

Liver stiffness measurements in patients with HBV vs HCV chronic hepatitis: A comparative study

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Abstract

AIM: To assess the values of liver stiffness (LS) in patients with hepatitis B virus (HBV) chronic hepatitis and to compare them with those in patients with hepatitis C virus (HCV) chronic hepatitis.

METHODS: The study included 140 patients with HBV chronic hepatitis, and 317 patients with HCV chronic hepatitis, in which LS was measured (FibroScan®-Echosens®) and liver biopsy was performed in the same session (assessed according to the Metavir score).

RESULTS: According to the Metavir score of the 140 HBV patients: one had F0, 32 had F1, 67 had F2, 33 had F3 and 7 had F4. Of the 317 HCV patients: 5 had F0, 34 had F1, 146 had F2, 93 had F3 and 39 had F4. For the same severity of fibrosis, the mean values of LS in HBV patients were similar to those in HCV patients: F1, 6.5 ± 1.9 kPa vs 5.8 ± 2.1 kPa ($P = 0.0889$); F2, 7.1 ± 2 kPa vs 6.9 ± 2.5 kPa ($P = 0.3369$); F3, 9.1 ± 3.6 kPa vs 9.9 ± 5 kPa ($P = 0.7038$); F4, 19.8 ± 8.6 kPa vs 17.3

± 6.1 kPa ($P = 0.6574$). A significant direct correlation between LS measurements and fibrosis was found in HCV patients (Spearman's $r = 0.578$, $P < 0.0001$), as well as in HBV patients ($r = 0.408$, $P < 0.0001$). The correlation was more significant in HCV than in HBV patients (Fisher's Z -test, $Z = 2.210$, $P = 0.0271$).

CONCLUSION: In our group, the mean values of LS in patients with chronic B hepatitis were similar to those in patients with chronic HCV hepatitis, for the same stage of fibrosis. Also, LS was correlated with the severity of fibrosis both in HBV and HCV chronic hepatitis patients.

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Key words: Chronic B hepatitis; Chronic C hepatitis; Fibrosis; Transient elastography; Liver biopsy

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INTRODUCTION

The non-invasive assessment of fibrosis in chronic hepatitis, especially of viral etiology, is accepted more and more, partially replacing liver biopsy (LB) in some countries^[1]. Guidelines from France^[1] recommend that the first-line test for untreated patients with hepatitis C virus (HCV)

chronic hepatitis, with no comorbidities, should be a non-invasive procedure (either FibroTest[®] or FibroScan[®]).

The non-invasive methods used for the evaluation of chronic hepatitis are: serum markers (the best known is FibroTest-ActiTest - a biochemical test which uses 6 serum biomarkers, correlated with the age and gender of the patient in a mathematical formula)^[2-5]; transient elastography (TE) (FibroScan[®])^[6,7]; SonoElastography (Real-Time Tissue Elastography)^[8-11] and magnetic resonance imaging elastography^[12,13].

Recent meta-analyses^[7,8] have tried to assess the practical value of TE for the evaluation of patients with chronic hepatitis. Many studies were published regarding the value of TE for evaluation of patients with HCV chronic hepatitis, but only a few studies in patients with chronic hepatitis B virus (HBV) infection. On the other hand, published data showed discordant results regarding liver stiffness (LS) in patients with HBV and HCV chronic hepatitis^[14,15].

The aim of our study was to determine whether the values of LS evaluated by means of TE (FibroScan[®]) were similar for the same degree of fibrosis (evaluated by means of LB), in patients with chronic HBV and HCV hepatitis.

MATERIALS AND METHODS

Patients

Our study included a total of 457 successive patients, 140 with HBV chronic hepatitis and 317 with HCV chronic hepatitis. All the patients were referred to our department during a 2-year period (January 2008 to December 2009) for hepatitis assessment (according to the guidelines valid in Romania in that period, LB was mandatory for fibrosis staging). LS was evaluated in all patients by means of FibroScan, and LB was performed in the same session during the standard of care evaluation of patients with chronic hepatitis. The inclusion criteria were: (1) HCV chronic hepatitis: patients with positive anti-HCV antibodies for at least 6 mo, with or without cytolysis; detectable viral load by polymerase chain reaction (PCR); pathological lesions of chronic hepatitis demonstrated by LB; no signs of decompensated liver disease (actual or history of jaundice, ascites); and (2) HBV chronic hepatitis: patients with positive HBsAg for at least 6 mo, with or without cytolysis; positive or negative HBeAg; HBV DNA > 2000 IU/mL (> 10000 copies/mL) by PCR; pathological lesions of chronic hepatitis demonstrated by LB; no signs of decompensated liver disease (actual or history of jaundice, ascites).

TE

TE was performed in all 457 patients with the FibroScan[®] (Echosens[®], Paris, France) by 3 experienced physicians (each having performed more than 1000 TE examinations). In each patient, 10 valid measurements were performed, after which a median value of LS was obtained, measured in kilopascals (kPa). Only patients in which LS measurements had a success rate of at least 60%, with an

interquartile range (IQR) < 30%, were included in our study. The success rate was calculated as the ratio of the number of successful acquisitions over the total number of acquisitions. IQR is the difference between the 75th percentile and the 25th percentile, essentially the range of the middle 50% of the data.

LB

Echo-assisted LB was performed in all 457 patients, using Menghini type modified needles, 1.4 and 1.6 mm in diameter. Only LB fragments of at least 2 cm, including at least 8 portal tracts, were considered adequate for the pathological interpretation. All the LBs were assessed according to the Metavir score, by a senior pathologist. Fibrosis was staged on a 0-4 scale: F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis and few septa extending into lobules; F3, numerous septa extending to adjacent portal tracts or terminal hepatic venules and F4, cirrhosis.

Statistical analysis

For a statistical analysis of quantitative variables, the mean and standard deviation were calculated. Two-way ANOVA test and *t*-tests were performed, to compare mean values of LS in various fibrosis subgroups in HBV vs HCV patients. To compare correlations, Fisher's Z test was used (hypotheses about the value of the population correlation coefficient ρ between variables X and Y can be tested using the Fisher transformation applied to the sample correlation coefficient r)^[16]. The diagnostic performance of LS measurements was assessed using receiver operating characteristics (ROC) curves. ROC curves were used for the detection of significant fibrosis (F \geq 2 Metavir) and severe fibrosis (F \geq 3 Metavir). Optimal cut-off values for LS measurements were chosen to maximize the sum of sensitivity and specificity. The statistical analysis was performed using Microsoft Excel 2007, GraphPad Prism 5 and MedCalc programs.

RESULTS

Patients

The subgroup of HBV patients consisted of 140 subjects (31 women, 109 men; mean age 39.2 ± 12.8 years). According to the Metavir scoring system, one had F0, 32 had F1, 67 had F2, 33 had F3 and 7 had F4.

The subgroup of HCV patients consisted of 317 subjects (213 women, 104 men; mean age 49.7 ± 10.2 years). According to the Metavir scoring system, 5 had F0, 34 had F1, 146 had F2, 93 had F3 and 39 had F4.

LS measurements by TE

The mean values of LS in HBV patients were not statistically significantly different from those of HCV patients for the same degree of fibrosis (Table 1).

A significant direct correlation of LS measurements with fibrosis was found to exist in HCV patients (Spearman's correlation coefficient $r = 0.578$, $P < 0.0001$), as

Table 1 Mean values of liver stiffness according to fibrosis stage in patients with hepatitis B virus vs hepatitis C virus chronic hepatitis

Category	Hepatitis B virus		Hepatitis C virus		P
	Cases	Mean values of LS (kPa)	Cases	Mean values of LS (kPa)	
Total cases	140	8.1 ± 4.2	317	8.9 ± 5.2	0.395 (NS)
F = 0	1	7.4	5	5.2 ± 0.7	-
F = 1	32	6.5 ± 1.9	34	5.8 ± 2.1	0.0889 (NS)
F = 2	67	7.1 ± 2	146	6.9 ± 2.5	0.3369 (NS)
F = 3	33	9.1 ± 3.6	93	9.9 ± 5	0.7038 (NS)
F = 4	7	19.8 ± 8.6	39	17.3 ± 6.1	0.6574 (NS)

F: Fibrosis; LS: Liver stiffness; NS: Not statistically significant.

Table 2 Predictive value of liver stiffness for the presence of significant fibrosis (F2), severe fibrosis (F3) and cirrhosis (F4) in hepatitis B virus vs hepatitis C virus patients

Parameter	Hepatitis B virus			Hepatitis C virus			All		
	F2	F3	F4	F2	F3	F4	F2	F3	F4
AUROC	0.658	0.753	0.974	0.750	0.797	0.933	0.712	0.786	0.943
Cut-off (kPa)	7	8.8	13.6	6.8	8.6	13.3	6.9	8.7	13.6
Sensitivity (%)	59	53	86	60	62	77	59	60	74
Specificity (%)	70	85	99	88	81	93	78	83	95
PPV (%)	86	58	78	97	71	61	93	68	64
NPV (%)	39	82	99	23	75	96	26	77	97

AUROC: Area under the receiver operating characteristics curve; PPV: Positive predictive value; NPV: Negative predictive value.

well as in HBV patients ($r = 0.408$, $P < 0.0001$). The correlation was more significant in HCV than in HBV patients (Fisher's Z-test, $Z = 2.210$, $P = 0.0271$).

The predictive values of LS measurements for the presence of significant fibrosis (F2), severe fibrosis (F3) and cirrhosis (F4) are presented in Table 2.

DISCUSSION

After a number of articles were published in France regarding the value of transient elastographic LS measurement in the evaluation of fibrosis in chronic hepatitis^[17-22], numerous papers have been published in other countries^[15,23-29] making this method a recognized test worldwide^[30]. A meta-analysis published in 2008^[30] proved that TE had an excellent diagnostic accuracy for the diagnosis of cirrhosis [mean area under the ROC (AUROC), 0.94 (95% CI: 0.93-0.95)]. However, a high variation of the AUROC was found regarding the diagnosis of significant fibrosis, dependent on the underlying liver disease [AUROC for significant fibrosis, 0.84 (95% CI: 0.82-0.86)].

The vast majority of studies assessing TE as compared to LB, were performed in patients with HCV chronic hepatitis^[22,24,28,31,32]. At the same time, many studies were performed to evaluate this method in other chronic hepatopathies, such as nonalcoholic steatohepatitis, hemochromatosis and primary biliary cirrhosis^[6,20,23,25].

Published studies regarding the value of LS measurement by means of TE in patients with HBV chronic hepatitis have shown conflicting results.

A Korean study performed by Seo *et al*^[14] included 64

patients with chronic HBV hepatitis and 27 patients with chronic HCV hepatitis who underwent LB and TE in the same session (about two-thirds male; mean age 40 years, range 14-68 years). In that study, LS measurements were better correlated with the fibrosis score in patients with chronic HCV hepatitis than in those with chronic HBV hepatitis (0.773 vs 0.557, $P < 0.001$). The AUROC was larger in the group of patients with chronic HCV hepatitis (0.944, 0.982, and 0.958 for $F \geq 2$, $F \geq 3$, and F4, respectively) than in those with chronic HBV hepatitis (0.881, 0.863, and 0.850, respectively). The optimal cut-off values for $F \geq 2$ and $F \geq 3$ were similar for patients with chronic HCV hepatitis (7.05 and 11.4 kPa, respectively) and chronic HBV hepatitis (7.15 and 10.75 kPa, respectively). However, sensitivity and specificity were superior in patients with chronic HCV hepatitis. The conclusion of the study was that the efficacy of LS measurement for the assessment of liver fibrosis was superior in patients with chronic HCV hepatitis than in patients with chronic HBV hepatitis.

In a study performed by Ogawa *et al*^[15] in 68 patients with chronic HBV hepatitis and 161 patients with chronic HCV hepatitis, the mean values of LS measurements were 3.5 kPa for F0, 6.4 kPa for F1, 9.5 kPa for F2, 11.4 kPa for F3, and 15.4 kPa for F4 in patients with chronic HBV infection, and 6.3 kPa for F0, 6.7 kPa for F1, 9.1 kPa for F2, 13.7 kPa for F3, and 26.4 kPa for F4 in those with chronic HCV infection. The values were significantly correlated with fibrosis stage for both groups of patients (HBV, $r = 0.559$, $P = 0.0093$, and HCV, $r = 0.686$, $P < 0.0001$). This study concluded that TE was an

Table 3 Cut-off values for different stages of fibrosis in patients with hepatitis B virus chronic hepatitis, proposed by various authors (kPa)

Fibrosis	Marcellin <i>et al.</i> ^[17]	Chang <i>et al.</i> ^[33]	Chan <i>et al.</i> ^[34]	Kim <i>et al.</i> ^[35]
F0	5.1	6.9	5.9	-
F1	6.0	12.2	5.9	9.1
F2	7.0	-	7.0	-
F3	12.8	24.8	8.8	-
F4	23.7	-	14.2	14.0

efficient and simple method for the evaluation of liver fibrosis in patients with chronic viral infection, both in HBV and HCV hepatitis.

Our study, performed on a large cohort of patients (457 subjects) aimed to find out if there were significant differences in LS in patients with HBV vs HCV chronic hepatitis for the same degree of fibrosis, as compared to the LB. LS measurement has a well established value for staging fibrosis in HCV chronic hepatitis, proved by 2 meta-analyses^[7,30]. In patients with HBV chronic infection, data regarding LS measurement for fibrosis staging are conflicting. Why? One explanation could be that the necroinflammatory activity in HBV infection can vary with time, as well as the fact that fluctuations in aminotransferases can occur. Different studies have proposed various cut-off values for different stages of fibrosis, as seen in Table 3.

In our cohort of 140 chronic HBV infected patients, the mean values for F1, F2, F3 and F4 were: 6.5, 7.1, 9.1 and 19.8 kPa, respectively, similar to those obtained in the study performed by Marcellin. Also, we must bear in mind that only the Marcellin study was performed in a Caucasian population (such as ours), the others being performed in Asian populations. In our study, the sensitivity of TE for cirrhosis prediction was better in HBV than in HCV patients, but this finding needs further confirmation since the number of F4 patients in the HBV group was small (only 7) vs 39 in the HCV group.

Regarding the correlation between fibrosis and LS, a significant direct correlation of TE measurements with fibrosis was found to exist in HCV patients (Spearman's correlation coefficient $r = 0.578$, $P < 0.0001$), more significant than in HBV patients ($r = 0.408$, $P < 0.0001$) ($Z = 2.210$, $P = 0.0271$). Thus it is likely that the correlation between LS and fibrosis in HBV patients can be of use in clinical practice.

As mentioned earlier, high levels of aminotransferases can influence the LS values obtained by means of TE, so that LS measurements have to be interpreted in a biochemical context, otherwise there is a risk of overestimating the severity of fibrosis. Also this is why LS measurements are not performed in acute hepatitis or during alanine aminotransferase (ALT) flares in HBV chronic hepatitis^[29,36]. In order to minimize the risk of overestimating fibrosis during ALT flares, Chan *et al.*^[34] calculated LS cut-off values for various stages of fibrosis considering also the aminotransferase levels. In this study, the LS

cut-off value for F3 was 9 kPa in patients with normal ALT and 12 kPa in patients with ALT higher than 5 times the upper limit of normal. The cut-offs for cirrhosis were 12 kPa in patients with normal ALT and 13.4 kPa in those with high ALT.

In conclusion, in our study, LS measured by TE was correlated with the degree of fibrosis both in HBV and HCV patients, the correlation being more significant in HCV patients. Our data showed that there were no statistically significant differences between the mean values of LS in HBV and in HCV patients for the same degree of fibrosis.

COMMENTS

Background

Non-invasive methods for fibrosis assessment in chronic hepatitis, such as transient elastography (TE), are being accepted more and more, replacing the invasive methods, especially in hepatitis C virus (HCV) chronic hepatitis.

Research frontiers

Many studies have been published regarding the value of TE evaluation of patients with HCV chronic hepatitis, but only a few studies in chronic hepatitis B virus (HBV) infection, showing discordant results.

Innovations and breakthroughs

This research article determined if the authors can also use liver stiffness (LS) measurement by TE for the evaluation of patients with HBV chronic hepatitis, and concluded that LS is correlated with fibrosis in both HBV and HCV patients, and that there are no statistically significant differences between the mean LS values in HBV vs HCV patients, for the same degree of fibrosis. These findings are concordant with previous studies by Wang *et al.*, Marcellin *et al.*, and Ogawa *et al.*, indicating that the diagnostic accuracy of LS is comparable in HBV and HCV infection related fibrosis.

Applications

This study showed that LS evaluated by means of TE was correlated with degree of fibrosis in both HBV and HCV patients and that there were no statistically significant differences between the mean values of LS in HBV vs HCV patients for the same degree of fibrosis, so the authors can also use this method for the evaluation of patients with HBV chronic hepatitis in daily practice.

Terminology

TE (FibroScan) is an ultrasound-based method that uses the transmission of low frequency vibrations to create an elastic shear wave that propagates into the liver, followed by the detection of wave propagation velocity, which is proportional to the tissue stiffness, with faster wave progression occurring through stiffer tissue.

Peer review

The authors present the data from their research on whether the accuracy of LS measurement in estimating liver fibrosis differs in people with chronic HCV or HBV infection. Although many reports on small or large populations exist on the same issue, the readers of the journal may find reading the data interesting.

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