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Original Article

The Association between Liver Fibrosis Measurement by Transient Elastography and Liver Biopsy in Chronic Hepatitis B Patients

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ABSTRACT

Background: Transient Elastography (TE) is a noninvasive, reproducible tool to assess liver stiffness. Previous systemic review showed that liver stiffness measured by TE has high accuracy to detect histological liver fibrosis. However, few studies are looking at this relationship in patients with chronic hepatitis B (CHB). We aimed to assess the correlation between liver stiffness and liver fibrosis in Thai CHB patients.

Patients and Methods: One hundred and four patients with CHB, mainly HBeAg negative, who underwent liver biopsy to assess liver histology before treatment at Siriraj Hospital from May 2007 to December 2007, were recruited. On the day of scheduled liver biopsy, complete liver tests and coagulogram were done. Liver stiffness was assessed by TE and expressed as kPa. Liver histology was evaluated and graded by METAVIR scoring system. The correlation between histological liver fibrosis and the liver stiffness was evaluated by the correlation statistics which describes the degree of relationship between both variables.

Results: Liver stiffness significantly correlated with fibrosis stage ($r = 0.52$ $p < 0.00001$). Areas under the receiver operating characteristic curve (AUROC) were 0.76 for patients with significant fibrosis (F≥2), and 0.79 for patients with severe fibrosis (F≥3). Cutoff value of 6.9 to detect significant fibrosis has a sensitivity, specificity, positive predictive value and negative predictive value of 70%, 79.5%, 82% and 66%, respectively.

Conclusion: Liver stiffness measured by TE has an acceptable correlation with histological liver fibrosis in Thai CHB patients.

Key words : liver fibrosis, transient elastography, liver biopsy, chronic hepatitis B

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INTRODUCTION

Chronic hepatitis B (CHB) virus is the major health problem worldwide especially in Asia including Thailand. Hepatic fibrosis in patients with CHB is silent and dynamic, usually requires several years before symptomatic. Accurate diagnosis of the stage of fibrosis will guide the proper treatment; however, there is no non-invasive test that can early diagnose such condition.

Liver biopsy is the gold standard for accurate diagnosis and staging degree of liver fibrosis. However, there are some drawback of performing a liver biopsy including, sampling error and interobserver variability. Smaller biopsy samples are associated with greater chance of sampling error which can be reduced by increasing the sample size and the number of biopsies performed[1]. The most important drawback is the invasive nature of liver biopsy with a morbidity of 0.1% and a mortality of 0.01%[2]. Thus, using liver biopsy to follow the improvement of liver disease is not accepted by most patients.

Several non-invasive methods have been developed including biochemical tests and transient elastography (TE). TE is a novel, rapid, and noninvasive technique to measure liver stiffness[3,4]. This system is equipped with a probe consisting of 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. In the meantime, pulse-echo ultrasonic acquisition is performed to follow the propagation of the shear wave and measure its velocity which is directly related to tissue stiffness. The harder the tissue, the faster the shear wave propagates.

Previous systemic review showed that liver stiffness measured by TE has high accuracy to detect histological liver fibrosis stages II-IV fibrosis with the sensitivity of 70% and specificity of 84%[5]. Sandrin et al had performed a study in chronic hepatitis C (CHC) patients and showed that liver stiffness measured by TE had a good correlation with liver fibrosis ($r = 0.72$, $p < 0.0001$)[6]. However, few studies of the liver stiffness measured by TE were reported in patients with CHB[7-9]. Chan et al showed that the optimal cutoff values for liver cirrhosis were 8.4 kPa (with 98% sensitivity), or 9.0 kPa (with maximum sensitivity and specificity)[9].

We aimed to assess the correlation of liver stiffness measured by TE and the histologic liver fibrosis assessed by liver biopsy in Thai CHB patients and to identify an appropriate cutoff value of liver stiffness for the assessment of the significant fibrosis ($F \geq 2$).

PATIENTS AND METHODS

Patients

We performed a cross sectional descriptive study and included all patients with CHB from June 1, 2007 to December 31, 2007 who underwent a liver biopsy at Siriraj Hospital. We excluded patients who had coinfection of chronic hepatitis C and/or human immune deficiency virus (HIV), patients with contraindication for liver biopsy, and patients with currently receiving any antiviral agents. We collected the following parameters including; patients characteristics, history of alcoholic consumption, co-morbidity, complete blood counts, liver tests (aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, platelet count, prothrombin time and serum albumin), and viral hepatitis studies.

Liver stiffness measurement

Liver stiffness measurements (LSM) were performed on the right lobe of the liver through intercostal spaces on patients lying in the dorsal decubitus position with the right arm in maximal abduction at the same day of liver biopsy by single operator experience in this procedure. Details of the procedure have been previously described[10].

Ten successful measurements were performed on each patient. Success rate was calculated as the ratio of the number of successful measurements over the total number of acquisition. The results of liver stiffness were expressed in kiloPascal (kPa). Median value of the successful measurements was kept as representative of liver stiffness. The whole examination duration was less than five minutes. Only liver stiffness measurements obtained with at least 10 successful measurements and a success rate of at least 80% were considered reliable.

Liver histology and assessment of liver fibrosis

All liver biopsies were processed by experienced pathologists blinded to the clinical data and the results of the liver stiffness measurements. Fibrosis was staged according to the METAVIR scoring system from F0 (no fibrosis) to F4 (cirrhosis).

Statistical analysis

Patient characteristics were analyzed by descriptive statistics and reported as mean, standard deviation and percent where appropriate. Spearman coefficients of correlation and their associated probability (P) were used to evaluate the relationship between liver stiffness and liver fibrosis. Optimal cutoff values for liver stiffness chosen to optimize the predictive value of liver stiffness.

The receiver operating characteristic (ROC) curve is a plot of sensitivity versus 100-specificity and use to identify the best cutoff values for detection of patients with METAVIR fibrosis F≥2 and F≥3. Area under the ROC curve (AUROC) was also calculated to assess the degree of diagnostic accuracy. All tests were two sided, and the chosen level of significance was $p<0.05$.

Results

One hundred and four patients were enrolled with 65 men (62.5%) and 39 women (37.5%). The mean age of patients was 44 years and their mean BMI was 23.6 ± 4.2 kg/m^2. Most patients were CHB with HBeAg negative (74.1%) as well as normal liver synthetic function. Liver biopsy results had shown significant fibrosis (F≥2) in 60 patients (57.7%) and 53 patients (50.9%) had moderate necroinflammation (activity score ≥ A2) as shown in Table 1.

Table1. Clinical and demographic data of the 104 patients.

Characteristics	N = 104
M : F (%)	65 : 39 (62.5% : 37.5%)
Age (year), mean	44
BMI (kg/m^2)	23.6 ± 4.2
AST (U/L)	48.8 ± 58
Albumin (g/dl)	4.4 ± 0.3
Platelet count (10^3/mm^3)	218.7 ± 52.9
HBeAg positive (%)	27 (25.9%)
Fibrosis Score (METAVIR) (%)	
F0	12 (11.5%)
F1	32 (30.8%)
F2	44 (42.3%)
F3	14 (13.5%)
F4	2 (1.4%)
Activity Score (METAVIR) (%)	
A0 (none)	5 (4.8%)
A1 (mild)	46 (44.2%)
A2 (moderate)	42 (40.4%)
A3 (severe)	11 (10.6%)

BMI = body mass index, AST = aspartate aminotransferase

Relationship between liver stiffness and histological parameters

All patients had undergone 10 valid measurements with success rate of 100%. Liver stiffness ranged from 3.3 to 46.4 kPa with the mean (SD) of 8.35 (5.23) kPa. Mean liver stiffness in each fibrosis stage was shown in Table 2. The liver stiffness was significantly correlated with histological liver fibrosis stage (r=0.52, $p<0.0001$) as shown in Figure 1. ROC curves of liver stiffness and fibrosis of at least stage 2 and 3 were showed in Figure 2 and 3, respectively. Since there were only 2 patients in F4, thus we excluded them from this analysis of the relationship. To determine the appropriate cutoff value of liver stiffness, we found that

Table 2. Mean of liver stiffness of each histological fibrosis stage.

Fibrosis score	Number	Liver stiffness (kPa) mean ± SD
F0	12	5.4 ± 1.0
F1	32	6.9 ± 3.3
F2	44	8.5 ± 3.4
F3	14	12.1 ± 10.1
F4	2	19.2 ± 2.6

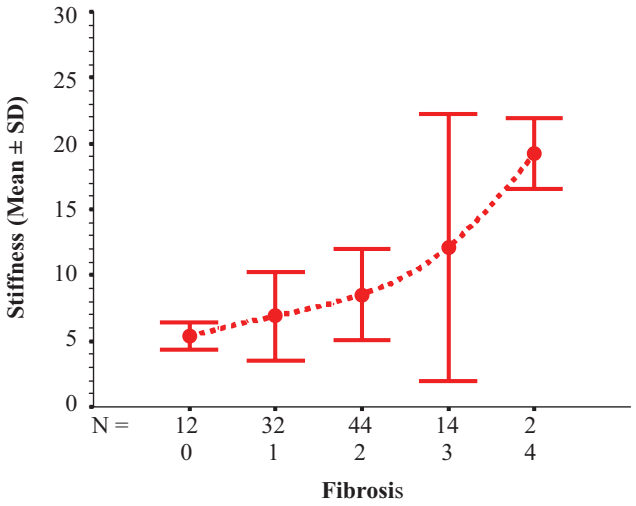
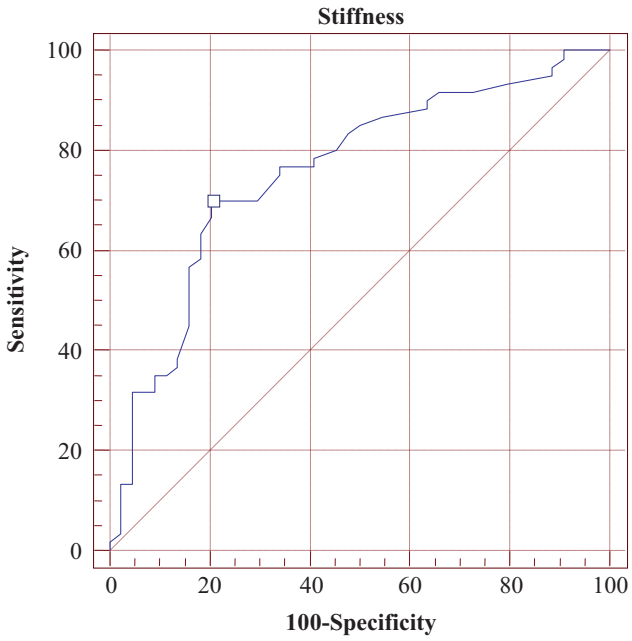
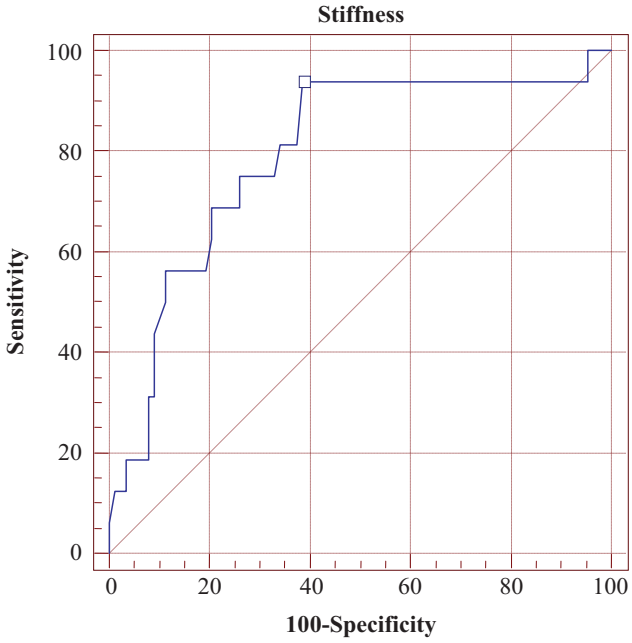


Figure 1. Relationship between liver stiffness level (mean ± SD) and liver fibrosis score. Liver stiffness had significantly correlated with histological liver fibrosis stage (r=0.52, $p<0.0001$)



Note: AUROC value (95% confidence interval, CI) was 0.76 (0.66-0.84) for F≥2.

Figure 2. ROC curve of liver stiffness measurements for significant fibrosis (F≥2).



Note: AUROC value (95%CI) was 0.79 (0.70-0.87) for F≥3.

Figure 3. ROC curve of liver stiffness measurements for severe fibrosis (F≥3).

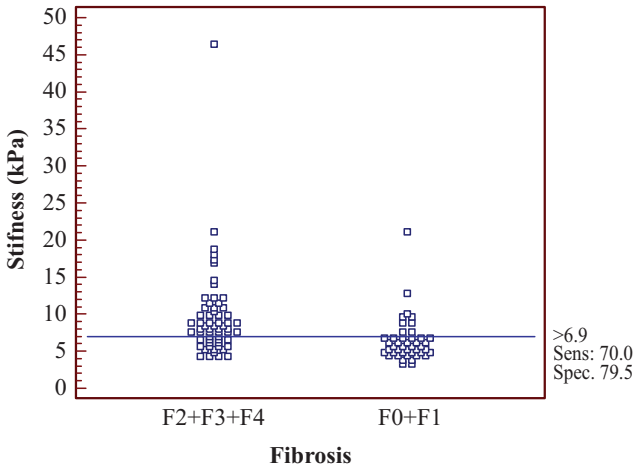


Figure 4. A best cut-off value of liver stiffness > 6.9 for F ≥2 had a sensitivity of 70%, specificity of 79%, positive predictive value (PPV) of 82% and negative predictive value (NPV) of 66%.

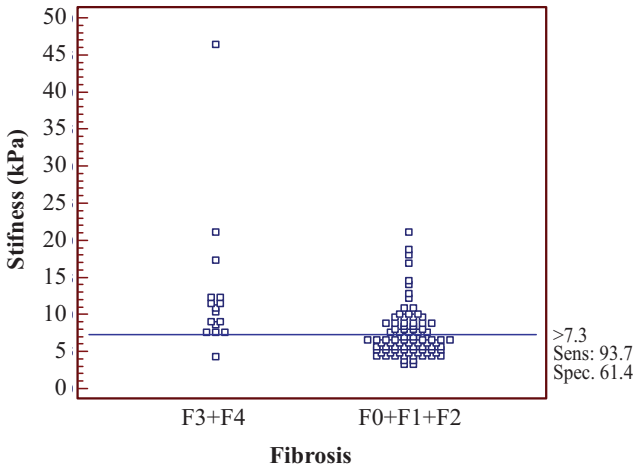


Figure 5. Based on ROC curves analysis, a cut-off value of liver stiffness >7.3 kPa for severe fibrosis (F≥3) had a sensitivity of 93%, specificity of 61%, PPV of 30.6% and NPV of 98%.

for F≥2 and F≥3, the best cutoff value of liver stiffness were 6.9 and 7.3 kPa, respectively as shown in Figure 4 and 5.

Discussion

The results of this study has showed an acceptable correlation of liver stiffness and histological liver fibrosis (r = 0.52, p <0.0001). This study was similar to the results reported by Castera *et al* (r = 0.61, p <0.001) in CHC patients and Kang *et al* showing the correlation of r = 0.56, p <0.001 in both CHB and CHC

patients[11,12]. The cut-off value of 6.9 kPa for F≥2 had high sensitivity and specificity, and this cutoff value was similar to the cutoff value result of 7.1 kPa for F≥2 reported by Castera *et al*[11]. Other cutoff values were reported ranging from 7.5 kPa to 8.8 kPa for F≥2[12, 13].

The AUROC for F≥2 and F≥3 were 0.76 and 0.79, respectively which were high accuracy for TE to diagnose the significant or severe liver fibrosis. Marcellin et al, reported the AUROC of 0.81 (95% CI 0.73-0.86) for F2, and 0.93 (95 CI 0.88-0.96) for F3 in patients with CHB[14].

Two patients in our study with F4 fibrosis showing liver stiffness values of 21.1, and 17.3 kPa, were not included into the correlation analysis due to the small number of patients. However, the previous studies showed that no effect of the degree of necroinflammation or steatosis in the measurement of liver elasticity[6].

In summary, TE is a highly reproducible and noninvasive technique for assessment liver stiffness and has good correlation with liver fibrosis in CHB patients. The cutoff value of 6.9 kPa for F≥2 had an acceptable correlation with histological liver fibrosis in Thai CHB patients.

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