

Liver Stiffness Measurement by Transient Elastography in Clinical Practice

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Abstract

The **aim** of our study was to evaluate the results of transient elastography assessment of liver stiffness (LS) in various categories of patients. **Material and method.** We performed transient elastography in 986 patients. We evaluated: the percentage of cases in which valid measurements could be obtained; the values of LS in 40 patients with no history of chronic liver disease (“normal” patients); 44 inactive HBsAg carriers; 173 patients with proven liver cirrhosis; and the correlation between liver biopsy results and LS in 93 patients with chronic HCV hepatitis. **Results.** We obtained valid measurements of LS in 94.6% of the 986 cases. Male gender, younger age and low BMI were positive predictive factors for obtaining valid measurements. The mean values of LS were: 5.2 ± 1.3 kPa in “normal” patients, 5.8 ± 2.6 kPa in inactive HBsAg carriers, 37.2 ± 20.9 kPa in patients with liver cirrhosis. In patients with chronic HCV hepatitis, we found that the mean value of LS in those with METAVIR $F \geq 2$ was 8.5 ± 4.2 kPa, higher than in those with $F < 2$: 5.3 ± 1.4 kPa ($p = 0.0017$). In patients with $F \geq 3$, the mean value of LS was 11.1 ± 4.3 kPa, significantly higher than in patients with $F < 3$: 6.1 ± 2.5 kPa ($p < 0.0001$). **Conclusions.** Liver stiffness, as a marker of fibrosis, can be evaluated by means of transient elastography in a great majority of patients. It is a useful method for the exclusion of significant liver fibrosis and for predicting liver cirrhosis. As compared to liver biopsy, transient elastography can discern significant fibrosis from no or mild fibrosis.

Key words

Transient elastography – chronic liver diseases – liver biopsy.

Introduction

Chronic liver diseases are frequent diseases in the general population, especially in areas with a high incidence of infection with hepatitis viruses. According to WHO data, in Romania approximately 5% of the population is infected with hepatitis B virus (HBV) and 4-5% with hepatitis C virus (HCV) [1]. Besides chronic viral hepatitis, alcoholic steatohepatitis (ASH) and non-alcoholic steatohepatitis (NASH) must be taken into consideration as frequent causes of liver damage. It is estimated that NASH incidence is rising, currently affecting 2-3% of the adult population [2-4].

In the evolution of chronic viral and non-viral hepatitis, liver fibrosis is a very important factor associated with prognosis. Therefore, a precise evaluation of the severity of fibrosis in those patients is compulsory, in order to perform a correct staging and eventually to decide the treatment. Currently, liver biopsy (LB) seems to be the optimal method to evaluate changes in fibrosis over time [5]. Nevertheless, LB has its shortcomings: the intra- and interobserver variability [6, 7]; the sampling variability [8]; its invasive character, with morbidity and mortality higher than 0.

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 LB. The most promising non-invasive methods are the FibroTest – ActiTest [9] and the transient elastography (TE) [10, 11].

Material and methods

Since a FibroScan device (EchoSens, Paris, France) was recently acquired in the Department of Gastroenterology and Hepatology Timișoara, we evaluated the clinical value of this method over an 8 month period. Between June 2007 and January 2008 we performed a TE evaluation of liver stiffness (LS) in 986 successive patients.

We analyzed LS in various diseases, and compared the results obtained with other “classic” methods of evaluation of liver fibrosis, namely LB.

We assessed the following: a. the percentage of cases in which valid measurements (VM) of LS could be obtained by

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means of TE; b. the LS values in “normal” subjects (patients with not known history of chronic liver disease - students, medical personnel, patients from departments other than gastroenterology and hepatology, i.e. nephrology, etc.); c. the LS values in inactive HBsAg carriers (subjects with persistent normal ALT/AST, HBeAg-, anti-HBe+, serum HBV DNA < 2,000 IU/ml); d. the LS diagnostic sensitivity in patients with proven liver cirrhosis and without ascites (as recommended in the literature); e. the TE results as compared to LB (performed in the same session) in patients with chronic HCV hepatitis.

The GraphPad Prism program was used for the statistical analysis of the group.

Results

The demographic data and the characteristics of our patients are presented in Table I.

a. Failure to obtain a VM was observed in 54 from the 986 patients (5.4% of cases). Failure was considered if no value was obtained after 10 measurements. Only measurements with a success rate >60% and with an IQR<30% were taken into consideration. The proportion of failure among females was significantly higher (35/480 – 7.3%) than in males (19/506 – 3.7%) ($p=0.017$, $RR=0.736$). The mean age in the failure group was 54.4 ± 9.6 , higher than in the VM group (50.5 ± 14.1) ($p=0.044$).

The mean body mass index (BMI) in the failure group was 30.4 ± 5.8 , higher than in the VM group (26.1 ± 4.5) ($p<0.0001$). We did not find significant differences between the mean height in the failure group (167.4 ± 9 cm) vs. the VM group (168.2 ± 9.3 cm) ($p=0.6577$).

Thus, male gender, younger age and low BMI had a positive influence for obtaining VM of LS by means of TE.

b. Liver stiffness was evaluated in 40 patients with no known history of chronic liver disease (“normal” subjects). The mean value of LS in normal patients was 5.2 ± 1.3 kPa, ranging from 3 to 8.1 kPa, but most of the patients had LS between 4 and 6 kPa.

c. In the subgroup of inactive HBsAg carriers (44 patients), the mean value of LS was 5.8 ± 2.6 kPa (ranges 3.3 - 20.1 kPa). In one case, VM could not be obtained. There was no statistically significant difference between the mean value of LS in inactive HBsAg carriers as compared to normal individuals (5.8 vs. 5.2 kPa) ($p=0.172$).

d. The subgroup of patients with liver cirrhosis comprised 181 patients. Liver cirrhosis was confirmed by LB in 30 cases and by clinical, biological, ultrasound and endoscopic criteria (esophageal varices) in the rest of the cases. The LS could be measured in 95.6% of the cases (173/181); in 4.4% of the cases, VMs could not be obtained.

The mean value of LS in this group (173 patients) was 37.2 ± 20.9 KPa (ranges 5.9 to 75 kPa): 41/173 (23.7%) of the patients had values of LS < 20 kPa, and 76.3% (132/173) had values > 20 kPa.

In our cohort of patients, using a cut-off value of 14 kPa, 89.6% of patients (155/173 subjects) were correctly classified. If a cut-off value of 13 kPa was used, 92.5% of patients (160/173 subjects) were correctly classified (7.5% of patients with proven cirrhosis had lower values).

The LS values in the subgroup of patients with liver cirrhosis were largely dispersed, reflecting the various degrees of fibrosis in various stages of cirrhosis.

d. In the 93 patients with chronic HCV hepatitis (Table II, Fig.1), in whom LB and LS assessment were performed in the same session, in 5 cases we could not obtain VMs of LS. In the remainder 88 cases, the mean value of LS was 7.8 ± 4 kPa (ranges 2.3 - 20.9 kPa).

The mean value of LS in patients with significant fibrosis (69 patients with $F\geq 2$ METAVIR) was 8.5 ± 4.2 kPa, significantly higher than in patients with no or mild fibrosis (19 patients with $F<2$) 5.3 ± 1.4 kPa ($p=0.001$). We found that the mean value of LS in patients with F0 and F1 was almost similar to the one we obtained in normal subjects (5.3 ± 1.4 vs. 5.2 ± 1.3 kPa, $p=0.792$). The mean value of LS in patients with severe fibrosis (30 patients with $F\geq 3$ METAVIR) was 11.1 ± 4.3 kPa, significantly higher than in patients with moderate fibrosis (58 patients with $F<3$): 6.1 ± 2.5 kPa ($p<0.0001$).

The statistical analysis of these subgroups showed that there were no significant differences between the mean values of LS in the F0 vs. F1 subgroup, F0 vs. F2 subgroup and F1 vs. F2 subgroup, respectively (meaning that cases with mild and no fibrosis cannot be differentiated by means of TE evaluation of LS). The comparison of the mean values of LS between the other subgroups showed significant differences: F0 vs. F3 $p=0.009$, F0 vs. F4 $p=0.001$, F1 vs. F3 $p=0.001$, F1 vs. F4 $p<0.0001$, F2 vs. F3 $p=0.005$, F2 vs. F4 $p<0.0001$. F3 vs. F4 $p=0.017$.

In our study, for a cut-off value of 6.8kPa, the AUROC analysis showed an accuracy of 73.6% in differentiating

Table I. Demographic data, BMI and technical parameters of TE measurements of the patients included in our study

Category	Total number	Females	Males	Mean age (years)	BMI (kg/m ²)	SR (%)	IQR
All patients	986	48.7% (480)	51.3% (506)	50.7±13.9	26.1±5	83.5±19.4	2.8±3.8
“Normal” patients	40	23 (57.5%)	17 (42.5%)	37±16.9	22.7±4	85.6±17.9	0.9±0.7
Inactive HBsAg carriers	44	23 (52.3%)	21 (21.7%)	39.4±13.2	25.5±4.5	84.2±19.8	1.2±0.8
Patients with liver cirrhosis	181	65 (35.9%)	116 (64.1%)	56.1±11.7	26±4.9	83.1±19.7	6.4±6.3
Patients with HCV chronic hepatitis	93	63 (67.7%)	28 (32.3%)	47.7±12.3	25.8±4.7	85.1±18.6	1.4±0.9

SR - success rate; IQR - interquartile range.

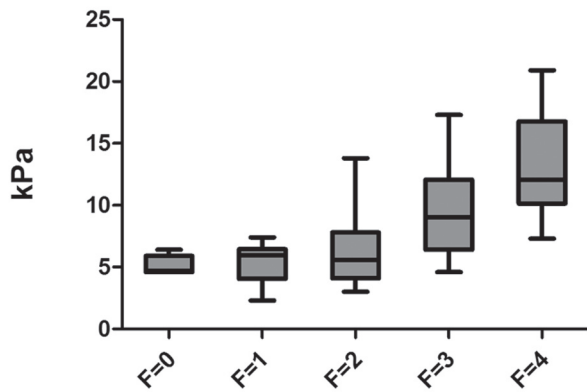


Fig 1. The mean values of liver stiffness in the subgroups of HCV patients, according to the degree of fibrosis.

Table II. Mean values of LS according to fibrosis in HCV patients

Fibrosis (METAVIR)	Number of cases	Mean value of LS (kPa)
F=0	5	5.1±0.8
F=1	14	5.3±1.5
F=2	39	6.5±2.8
F=3	16	9.3±3.5
F=4	14	13.2±4.4

patients with significant fibrosis (at least F2 METAVIR) from patients with no or mild fibrosis (F0 and F1), with a sensitivity of 56.5%, specificity of 94.7%, PPV of 97.5% and NPV of 37.5% (Fig.2). For a cut-off value of 8.8kPa, the AUROC analysis showed an accuracy of 85.4% in differentiating patients with severe fibrosis (\geq F3), from patients with at most moderate fibrosis (F0, F1 and F2), with a sensitivity of 63.3%, specificity of 87.9%, PPV of 73.1% and NPV of 82.3% (Fig.3).

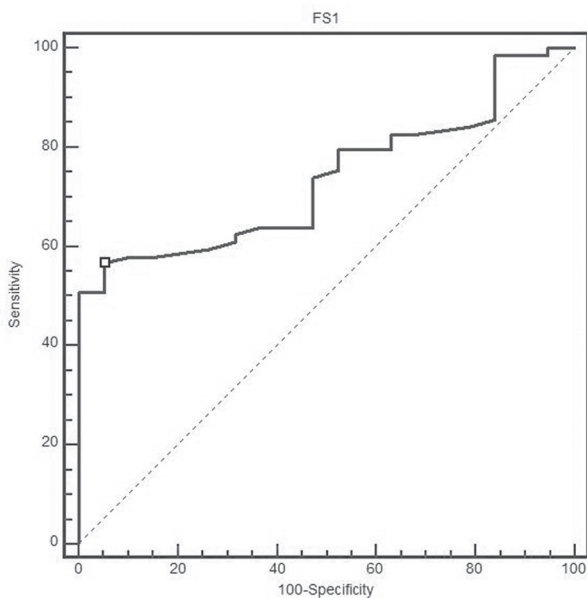


Fig 2. The AUROC for the liver stiffness predictive value of the presence of significant fibrosis (at least F2 METAVIR).

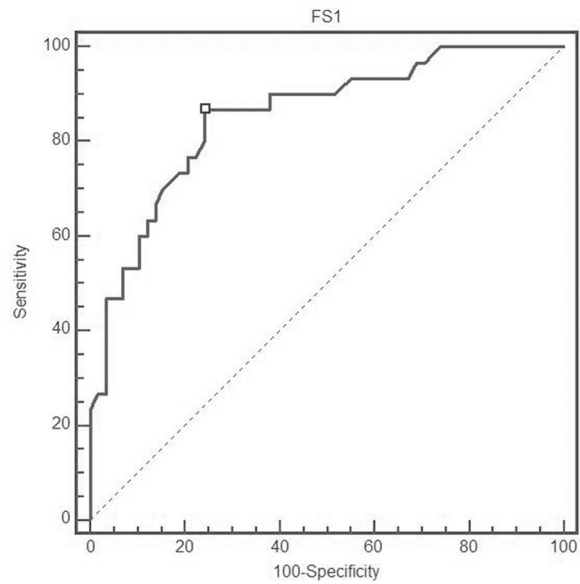


Fig 3. The AUROC for the liver stiffness predictive value of the presence of severe fibrosis (at least F3 METAVIR).

Discussion

As expected, the rate of VMs obtained is not 100%, failure to obtain VMs being associated with the presence of obesity and with the lack of adequate intercostal spaces. In a study performed on 2,114 LS measurements by means of TE, failure to obtain VM was reported in 4.5% of the cases [12]. The univariant analysis showed that it was associated with BMI>28 (p<0.001), diabetes mellitus (p=0.01), age >50 years (p<0001), steatohepatitis (p=0.001). Failure to obtain VM was not operator dependent and was not associated with the patient gender, or with the transaminase level. In the multivariate analysis, the only factor associated with failure to obtain VM was BMI>28 (p=0.001) [12].

In our study, a similar percentage failure to obtain VM was observed (5.6% of the cases). Male gender, younger age and low BMI were the factors that had a positive influence on obtaining VM by TE. The height of the patients did not influence the ability to obtain VM.

We assessed the value of TE in patients with not known history of chronic liver disease, in order to determine the normal values of LS in healthy subjects. The subgroup of “normal” subjects did not undergo any complementary investigation (such as abdominal ultrasound, liver laboratory work-out or viral markers). In these subjects, the mean value of LS was 5.2±1.3 kPa, ranging from 3 to 8.1 kPa. We observed a wide range of values in “normal” subjects, as well as the fact that a rather large proportion of the patients with not known history of chronic liver disease had LS > 6 kPa (22.5%). In all these cases the questions to be answered are: what are the limits of “normal” LS as measured by TE or whether, in these cases, we encountered a rather atypical Gauss distribution of LS. Further LS evaluation of “normal” subjects, in order to cover all age groups, and further investigation of individuals with higher values of LS in order

to exclude a latent liver disease are necessary.

Transient elastography was developed to evaluate mainly patients with chronic HCV hepatitis. Lately, TE has been successfully used for the assessment of fibrosis in other chronic liver diseases [13-15] especially in chronic HBV hepatitis [13]. In the inactive HBsAg carriers evaluated in the present study, the mean value of LS was 5.7 ± 2.7 kPa, ranging from 3.5 to 20.1 kPa. The great majority of cases had LS < 8 kPa (thus excluding significant fibrosis), and only in two cases the LS was > 8 kPa (confirmed by repeated, "blinded", measurements). These two patients should undergo LB to see if they really have significant fibrosis, or if it is only an artefactual error. The mean value of LS in "normal" patients was not significantly different from that in inactive HBsAg carriers (5.8 vs. 5.2 kPa, $p=0.172$). Therefore, the TE evaluation of LS in these patients could be a good surveillance method for the evolution of liver disease.

Although in advanced liver cirrhosis the clinical signs are diagnostic, compensated liver cirrhosis is not always easy to diagnose. Liver biopsy can miss diagnosis in up to 20% of the cases [6], and diagnostic laparoscopy is an invasive method. The studies that investigated the utility of abdominal ultrasound for the diagnosis of liver cirrhosis found an accuracy of 80.7% [16, 17]. Transient elastography seems to be a promising diagnostic method in these patients. Using a cut-off value of 14 kPa, 89.6% of our patients were correctly classified. If the cut-off value of 13 kPa was used, 92.5% of patients were correctly classified. According to various authors, the cut-off value of LS for the diagnosis of cirrhosis varies between 13 and 17.6 kPa. In a study performed by Foucher et al, the cut-off value was established at 17.6 kPa [18]. In this study, NPV and PPV for the diagnosis of cirrhosis were 92% and 91%, respectively.

In a recent meta-analysis [19], the sensitivity of TE for the diagnosis of liver cirrhosis was 87% (95% CI 84%-90%), the specificity 91% (95% CI, 89%-92%), the positive likelihood ratio 11.7 (95% CI, 7.9-17.1) and the negative likelihood ratio 0.14 (95% CI 0.10-0.20).

We also studied the correlation between the LS values measured by means of TE and the severity of fibrosis as assessed by LB in patients with HCV chronic hepatitis. In a prospective multicentric French study performed on 327 HCV patients who were evaluated by means of percutaneous LB and valid TE examination, a significant correlation was found between fibrosis and the LS measured by TE ($r=0.55$) ($p<0.001$) [20]. This study tried to establish cut-off values for LS that could differentiate between various stages of fibrosis. The cut-off value of 8.7 kPa differentiated F0 and F1 from F2, F3 and F4 with a sensitivity of 55%, specificity of 84%, PPV 87% and NPV of 51%. The conclusion of this study was that the evaluation of LS by means of TE is a reliable method for the assessment of liver fibrosis in patients chronically infected with HCV.

In our study the optimal cut-off value for significant fibrosis (at least F2 METAVIR) was 6.8 kPa. The diagnostic performance of the LS measurement in our patients, for cut-off values of 6.8 kPa (optimal in our study), 7.1 kPa (optimal

in a study by Castera et al) [11] and 8.7 kPa (optimal in a study by Zioli et al) [20] are presented in Table III.

Table III. Diagnostic performance of TE measurements for predicting significant fibrosis (at least F2 METAVIR) in patients with chronic HCV hepatitis

Cut-off value	Sensitivity	Specificity	PPV	NPV
6.8 kPa	56.5%	94.7%	97.5%	37.5%
7.1 kPa	54.3%	94.7%	97.4%	36.3%
8.7 kPa	39.1%	100%	100%	31.1%

All these data, added to previous studies [11, 21, 22], demonstrate the value of TE in the non-invasive evaluation of fibrosis. Accordingly, TE could be used in patients with chronic HCV hepatitis to differentiate patients that should be treated ($F \geq 2$) from those that do not need treatment ($F \leq 1$).

Conclusions

The liver stiffness evaluation by means of transient elastography allows to obtain valid measurements in the great majority of scanned patients. It is a good method for excluding with sufficient accuracy significant fibrosis and also for predicting the presence of liver cirrhosis. In patients with chronic HCV hepatitis, when evaluating it in comparison with liver biopsy as the "gold standard", transient elastography can differentiate between significant fibrosis and absent or mild fibrosis. Liver stiffness assessment by transient elastography is a useful non-invasive method for the evaluation of chronic liver disease in clinical practice.

Conflicts of interest

None of the authors have any conflicts of interest.

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