

Transient Elastography (Fibroscan) in Patients with Chronic Hepatitis B

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ABSTRACT

AIM: To evaluate the efficacy of transient elastography (TE) in liver fibrosis assessment in chronic hepatitis B (CHB) patients.

METHODS: Patients from two Greek referral centers were included. All patients were antiHBe (+) and underwent liver biopsy (LB) and liver stiffness measurements (LSM) within a 6-month maximum interval. LB had at least 1.5 cm length and was evaluated using the Ishak scoring system by two experienced liver pathologists. Unreliable LSM was defined as an interquartile range (IQR)/LSM >0.3 and/or a success rate (SR) <60%. LSM operators had adequate experience (>100, <500 examinations).

RESULTS: 79 patients were analyzed. LSM was considered unreliable in 20/79 (25.3%). Patients with unreliable LSM tended to be older (54 vs. 47 years, $p=0.08$) and heavier - as measured by body mass index - (27.1 vs. 24.6, $p=0.08$) as compared to those with reliable LSM. The median age of patients with reliable LSM was 47 years (range 22-71). 74% were male and the mean BMI was 25.2 \pm 3.2. The median AST, ALT and HBV-DNA values were: 30 IU/L (12-300); 42 IU/L (13-360); 8.4×10^3 IU/ml ($0-2 \times 10^9$), respectively. The distribution of patients in different fibrosis stages was: 0 ($n=7$), 1 ($n=18$), 2 ($n=17$), 3 ($n=7$), 4 ($n=5$), 5 ($n=2$), 6 ($n=3$). Fibrosis stage was significantly associated with LSM ($r=0.46$, $p=0.0002$). In addition, LSM was associated with AST and ALT levels ($r=0.38$, $p=0.01$; $r=0.32$, $p=0.03$, respectively) and male gender as compared to female (6.7 vs. 5.2, $p=0.04$). The area under receiver-operating characteristic curves were 0.74 for stage ≥ 3 , 0.85 for ≥ 4 , 0.87 for \geq

5 and 0.86 for stage=6. For stage ≥ 5 , the optimal LSM cut-off value was 7.7 kPa by maximizing the sum of sensitivity and specificity (positive predictive value: 26.3%, negative predictive value: 100%).
CONCLUSION: LSM in CHB patients correlates well with fibrosis stages. The cut-off of 7.7 kPa can exclude cirrhosis offering a useful tool for assessing these patients.

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Key words: Transient elastography; Chronic hepatitis B; Liver stiffness; Fibrosis stage; Fibroscan

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INTRODUCTION

Diagnosis and treatment of patients with chronic hepatitis B (CHB) depends significantly on liver fibrosis staging. Liver biopsy (LB) is still considered the "gold standard" to evaluate liver fibrosis and is recommended by the international guidelines. Although generally safe, this procedure is invasive and has a minor possibility of serious adverse events (hemorrhage, death)^[1]. In addition, the accuracy of LB in assessing liver fibrosis varies depending on inter-observer variability and sampling error, resulting in up to 30% false negative results and underestimation of cirrhosis, especially for small (<1.5 cm) or fragmented specimens^[2-5].

Measurement of liver stiffness using transient elastography (TE) (Fibroscan, Echosens, Paris, France) is increasingly used as a non-invasive method of assessing liver fibrosis. Initial results have shown good diagnostic performance for chronic hepatitis C and excellent correlation with underlying liver fibrosis^[6-7]. However, conflicting results regarding the reliability of liver stiffness measurement (LSM) by TE in patients with CHB are reported up to now^[8,9]. While in European countries Fibroscan is widely accepted and used in clinical practice, FDA has not yet approved the use of Fibroscan and it is only used for investigation purposes in the USA. Also, it has been

recently suggested that underlying inflammatory activity and the aminotransferase levels significantly affect TE's accuracy in these patients^[10,11]. The mechanism by which liver stiffness is increased at the time of liver inflammation is unclear.

Aim of our study was to evaluate the accuracy and efficacy of TE in liver fibrosis assessment in CHB patients in everyday clinical practice. Secondary objective was to evaluate the effect of alanine aminotransferase levels (ALT) on TE's accuracy. This is the first Greek multicenter study evaluating the use of Fibroscan for the evaluation of liver fibrosis in chronic hepatitis B Greek patients.

MATERIALS AND METHODS

Patients

CHB antiHBe (+) patients from two Greek referral centers, in whom liver fibrosis assessment was indicated, were included in this retrospective study. CHB was defined as the presence of serum HBsAg for more than 6 months. No patient had HCV or HIV coinfection. Patients with alcoholic liver disease (alcohol consumption >40 g/d) were excluded from this study. All patients underwent LB and TE within a 6-month interval.

Transient elastography

TE was performed by physicians with adequate experience (>100, <500 examinations). Unreliable LSM was defined as an interquartile range (IQR)/LSM >0.3 and/or a success rate (SR) <60%. The diagnostic accuracy of TE was estimated versus LB as the reference standard.

Liver biopsy

LB procedures were performed by experienced hepatologists by the intercostal approach using 1.6 and 1.8 mm diameter Mengini needles. All biopsies had at least 1.5 cm length and were evaluated by experienced liver pathologists using the Ishak scoring system.

ALT measurements

ALT was measured with conventional assays. Patients were stratified according to the level of ALT in two groups: those with ALT levels < 1.5 × upper limit of normal (ULN) and those with ALT levels > 1.5 × upper limit of normal (ULN). The cut-off of 1.5 × ULN was chosen because few patients had ALT levels greater than 2 × ULN, thus precluding from a proper statistical analysis in case a higher cut-off had been chosen.

Statistical analysis

Continuous variables were presented as means±standard deviation or median (range). Comparisons between the two groups were performed using independent t-tests if values were normally distributed or by the Wilcoxon rank sum test if the distribution was not normal. Frequency data were presented as number and percentage and compared using the chi-square test or Fisher's exact test where appropriate. Baseline laboratory values with a significance of $p \leq 0.1$ were entered in a multivariate model of multiple linear regression analysis to explore possible correlations of LSM.

RESULTS

79 patients were included in our study. LSM was considered unreliable in 20/79 (25.3%). Patients with unreliable LSM tended to be older (54 vs. 47 years, $p=0.08$) and heavier -as measured by body mass index- (27.1 vs. 24.6, $p=0.08$) as compared to those with reliable LSM. Further analysis was conducted in the remaining 59

patients. The median age of patients with reliable LSM was 47 years (range 22-71). 74% were male and the mean BMI was 25.2±3.2. The distribution of patients in different fibrosis stages was: 0 ($n=7$), 1 ($n=18$), 2 ($n=17$), 3 ($n=7$), 4 ($n=5$), 5 ($n=2$), 6 ($n=3$).

Liver stiffness measurement

The mean LSM was 6.9±3.2 Kpa. LSM was significantly associated with fibrosis stage (Figure 1). Table 1 presents different correlation coefficient of LSM with demographic and laboratory parameters. As shown, AST and ALT levels were also significantly associated with LSM. However, in multivariate analysis only the fibrosis stage was significantly associated with LSM ($p=0.02$). The area under receiver-operating characteristic curves (AUCs) were 0.74 for stage ≥ 3 (Figure 2), 0.85 for ≥ 4 , 0.87 for ≥ 5 (Figure 3) and 0.86 for stage=6. For stage ≥ 3 , the optimal LSM cut-off value was 6.4 kPa by maximizing the sum of sensitivity and specificity [positive predictive value (PPV): 48.2%, negative predictive value (NPV): 90%]. For stage ≥ 5 , the optimal LSM cut-off value was 7.7 kPa (PPV: 26.3%, NPV: 100%).

Effect of transaminases

Patients were stratified according to ALT elevation in two groups as previously outlined. A significant discrepancy in the correlation of LSM with fibrosis stage was detected between the two groups ($r=0.62$, $p=0.0002$ for patients with ALT < 1.5 × ULN and $r=0.01$, $p=0.96$ for patients with ALT > 1.5 × ULN).

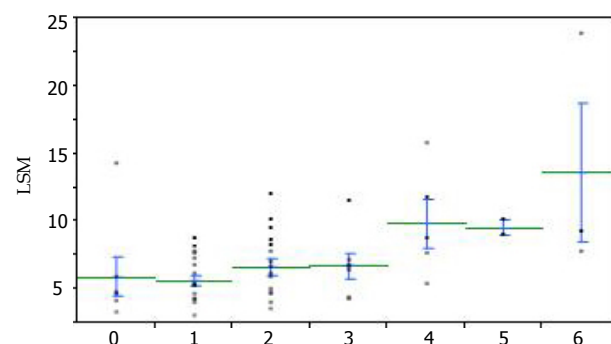


Figure 1 Correlation of different fibrosis stages with liver stiffness measurements.

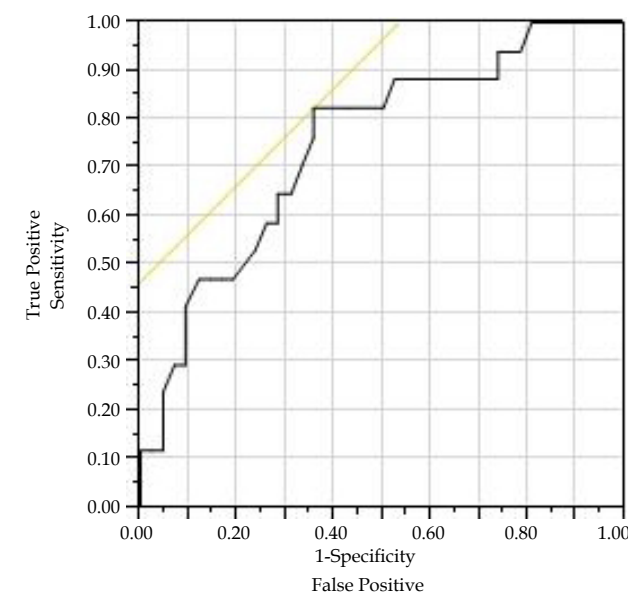


Figure 2 The area under receiver-operating characteristic curve for LSM in patients with fibrosis stage ≥ 3 .

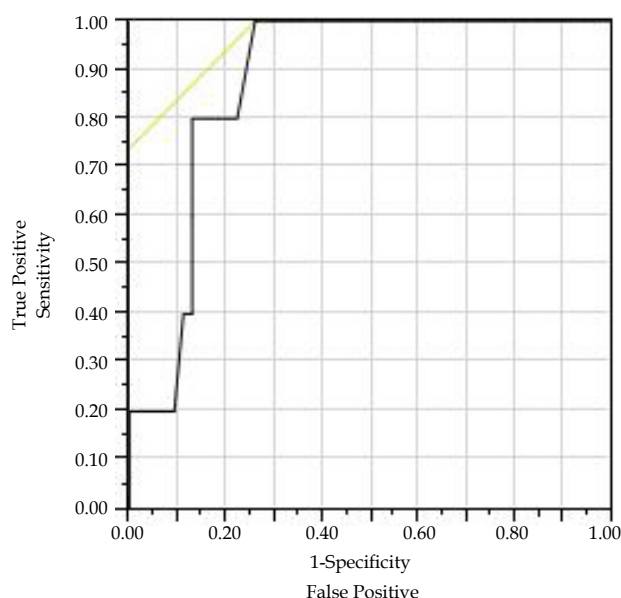


Figure 3 The area under receiver-operating characteristic curve for LSM in patients with fibrosis stage ≥ 5 .

Table 1 Patients' characteristics.

N	59
Age, years	47 (22-71)
Male gender, n (%)	44 (74)
Body mass index	24.6 (18-33)
Fibrosis stage	
0, n (%)	7 (12)
I, n (%)	18 (31)
II, n (%)	17 (29)
III, n (%)	7 (12)
IV, n (%)	5 (8)
V, n (%)	2 (3)
VI, n (%)	3 (5)
AST (IU/L)	30 (12-300)
ALT (IU/L)	42 (13-360)
HBV DNA (IU/mL)	8.4×10^3 ($< 6-2 \times 10^9$)

Data are presented as the median (range) unless otherwise indicated.

Table 2 Pearson's correlation coefficient of LSM.

Parameters	r	P
Age	0.21	NS
Body mass index	0.08	NS
Activity grade	0.25	NS
Fibrosis stage	0.46	0.0002
AST (IU/L)	0.38	0.01
ALT (IU/L)	0.32	0.03
HBV DNA (IU/mL)	0.02	NS

DISCUSSION

Our study assessed the performance of TE in CHB patients using LB as the reference standard. LSM appears to correlate well with fibrosis stages in patients with CHB and ALT levels less than $\times 1.5$ ULN. In patients with ALT levels more than $\times 1.5$ ULN this correlation is poor. It is known that in patients with acute liver disease or acute reactivation on chronic liver damage, LSM is influenced by acute necro-inflammation induced edema and should be avoided^[12-14]. Even a mild-to-moderate elevation in ALT levels may increase LSM regardless of underlying liver fibrosis^[10]. In addition, we found that obesity and age were independent factors of unreliable stiffness measurements. Rigamonti *et al* concluded that TE measurements are significantly affected in both obese and overweight patients by technical limitations and by underestimation of the histological fibrosis stage^[15]. Wong *et al* found that valid measurements were

less likely to be obtained as BMI increased especially above 30 kg/m^2 in non alcoholic fatty liver disease patients^[16]. In another study, age greater than 52 years [OR 1.8 (1.6-2.1); $p < 0.0001$] was an independent factor of invalid measurements^[17].

In our study TE could poorly predict significant fibrosis. However, the performance of TE in excluding cirrhosis was high. Cut-off value of 7.7 kPa can reliably exclude cirrhosis offering a useful everyday tool in the assessment of CHB patients. Marcellin *et al* showed that LSM was significantly ($P < 0.001$) correlated with METAVIR ($r = 0.65$) and Ishak fibrosis stage (0.65). The area under receiver operating characteristic curves were 0.81 for $F > 2$, 0.93 for $F > 3$ and 0.93 for $F = 4$. Optimal LSM cut-off values were 7.2 and 11.0 kPa for $F > 2$ and $F = 4$ respectively^[8]. Gaia *et al* showed that LSM range irregularly from mild fibrosis to cirrhosis, compared to the histological standard in CHB patients. Although the correlation between fibrosis stages and LSM was statistically significant, an overlap of mean stiffness values was observed among patients with both low and high degrees of fibrosis^[9]. Recently, Cardoso *et al* reported that TE measurement accurately predicts the absence or presence of significant fibrosis, advanced fibrosis or cirrhosis in 202 CHB patients and was comparable to that observed in HCV patients^[18]. Verweir *et al* showed that for the diagnosis of fibrosis stages $F \leq 2$ in CHB patients TE is suboptimal, and inflammation may induce higher values. For stages $F \geq 3$ TE performance was good (AUROC's were 0.91 for $F \geq 3$ and 0.90 for $F = 4$)^[19].

In conclusion, TE can reliably exclude cirrhosis offering a useful tool in the clinical assessment of CHB patients. However, current findings do not support the replacement of liver biopsy in routine clinical practice for the detection of significant fibrosis that may warrant antiviral treatment especially in aged patients with a high BMI. In addition, the effect of ALT elevation on TE accuracy suggests that LSM should be optimally used following ALT normalization with antiviral treatment.

REFERENCES

- 1 Bravoo AA, Sheth S, Chopra S. Liver biopsy. *N Eng J Med* 2001; **344**: 495-500
- 2 Castéra L, Nègre I, Samii K, Buffet C. Pain experienced during percutaneous liver biopsy. *Hepatology* 1999; **30**: 1529-1530
- 3 Colloredo G, Guido M, Sonzogni A, Leandro G. Impact of liver biopsy size on histological evaluation of chronic viral hepatitis: the smaller the sample, the milder the disease. *J Hepatol* 2003; **39**: 239-244
- 4 Regev A, Berho M, Jeffers LJ, Milikowski C, Molina EG, Pylsopoulos NT, Feng ZZ, Reddy KR, Schiff ERL. Sampling error and intraobserver variation in liver biopsy in patients with chronic HCV infection. *Am J Gastroenterol* 2002; **97**: 2614-2618
- 5 Siddique I, El-Naga HA, Madda JP, Memon A, Hasan F. Sampling variability on percutaneous liver biopsy in patients with chronic hepatitis C virus infection. *Scand J Gastroenterol* 2003; **38**: 427-432
- 6 Castéra L, Vergniol J, Foucher J, Le Bail B, Chanteloup E, Haaser M, Darriet M, Couzigou P, De Ledinghen V. Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. *Gastroenterology* 2005; **128**: 343-350
- 7 Fraquelli M, Rigamonti C, Casazza G, Conte D, Donato MF, Ronchi G, Colombo M. Reproducibility of transient elastography in the evaluation of liver fibrosis in patients with chronic liver disease. *Gut* 2007; **56**: 968-973
- 8 Marcellin P, Zioli M, Bedossa P, Douvin C, Poupon R, de Ledinghen V, Beaugrand M. Non-invasive assessment of liver fibrosis by stiffness measurement in patients with

- chronic hepatitis B. *Liver Int* 2009; **29**: 242-247.
- 9 Gaia S, Carezzi S, Barilli AL, Bugianesi E, Smedile A, Brunello F, Marzano A, Rizzetto M. Reliability of transient elastography for the detection of fibrosis in non-alcoholic fatty liver disease and chronic viral hepatitis. *J Hepatol* 2011; **54**: 64-71
 - 10 Fung J, Lai CL, Cheng C, Wu R, Wong DK, Yuen MF. Mild-to-moderate elevation of alanine aminotransferase increases liver stiffness measurements by transient elastography in patients with chronic hepatitis B. *Am J Gastroenterol* 2011; **106**: 492-496
 - 11 Cho HJ, Seo YS, Lee KG, Hyun JJ, An H, Keum B, Kim JH, Yim HJ, Jeon YT, Lee HS, Chun HJ, Um SH, Kim CD, Ryu HS. Serum aminotransferase levels instead of etiology affects the accuracy of transient elastography in chronic viral hepatitis patients. *J Gastroenterol Hepatol* 2011; **26**: 492-500
 - 12 Sagir A, Erhardt A, Schmitt M, Häussinger D. Transient elastography is unreliable for detection of cirrhosis in patients with acute liver damage. *Hepatology* 2008; **47**: 592-595
 - 13 Arena U, Vizzutti F, Corti G, Ambu S, Stasi C, Bresci S, Moscarella S, Boddi V, Petrarca A, Laffi G, Marra F, Pinzani M. Acute viral hepatitis increases liver stiffness values measured by transient elastography. *Hepatology* 2008; **47**: 380-384
 - 14 Chan HLY, Wong GLH, Choi PCL, Chan AWH, Chim AML, Yiu KK, Chan FK, Sung JJ, Wong VW. Alanine aminotransferase-based algorithms of liver stiffness measurement by transient elastography (Fibroscan) for liver fibrosis in chronic hepatitis B. *J Viral Hepat* 2008; **16**: 36-44
 - 15 Rigamonti C, Fraquelli M. Do not trivialize the Fibroscan examination, value its accuracy. *J Hepatol* 2007; **46**: 1149
 - 16 Wong VW, Vergniol J, Wong GL, Foucher J, Chan HL, Le Bail B, Choi PC, Kowo M, Chan AW, Merrouche W, Sung JJ, de Ledinghen V. Diagnosis of fibrosis and cirrhosis using liver stiffness measurement in non alcoholic fatty liver disease. *Hepatology* 2010; **51**: 454-462.
 - 17 Castera L, Foucher J, Bernard PH, Carvalho F, Allaix D, Merrouche W, Couzigou P and de Ledinghen D. Pitfalls of Liver Stiffness Measurement: A 5-Year Prospective Study of 13,369 Examinations. *Hepatology* 2010; **51**: 828-35
 - 18 Cardoso AC, Carvalho-Filho RJ, Stern C, Dipumpo A, Giuly N, Ripault MP, Asselah T, Boyer N, Lada O, Castelnau C, Martinot-Peignoux M, Valla DC, Bedossa P, Marcellin P. Direct comparison of diagnostic performance of transient elastography in patients with chronic hepatitis B and chronic hepatitis C. *Liver Int* 2011; **32**: 612-621
 - 19 Verveer C, Zondervan PE, Ten Kate FJ, Hansen BE, Janssen HL, de Knegt RJ. Evaluation of transient elastography for fibrosis assessment compared with large biopsies in chronic hepatitis B and C. *Liver Int* 2012; **32**: 622-628

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