Original Article

Transient Elastography for Detecting Significant Liver Fibrosis in Thai Patients with Chronic Hepatitis C

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Objective: Transient elastography [TE] has been validated as a non-invasive test to measure liver stiffness with high accuracy to as certain the stage of liver fibrosis. However, the liver stiffness value is confounded by food intake. Previous studies have yielded little data regarding the cutoff point for liver stiffness as measured after fasting, and there are no studies available regarding chronic hepatitis C [HCV] in Thai patients. The present study aimed to demonstrate the cutoff liver stiffness value to predict significant fibrosis (METAVIR stage ≥F2) using TE compared with that found through liver biopsy.

Materials and Methods: We prospectively enrolled 84 chronic HCV patients, who underwent liver biopsy to assess liver fibrosis before treatment at Srinagarind hospital from March 2016 to February 2017. On the day of the liver biopsy, liver stiffness was assessed using TE after fasting for at least three hours. Liver histology was evaluated using the METAVIR scoring system. Optimal cutoff values for liver stiffness were chosen and the area under the receiver operating characteristic curve [AUROC] was also calculated in order to identify the best cutoff values for detection of patients with METAVIR fibrosis ≥F2.

Results: The AUROC was 0.79 for patients with significant fibrosis (≥F2). There was a cutoff value of 8.1 to detect significant fibrosis with a sensitivity, specificity, positive predictive value, and negative predictive value of 84.4%, 61.5%, 71.7%, and 77.4%, respectively. Age, sex, body mass index, history of alcohol consumption, and ALT did not significantly affect the cutoff value.

Conclusion: A liver stiffness measurement ≥8.1 kPa was a predictor of the significant fibrosis (F2) in Thai chronic HCV patients. This result may be useful in identifying patients for priority treatment.

Keywords: Chronic hepatitis C, Cutoff, Liver biopsy, Liver fibrosis, Transient elastography

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Chronic hepatitis C virus [HCV] infection is an important health problem, with an estimated 185 million patients infected worldwide[1]; Over 50% of infected individuals live in the Asia Pacific region[2] and 399,000 people die from HCV-related liver diseases annually[3]. In Thailand, there are 758,940 HCV antibody-positive individuals, 356,670 of whom have HCV viremia[4]. In terms of disease progress, approximately 30% of chronic HCV patients will develop liver cirrhosis after 20 years, 3% of whom have a risk of decompensated cirrhosis, and 5% of whom may develop liver cancer after cirrhosis[5]. Hence, HCV is considered to be a major health problem facing doctors and patients today. HCV eradication is the only way to reduce liver cancer.

Presently, treatment of HCV using pegylated interferon alpha and ribavirin yields satisfactory results. Patients who have the HCV genotypes 2 and 3, in

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particular, have an 80% chance of sustained virological response [SVR], making the drug the standard medication covered by all plans under Thailand's universal healthcare program[6]. It should be noted that in order to qualify for reimbursement for prescription drugs under the national policy, there must be significant fibrosis. In the past, this was determined through liver biopsy and interpreted based on the METAVIR staging fibrosis score (it must be ≥2)[6]. However, there are a number of drawbacks of liver biopsy, as follows: 1) there are severe complications in roughly 0.05% to 5.3% of patients such as artery lacerations, blood hypovolemic shock, or pneumothorax, 2) the biopsy needs to be at least 2.5 cm to avoid sampling error, and 3) an expert pathologistis required to interpret the biopsied liver[7].

Recently, a new approach to measuring liver stiffness has become available and has gained acceptance around the world, i.e., transient elastography [TE]. This device measures liver stiffness, as well as clinical correlations such as significant fibrosis, cirrhosis, portal hypertension,predicted variceal bleeding, etc[8-10]. Studies from overseas have found a TE cutoff score of 7.1 kPa to be equal to a METAVIR score of F2 in HCV patients, indicating significant fibrosis[11]. Parameters differ by country and from one study to another, owing to influential variables on TE measurement, e.g., severe hepatitis,3-hour fasting before measurement, congestion of the biliary tract, high body mass index [BMI], alcohol consumption, right-sided heart failure, and the experience levels of the pathologists. The most important of these is the 3-hour fasting before undergoing the procedure. One study reported that measurement after a meal affects the liver stiffness value in 90% of cases, making it 1 kpa higher than after fasting,which may result in erratic interpretation of significant fibrosis[12].

To date, no study has been conducted on the cutoff value of TE to indicate significant fibrosis in HCV patients in Thailand. The criterion currently being used in HCV treatment in Thailand is a cutoff value of 7.0 kPa, the disadvantage of this being that the reference was obtained from research on patients with the hepatitis B virus [HBV] who had not fasted before examination with a cutoff of 6.9 kPa[6,13]. Moreover, studies conducted overseas have found HBV and HCV to have different cutoff values[14]. This study aims to demonstrate the cutoff liver stiffness value to predict significant fibrosis using TE after fasting for at least 3 hours compared with liver biopsy in Thai patients with HCV.

Material and Method

Patients

We prospectively enrolled chronic HCV patients who underwent liver biopsy before treatment at the Khon Kaen University, Faculty of Medicine's Srinagarind Hospital from March 2016 to February 2017. Inclusion criteria were age 18 to 65 years, detectable serum anti-HCV antibodies, and HCV RNA, ECOG performance status of 0 and no treatment contraindications. Exclusion criteria were contraindication for liver biopsy, coinfection of chronic hepatitis B and/or human immune deficiency virus [HIV)], Child-Pugh score >6, previously treatment with interferon, peginterferon alfa 2a or 2b and ribavirin, consumption of alcohol within 6 months or use of addictive drugs, hepatocellular carcinoma or other active cancer, comorbid disease that could not be adequately controlled such as hypertension, diabetes, coronary artery disease, emphysema, hyperthyroidism, alcoholism, major uncontrollable depressive disorder, pregnancy or unwillingness to use contraception, and history of kidney, heart, or lung transplant. Patients were enrolled after giving their written informed consent.

We collected data on the following parameters; patient characteristics, history of alcohol consumption, co-morbidity, complete blood count with platelet count, prothrombin time with INR, liver tests (serum albumin, total bilirubin, alanine aminotransferase [ALT], aspartate aminotransferase [AST], and alkaline phosphatase [ALP]), viral hepatitis studies, HCV RNA, and genotypes.

Liver stiffness measurement

Liver stiffness measurement using a FibroScan® 502 Touch 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 the liver biopsy conducted by a single operator experienced in this procedure (at least 100 cases) after the patient had fasted for at least three hours. The examination takes no more than five minutes. Measurement is made at least 10 times. The results were expressed in kilopascals [kPa]. A success rate of higher than 80% with an IQR/Median value at <30% is considered reliable.

Liver biopsy and interpretation

Percutaneous liver biopsy was performed with a 1.6-mm diameter trucut needle with a length of at least 2.5 cm. All specimens were fixed in formalin, embedded

in paraffin, cut, and stained with hematoxylin and eosin. All liver histology interpretations were performed by 2 pathologists with experience in reading biopsied liver samples and blinded to the TE results. Disagreements between pathologists were resolved through discussion and mutual decision with regard to the final results.Reports were based on the METAVIR scoring system,which specifies a fibrosis score from 0 to 4 (F0: no fibrosis; F1: stellate enlargement of portal tract without septa formation; F2: enlargement of the portal tract with rare septa formation; F3: numerous septa without cirrhosis; F4: cirrhosis) and a histologic activity score from 0 to 3 (A0: no activity; A1: mild activity; A2: moderate activity; A3: severe activity).

Statistical analysis

Baseline demographic and clinical characteristics of patients were summarized using descriptive statistics. For categorical variables, numbers for all categories were presented with percentages. For continuous variables, mean, standard deviation, median, minimum, and maximum were presented. The diagnostic performance of TE was assessed by using receiver operating characteristic [ROC] curves. The ROC curve was used to identify the best cutoff values for detection of patients with METAVIR fibrosis ≥F2. Sensitivity, specificity, positive predictive value [PPV], negative predictive value [NPV] with 95% confidence interval [CI] and area under the ROC curve [AUROC] were also calculated to obtain diagnostic accuracy. Statistical analyses were performed with STATA®10 software.

Results

Of the 84 patients who were included in the study, 57 were male (67.9%) and 27 were female (32.1%). The average age was 49.5±7.4 years. The average body mass index [BMI] was 23.7±3.5 kg/m^2. The average ALT level was 84.5±66.3 U/L, with 30 cases (35.7%) of genotype 3a, 25 cases (29.8%) of genotypes 1a (12 cases) and 1b (13 cases), 24 cases (28.6%) of genotype 6, and five cases (5.9%) of genotype 2. Liver biopsy indicated 45 patients with significant fibrosis (≥F2, 53.6%) and 82 patients (97.6%) with histologic activity scores of ≥A2 (Table 1). The inter-observer reliability of METAVIR fibrosis score showed moderate agreement between the 2 pathologists. The weighted kappa was 0.58 (*p*-value <0.0001).

The findings indicated that liver stiffness ranged from 4.8 to 60.2 kPa. The TE results and box-plots of liver stiffness for each fibrosis stage were shown in Table 2 and Figure 1, respectively. The ROC curve of liver stiffness and fibrosis at stage 2 or higher is showed in Figure 2.

Table 1. Baseline characteristics of the 84 patients

Characteristics	Results
Male: female	57:27
Age (years)	49.5±7.4
BMI (kg/m^2)	23.7±3.5
Hemoglobin (g/dL)	13.7±1.5
Platelet count (10^3/mm^3)	192.0±60.0
Albumin (g/dL)	4.4±0.6
Total bilirubin (mg/dL)	0.7±0.3
ALT (U/L)	84.5±66.3
AST (U/L)	67.8±41.8
ALP (U/L)	87.5±30.8
INR	1.0±0.1
Fibrosis score (METAVIR)	
F0	5 (6.0)
F1	34 (40.5)
F2	31 (36.9)
F3	6 (7.1)
F4	8 (9.5)
Activity score (METAVIR)	
A0	0
A1	2 (2.4)
A2	8 (9.5)
A3	74 (88.1)

Data are expressed as mean ± standard deviation or number (percentage).
BMI = body mass index; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ALP = alkaline phosphatase; INR = international normalized ratio

The most reliable cutoff for diagnosis of significant fibrosis (≥F2) using TE obtained from the population in this study was 8.1 kPa, with a sensitivity of 84.4% (95% CI 70.5 to 93.5%), specificity of 61.5% (95% CI 44.6 to 76.6%), positive predictive value of 71.7% (95% CI 57.7 to 83.2%), negative predictive value of 77.4% (95% CI 58.9 to 90.4%), likelihood ratios for positive test of 2.2 (95% CI 1.5 to 3.3), likelihood ratios for negative test of 0.3 (95% CI 0.1 to 0.5), false positive rate of 38.5%, false negative rate of 15.6%, and AUROC of 0.79 (95% CI 0.69 to 0.88). Because of the low specificity of an 8.1 kPa cutoff, we also analyzed TE values with a cutoff of 12.1 kPa, which yielded a specificity of 87.18% (95% CI 72.6 to 95.7%), AUROC 0.74 (95% CI 0.66 to 0.84), as shown in Table 3.

The authors analyzed the factors that might affect the cutoff TE values in this study such as age,

Table 2. Means and medians of the transient elastography results at each stage of liver fibrosis

Fibrosis score	n	Liver stiffness (kPa), mean ± SD	Liver stiffness (kPa), median (IQR)
F0	5	8.1± 3.3	7.2 (5.4 to 10.7)
F1	34	8.9±4.5	7.8 (6.1 to 9.6)
F2	31	15.6±11.0	12.1 (8.1 to 21.8)
F3	6	17.2±5.5	16.3 (13.3 to 20.0)
F4	8	36.9±23.3	28.1 (24.1 to 53.0)

SD = standard deviation; IQR = interquartile range

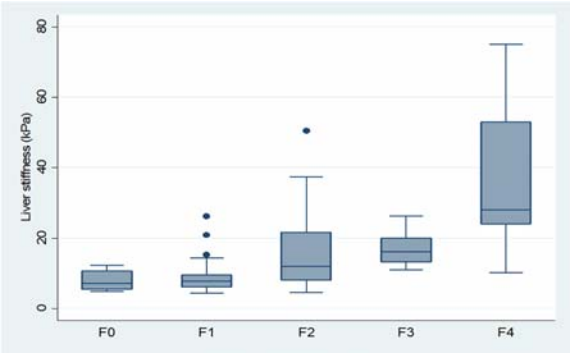

Figure 1. box-plots of liver stiffness for each fibrosis stage.

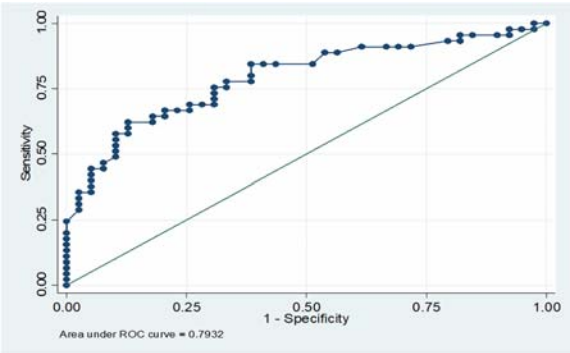

Figure 2. Receiver operating characteristic [ROC] curve for significant fibrosis (≥F2) measurement using TE.

sex, BMI, history of alcohol consumption, ALT level, and activity score. It was found that these variables did not affect the cutoff required in order to retain the best AUROC, as shown in Table 4.

Discussion

The results of the present study demonstrated that the cutoff yielding the highest AUROC for diagnosing significant fibrosis in chronic HCV patients was 8.1 kPa. This finding differs from those of previous studies. For instance, Castera et al, who performed a study of chronic HCV patients, obtained a cutofff or significant fibrosis of 7.1 kPa. In addition, a study of chronic hepatitis B virus in Thai patients conducted by Wiboonsirikul et al found a cutoff of 6.9 kPa, which differs greatly from that found in our study. It should be noted that 97.6% of the patients included in this research had relatively high liver inflammatory activity, with METAVIR activity scores of ≥2. The mean ALT value was 84.5±66.3 U/L, which directly influenced the reliability of the TE results. In other words, severe hepatitis can cause artificially highTE values. Thus, it was assumed that the cutoff indicating liver stiffness could be less than 8.1 kPa.

The TE results in this study indicated that the procedure had a high sensitivity and negative predictive value, which means that it could be used as a screening test for diagnosing significant fibrosis. If the value is lower than the cutoff, the chance of finding fibrosis Metavir ≥F2 through other methods of examination, such as liver biopsy, will be low. We aimed to apply the TE technique in order to reduce the unnecessity of liver biopsy. If the TE value is below 8.1 kPa, there is no need for additional treatment because of its high sensitivity in screening for non-significant fibrosis. If the TE value is above 12.1 kPa, there is no need to liver biopsy because of its high specificity in indicating significant fibrosis.Only TE values of 8.1 to 12.1 kPa require other high-specificity tests, such liver biopsy, to confirm significant fibrosis.

This study had limitation that the liver histology was not stained by Masson trichrome, which might affect the fibrosis assessment. In the future, if any scholar is interested in performing an extended study that aims to determine the cutoff that indicates

Table 3. Transient elastography cutoff value for the diagnosis of significant fibrosis (METAVIR ≥F2) and 95% confidence interval

	TE cutoff (kPa)	
	≥8.1	≥12.1
Sensitivity (%)	84.4 (70.5 to 93.5)	62.2 (46.5 to 76.2)
Specificity (%)	61.5 (44.6 to 76.6)	87.2 (72.6 to 95.7)
AUROC	0.79 (0.69 to 0.88)	0.74 (0.66 to 0.84)
Positive predictive value (%)	71.7 (57.7 to 83.2)	84.8 (68.1 to 94.9)
Negative predictive value (%)	77.4 (58.9 to 90.4)	66.7 (52.1 to 94.9)
Positive likelihood ratio	2.2 (1.5 to 3.3)	4.9 (2.1 to 11.3)
Negative likelihood ratio	0.3 (0.1 to 0.5)	0.4 (0.3 to 0.6)

AUROC = area under the receiver operating characteristic curve; TE = transient elastography

Table 4. Subgroup analysis of factors that might affect the cutoff TE values

Factors	n	Cutoff (kPa)	AUROC	Sensitivity (%)	Specificity (%)
Male	57	8.1	0.79	90.9	66.7
BMI ≤23 kg/m^2	34	8.1	0.71	89.5	53.3
ALT ≤100 U/L	64	8.1	0.72	82.8	62.9
ALT ≤50 U/L	28	8.1	0.70	77.8	63.2
No drinking alcohol	74	8.1	0.72	82.5	61.8
Activity score 3	74	8.1	0.73	83.7	61.3

AUROC = area under the receiver operating characteristic curve

significant fibrosis, one inclusion criterion should be low hepatitis values. In addition, the study should include a much larger population, as this will lead to obtaining a more accurate result.

Conclusion

Liver stiffness measurement by transient elastography is reliable. A cutoff of ≥8.1 kPa indicates significant fibrosis (≥F2) in chronic HCV patients.

What is already known on this topic?

Studies from overseas have found a transient elastography cutoff score of 7.1 kPa to be equal to a fibrosis METAVIR score of F2 in HCV patients, indicating significant fibrosis. Studies have reported that measurement after a meal affects the liver stiffness value.

What this study adds?

The cutoff yielding the highest AUROC is 8.1 kPa in Thai HCV patients. This finding differs from those of previous studies.

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Potential conflicts of interest

None.

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