measurement had a good sensitivity (72.1%) and very good specificity (87.8%) for predicting the presence of large EV, also with good PPV (71%) and NPV (87.3%), AUROC=0.8811 (p<0.0001) (Fig. 3). Our data is consistent with previous published ones, confirming the value of LS measurement for predicting the presence of large EV [22, 23, 28]. Also, we found a strong, direct, statistically significant correlation between the value of LS measurements and the severity of EV: Spearman correlation index r=0.703, (p<0.0001).

Another problem arising from these studies is the wide range of proposed cut-offs, varying from 13.9 to 21.3 kPa for all varices, from 19 to 30 kPa for grade II varices and from 55 to 63 kPa for bleeding varices [20, 29]. The optimal cut-offs therefore are still to be defined. Foucher and colleagues (2006) assessed the accuracy of FibroScan for the detection of large EV and the risk of variceal bleeding in patients with chronic liver disease. For the presence of grade II and III EV, and for variceal bleeding, the proposed cut-offs were 27.5, and 62.7 kPa, respectively [20]. The authors concluded that LS measurement for the follow-up and management of cirrhotic patients could be of great interest and should be further evaluated.

In our study, even if the mean value of LS in the subgroup of patients with a history of variceal bleeding was statistically significant higher than in patients with no history of bleeding (55.2±19.4 kPa vs. 28.1±16.4 kPa, p<0.001), the predictive value of LS for predicting variceal bleeding was not as good as expected. For a cut-off value of 41.3 kPa (chosen in order to maximize the sum of sensitivity and specificity), LS measurement had only 54.7% sensitivity and 80.0% specificity for predicting variceal rupture, with 85% PPV and 45.9% NPV, AUROC=0.6816 (p<0.0001). Considering the data presented above, we consider that upper digestive endoscopy could be avoided in patients with LS values smaller that 23 kPa, due to the low probability of them having large EV, but at higher values, endoscopy should be mandatory in order to accurately assess the severity of EV and the need for prophylactic therapy.
**Conclusion**

Based on the data from our study we can conclude that LS measurement is a reliable tool for predicting the presence of cirrhosis and of large EV. However, in patients with high values of LS, endoscopy should be performed in order to accurately assess their presence and severity.

**References**

26. Lim JK, Groszmann RJ. Transient elastography for diagnosis of portal hypertension in liver cirrhosis: is there still a role for hepatic venous pressure gradient measurement? Hepatology. 2007 May; 45 (5) : 1087-90.