Original Article

Prevalence and Predictive Factors of Liver Cirrhosis Identified by Vibration-Controlled Transient Elastography (FibroScan®) in Chronic Viral Hepatitis C Patients at Rajavithi Hospital

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Background: Chronic viral hepatitis C (CHC) infection is a well-known cause of chronic liver disease and cirrhosis worldwide. In evaluation of the status of liver cirrhosis, liver biopsy remains the gold standard; however, it is associated with some rare but serious complications. Recently, non-invasive tests using vibration-controlled transient elastography (VCTE) have been increasingly used in clinical practice instead of liver biopsy.

Objectives: To describe the prevalence of liver cirrhosis identified by VCTE in Thai CHC patients and also to find the predictive factors of liver cirrhosis.

Materials and Methods: The data were retrospectively retrieved of consecutive CHC patients who underwent VCTE and Controlled Attenuation Parameter (CAP) at Rajavithi Hospital, Bangkok between 1 January 2015 and 31 December 2017. Clinical characteristics, CAP, VCTE, HCV genotype, HCV viral load and laboratory data were reviewed. Liver fibrosis status was described and predictors of liver cirrhosis were analyzed.

Results: A total of 216 patients were included, none of whom had received any antiviral therapy. Males accounted for 73.1% of subjects, whose mean age was 49.63±8.33 years. Obesity was found in 37.5% of patients (BMI ≥25 kg/m^2) and hepatic steatosis, defined as CAP ≥248 (dB/m), was found in 34.7%. HCV genotype 3 was the most predominant subtype (50.9%), and cirrhosis defined as VCTE ≥12.5 kPa was found in 51.4%. Multivariate analysis revealed that AST level and platelet count were associated with cirrhosis with aOR of 1.02 (95% CI: 1.01 to 1.02) and 0.99 (95% CI: 0.98 to 0.99) respectively.

Conclusion: More than half of these Thai chronic hepatitis C patients had liver cirrhosis. The simple surrogate biomarkers of liver fibrosis, high AST level and low platelet count, are indicators of advanced liver disease. This positive finding should encourage further evaluation by either VCTE or liver biopsy to delineate the underlying liver fibrosis status of patients.

Keywords: Chronic viral hepatitis C, Fibrosis, Liver cirrhosis, Elasticity imaging techniques

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The majority of patients infected with hepatitis C virus (HCV) develop chronic infection[(1)], which often follows a progressive course of fibrotic change in the liver ultimately resulting in cirrhosis[(2)] with increased risk of hepatocellular carcinoma[(3)] and need for liver transplantation. Worldwide, the population infected with HCV is estimated at 180 million individuals, or 3%, and in Thailand the incidence of HCV infection is 1 to 2% of the population[(4)].

Several factors appear to be important determinants of fibrosis progression in HCV-infected patients, including host characteristics such as age, gender, and obesity, and viral factors, which are less clear than host characteristics. Hepatic steatosis in chronic viral hepatitis C (CHC) has an impact on the degree of hepatic inflammation and is associated with fibrosis progression[(5)]. The pathogenesis of hepatic steatosis in CHC is associated with obesity, dyslipidemia, insulin resistance[(5)] and HCV genotype 3[(6)].

Controlled attenuation parameter (CAP) is a new technique that measures the attenuation of an ultrasound beam in the liver, which is directly related to lipid accumulation. The results of a previous study showed that CAP is highly and significantly correlated with the extent of liver fat accumulation and that it could be a useful tool for detecting liver steatosis in the clinical management of patients with chronic viral hepatitis[(7)].

In evaluation of the status of liver cirrhosis, liver biopsy remains the gold standard. It has several disadvantages, however, including invasiveness, association

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with rare but serious complications, and susceptibility to sampling variation. Several less invasive methods for assessment of liver cirrhosis, including ultrasound-based modalities and vibration-controlled transient elastography (VCTE), are being increasingly used in clinical practice instead of liver biopsy. VCTE is the most-studied radiologic method and is reliable for staging liver fibrosis in hepatitis B virus (HBV) or HCV-infected patients, and also in other liver diseases[8-12]. Recent guidelines from the European Association for the Study of Liver Disease and the Latin American Association for the Study of the Liver advocate VCTE, which has a >90% negative predictive value for ruling out cirrhosis[13], as a valid non-invasive test for assessing liver fibrosis in HBV- and HCV-infected patients.

There have been few studies of the prevalence of liver cirrhosis in chronic viral hepatitis C patients in Thailand. These patients should immediately commence antiviral treatment and receive surveillance for hepatocellular carcinoma. We aimed to describe the prevalence of liver cirrhosis using a non-invasive test (VCTE) in Thai chronic viral hepatitis C patients at Rajavithi Hospital, and we also attempted to identify its predictive factors.

Materials and Methods

Patients

This cross-sectional study was conducted by reviewing the medical records of all chronic hepatitis C patients who underwent VCTE and CAP from 1 January 2015 to 31 December 2017 at the out-patients clinic of the Department of Medicine at Rajavithi Hospital, a tertiary referral center in Bangkok, Thailand. Patients older than 18 years old with chronic hepatitis C infection who were identified as having a persistence of anti-HCV antibodies and serum HCV RNA for at least 6 months were included. None of the subjects had had antiviral treatment before VCTE was performed. The exclusion criteria were (1) HBV or human immunodeficiency virus co-infection; (2) positive test for anti-nuclear antibody, anti-smooth muscle antibody or anti-mitochondrial antibody; and (3) patients whose VCTE result was invalid. The study protocol was reviewed and approved by the ethics committee of Rajavithi Hospital (No. 079/2561).

Vibration-controlled transient elastography (VCTE)

VCTE was performed by a single qualified operator with three years' experience using a FibroScan® device (Echosens, France), which sends a shear wave through the liver. The velocity of the propagation of this wave is assessed as a measure of the elasticity, or the stiffness, of the liver. Higher liver stiffness causes the shear wave to move faster, and higher liver stiffness indicates the presence of fibrosis. The VCTE measurement technique uses a piston vibrator placed in the 9th to 11th intercostal space on the right lobe of the liver with the patient in supine position with the right arm in maximal abduction. The velocity is measured in a region 25 to 65 mm below the skin surface with the standard adult M probe. The unit of measurement is kPa with a range from 2.5 to 75 kPa. A valid VCTE result requires at least 10 successful measurements and an interquartile range (which reflects variations among measurements) <30% of the median value[14,15]. Factors influencing viscoelasticity of the liver, such as non-fasting state[16], may also contribute to increased liver stiffness, so patients need to fast for at least 2 hours pre-operatively.

Liver cirrhosis was defined as a liver stiffness score of ≥12.5 kPa, in accordance with American Gastroentero-logical Association recommendations[17]. Thus, we classified the patients into two groups, namely a non-cirrhosis group and a cirrhosis group, based on the different management strategies for the cirrhotic patients, e.g. whether they should be screened for gastro-esophageal varices[18] and receive ultrasound surveillance for hepatocellular carcinoma[19].

Controlled attenuation parameter (CAP)

Liver histology is the reference method for grading hepatic steatosis, even though sampling variability due to the uneven distribution of lipid accumulation throughout the liver parenchyma does exist[20]. Recently, a CAP for the assessment of liver steatosis has been developed[21]. CAP measures the properties of ultrasound signals obtained from VCTE (FibroScan®, Echosens, Paris) based on the hypothesis that fat affects ultrasound propagation[22]. CAP is evaluated utilising the same radio-frequency data, and the same region of interest that are used to assess liver stiffness[23]. The device estimates hepatic steatosis in decibels per meter (dB/m). We used a CAP cutoff value of 248 (dB/m), based on a recent meta-analysis[24], for identifying hepatic steatosis grade of more than S0, where S0 means steatotic hepatocytes <5% by histology.

Clinical and laboratory data

Patient data were collected retrospectively from medical records for description, as well as comparison, of VCTE-classified groups by status of liver cirrhosis, including demographic and baseline characteristics such as body mass index (BMI), CAP (dB/m), HCV genotype, HCV viral load (IU/mL), serum albumin (g/dL), total bilirubin (mg/dL), serum creatinine (mg/dL), aspartate transaminase (AST) level (U/L), alanine transaminase (ALT) level (U/L), international normalized ratio (INR), white blood cell count (WBC) (/mm^3), hemoglobin (g/dL), and platelet count (x10^9/L).

BMI was categorized as follows: normal (BMI <23 kg/m^2); overweight (BMI ≥23 kg/m^2 and <25 kg/m^2); or obese (BMI ≥25 kg/m^2) in accordance with World Health Organization guidelines for adult Asian populations[25]. The ULN for AST and ALT were both defined as 40 U/L, and a normal range of INR was defined as 0.80 to 1.10.

Serum HCV VL was measured using real-time HCV assays by polymerase chain reaction using the COBAS® AmpliPrep/COBAS® TaqMan® HCV test, (Roche Molecular Diagnostics, CA, USA) and samples were genotyped by direct sequencing of the HCV core gene using the ABI 3500 Genetic Analyzer instrument (Applied

Biosystem, CA, USA).

Statistical analysis

Data analysis was performed using the IBM SPSS statistics version 22.0. Descriptive statistics were presented as mean (SD) or median (range and IQR) as appropriate for continuous data, and as numbers and prevalences for categorical data. Categorical variables were compared using the Chi-square or Fisher exact test as appropriate. Continuous variables were compared for significant differences between multiple groups using one-way ANOVA test or Kruskal-Wallis test. Multivariate logistic regression analysis was used to identify the predictive factors of liver cirrhosis, and results were presented as adjusted odds ratios (aOR) with 95% confidence intervals. A *p*-value <0.05 was considered statistically significant.

Results

In total, 237 chronic hepatitis C patients were identified and assessed for eligibility. Three patients (1.3%) with invalid VCTE results and 18 patients (7.6%) with missing laboratory data were excluded. The remaining 216 patients, none of whom had received any antiviral therapy, were included.

Median liver stiffness was 12.52 kPa (range 3.70 to 75.0; IQR 1.60 to 22.40). Of the 216 included patients, 158 (73.1%) were male. The mean age of patients was 49.63±8.33 years, and 37.5% were obese (BMI ≥25 kg/m^2). Hepatic steatosis, defined as CAP ≥248 (dB/m), was found in 34.7% of the patients. HCV genotype 3 was the most predominant subtype (50.9%), followed by genotype 1 (28.7%) and genotype 6 (20.4%). The median serum HCV VL was 1,095,000 IU/mL (range 480 to 197,100,000). VCTE results, demographics, and laboratory data of the patients are summarized in Table 1.

The prevalence of liver cirrhosis in chronic hepatitis C patients, defined by VCTE ≥12.5 kPa, was 51.4%, as shown in Figure 1.

Comparisons of the baseline characteristics of the non-cirrhosis and cirrhosis patients are shown in Table 2. Cirrhotic patients were older than those in the non-cirrhotic group with a mean age of 51.14 vs. 48.03 years ($p = 0.006$). Gender, BMI and CAP were not significantly different between the two groups; nor were viral factors, such as HCV genotype and HCV viral load. Laboratory data showed significantly higher levels of TB, AST and INR in the cirrhotic patients than in their non-cirrhotic counterparts ($p<0.05$). On the other hand, albumin, WBC, hemoglobin and platelet count were significantly lower in patients with cirrhosis than in those without it ($p<0.05$).

Univariate analysis showed that the associated risk factors of liver cirrhosis were age, AST, albumin, INR, hemoglobin and platelet count. Multivariate logistic regression analysis, however, showed that only AST level and platelet count were significant determinants of cirrhosis with aOR of 1.02 (95% CI: 1.01 to 1.02) and 0.99 (95% CI: 0.98 to 0.99) respectively (Table 3).

Table 1. Demographic and laboratory data of chronic hepatitis C patients (n = 216)

Variables	Value
Liver stiffness, median (range), kPa	12.52 (3.70 to 75.0)
Interquartile range, median (range)	11.00 (1.60 to 22.40)
Failed scan, n (%)	3 (1.3)
Success rate, %	98.7
Treatment naive patients, n (%)	216 (100.0)
Age, mean (SD), year	49.63 (8.33)
Gender, n (%)	
Female	58 (26.9)
Male	158 (73.1)
BMI, mean (SD), kg/m^2	24.61 (4.37)
<23, n (%)	84 (38.9)
≥23, n (%)	51 (23.6)
≥25, n (%)	81 (37.5)
CAP, mean (SD), dB/m	227.88 (54.70)
<248, n (%)	141 (65.3)
≥248, n (%)	75 (34.7)
HCV genotype, n (%)	
1	62 (28.7)
3	110 (50.9)
6	44 (20.4)
HCV VL, median (range), IU/mL	1,095,000 (480 to 197,100,000)
<400,000 IU/mL, n (%)	72 (33.3)
≥400,000 IU/mL, n (%)	144 (66.7)
Biochemical markers	
Total bilirubin, median (range), mg/dL	0.73 (0.18 to 6.00)
AST, median (range), U/L	72 (19 to 290)
ALT, median (range), U/L	87 (11 to 380)
Albumin, mean (SD), g/dL	4.26 (0.47)
INR, median (range)	1.04 (0.90 to 2.90)
WBC, median (range), mm^3	6,600 (2,000 to 64,300)
Hemoglobin, mean (SD), g/dL	13.79 (1.83)
Platelet, mean (SD), x10^9/L	185.70 (72.30)
Creatinine, median (range), mg/dL	0.91 (0.50 to 16.20)

kPa = Kilopascal; BMI = Body mass index; CAP = Controlled attenuation parameter; dB = Decibel; HCV VL = Hepatitis C Viral load; AST = Aspartate aminotransferase; ALT = Alanine aminotransferase; INR = International normalized ratio

Discussion

Chronic HCV infection is a well-known cause of chronic liver disease and cirrhosis both in patients with histories of exposure to parenterally transmitted viral diseases[26] and in patients who have no recognizable source of infection[27]. The development of cirrhosis is silent in the majority of patients in whom it occurs[28]; therefore, identifying these groups of patients is vital for proper management including early initiation of antiviral treatment, screening for gastro-esophageal varices and employment of ultrasound surveillance for hepatocellular carcinoma.

The present study described the prevalence of liver cirrhosis identified by VCTE in Thai chronic hepatitis C patients, and found that its prevalence was 51.4%. In

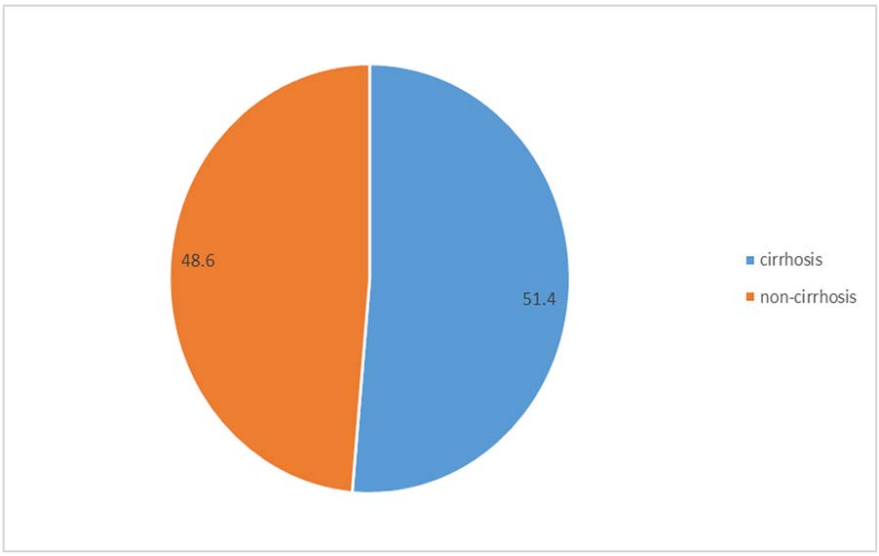

Figure 1. The prevalence of liver cirrhosis in chronic hepatitis C patients identified by VCTE.

Table 2. Comparison of the baseline characteristics of chronic hepatitis C patients with and without cirrhosis

Variables	Non-cirrhosis (n = 105)	Cirrhosis (n = 111)	*p*-value
Age, mean (SD), year	48.03 (8.22)	51.14 (8.19)	0.006*
Male gender, n (%)	76 (72.4.0)	82 (73.9)	0.805
BMI, mean (SD), kg/m^2	24.45 (4.07)	24.77 (4.65)	0.588
<23, n (%)	42 (40.0)	42 (37.8)	0.845
≥23, n (%)	23 (21.9)	28 (25.2)	
≥25, n (%)	40 (38.1)	41 (37.0)	
CAP, mean (SD), dB/m	225.90 (59.29)	229.75 (50.19)	0.606
<248, n (%)	65 (61.9)	76 (68.5)	0.311
≥248, n (%)	40 (38.1)	35 (31.5)	
HCV genotype, n (%)			0.306
1	33 (31.4)	29 (26.1)	
3	55 (52.4)	55 (49.5)	
6	17 (16.2)	27 (24.4)	
HCV VL, median (range), IU/mL	5,311,775.04 (480 to 197,100,000)	3,815,396.50 (900 to 56,250,000)	0.466
<400,000 IU/mL, n (%)	37 (35.2)	35 (31.5)	0.564
≥400,000 IU/mL, n (%)	68 (64.8)	76 (68.5)	
Biochemical markers			
TB, median (range), mg/dL	0.62 (0.18 to 4.65)	0.80 (0.19 to 6.00)	0.041*
AST, median (range), U/L	58 (20 to 200)	87 (19 to 290)	<0.001*
ALT, median (range), U/L	74 (11 to 314)	95 (12 to 380)	0.105
Albumin, mean (SD), g/dL	4.38 (0.41)	4.14 (0.49)	<0.001*
INR, median (range)	1.02 (0.90 to 1.70)	1.09 (0.90 to 2.90)	<0.001*
WBC, median (range), mm^3	6,800 (2,000 to 64,300)	6,400 (2,000 to 12,200)	0.027*
Hemoglobin, mean (SD), g/dL	14.12 (1.70)	13.47 (1.90)	0.008*
Platelet, mean (SD), x10^9/L	218.85 (67.77)	154.29 (61.89)	<0.001*
Creatinine, median (range), mg/dL	0.92 (0.50 to 13.20)	0.92 (0.50 to 16.20)	0.928

BMI = Body mass index; CAP = Controlled attenuation parameter; dB = Decibel; HCV VL = Hepatitis C Viral load; AST = Aspartate aminotransferase; ALT = Alanine aminotransferase; TB = Total bilirubin; INR = International normalized ratio.
* = significant at $p<0.05$

Table 3. Multivariate logistic regression analysis of factors associated with liver cirrhosis

Variables	Crude OR (95% CI)	*p*-value	Adjusted OR (95% CI)	*p*-value
Age	1.05 (1.01 to 1.08)	0.013*	1.00 (0.96 to 1.05)	0.910
Total bilirubin	1.77 (0.98 to 3.21)	0.057	1.35 (0.80 to 2.27)	0.216
AST	1.02 (1.01 to 1.03)	<0.001*	1.02 (1.01 to 1.02)	0.001*
Albumin	0.29 (0.15 to 0.57)	<0.001*	0.77 (0.33 to 1.83)	0.560
INR	1,109.40 (35.77 to 34,411.48)	<0.001*	9.37 (0.33 to 263.08)	0.189
WBC	1.00 (0.99 to 1.00)	0.022	1.00 (0.99 to 1.00)	0.866
Hemoglobin	0.82 (0.70 to 0.95)	0.010*	0.83 (0.67 to 1.01)	0.062
Platelet	0.99 (0.98 to 0.99)	<0.001*	0.99 (0.98 to 0.99)	<0.001*

* = significant at $p<0.05$

previous studies the incidence rates have varied from 6.3 to 51.1%[28-30], and this difference may be explained by the fact that there were variables in those study populations that may have harboured other risk factors for fibrosis progression. In terms of HCV genotype, our data showed that genotype 3 was the most predominant subtype (50.9%), followed by genotype 1 (28.7%) and genotype 6 (20.4%), similar to the findings of a recent report by Wasitthankasem et al[31].

In observational studies of individuals with chronic HCV, various host factors have been associated with faster fibrosis progression, including (in a study by Poynard et al[32]) age at infection older than 40 years, daily alcohol consumption of 50 g or more, and being of male sex; and male gender and hepatic steatosis in one by Marabita et al[33]. In the present research, the mean age in the cirrhosis group was significantly higher than in the non-cirrhosis group (51.14 vs. 48.03 years; $p = 0.006$); however, in multivariate logistic regression analysis, age was not identified as having an association with cirrhosis. In our study, it was difficult to clearly establish whether age was a determinant factor for cirrhosis because of the long course of the disease, the difficulty in pinpointing precisely the age at infection, and other confounding factors that cannot be excluded but were not examined in our research, such as alcohol consumption. Others host factors, such as gender, obesity (BMI) and hepatic steatosis (CAP), were not associated with cirrhosis in this study.

The impact of viral factors on fibrosis progression is less clear than that of host factors. Data regarding the viral genotype in predicting outcomes are too contradictory to allow definitive conclusions to be drawn. Nousbaum et al's study suggested that genotype 1b is responsible for most HCV-related cirrhosis[34], while another study found no such association after adjustment for disease duration[35]. The present study also showed no correlation between HCV genotype and cirrhosis status in chronic HCV patients.

Elevations in AST levels greater than those of ALT have been associated with more advanced fibrosis[36,37] and are partially related to delayed clearance of AST relative to ALT[38] or to mitochondrial injury associated with more advanced fibrosis[39]. Our finding that a high AST level was associated with cirrhosis was, therefore, consistent with the results of previous studies[37,40,41]. Our research showed that patients with cirrhosis had significantly higher median AST levels than non-cirrhotic subjects (87 vs. 58 IU/mL; $p<0.001$). Multivariate analysis identified increased AST levels as slightly associated with cirrhosis with an aOR of 1.02 (95% CI: 1.01 to 1.02).

The pathogenesis of thrombocytopenia in chronic hepatitis C is not well known. Adinolfi et al investigated the relationship between liver fibrosis, serum thrombopoietin, splenomegaly and thrombocytopenia in HCV patients, and found that advanced hepatic fibrosis, causing an altered production of thrombopoietin and portal hypertension, played a central role in the pathogenesis of thrombocytopenia in their patients[42]. We found similar results in the present study, in which the non-cirrhotic group had a significantly higher mean platelet count than the cirrhosis group (218.85 vs. 154.29 x10^9/L; $p<0.001$). In multivariate analysis, platelet count was an independent factor of liver cirrhosis, in that increased platelet count had an inverse correlation with cirrhosis with an aOR of 0.99 (95% CI: 0.98 to 0.99).

Our study had several limitations including its retrospective design, the limited number of patients, and the fact that diagnosis of liver cirrhosis was not based on liver biopsy. There was also a rather high prevalence of cirrhosis in the present study (51.4%), possibly reflecting referral bias in retrospective studies; this was because most of our patients had already been referred to a tertiary care center, to which more advanced liver diseases patients with abnormal liver biochemistries and hematologic indices are likely to be referred. Finally, our cross-sectional study used routinely collected data and did not take into consideration confounding factors that cannot be excluded such as unavailable data about the amounts and duration of alcohol consumption.

In conclusion, our study demonstrated that more than half of Thai chronic hepatitis C patients (51.4%) had liver cirrhosis. Simple surrogate biomarkers of liver fibrosis such as high AST level and low platelet count, which are routinely collected, are thus valuable because they are indicators of advanced liver disease. This positive finding should encourage further evaluation by either VCTE or liver biopsy to delineate the underlying liver fibrosis status of the patients.

What is already known on this topic?

Chronic viral hepatitis C infection is a well-known cause of chronic liver disease and cirrhosis worldwide, including in Thailand.

EASL-ALEH Clinical Practice Guidelines recommend VCTE, which has a >90% negative predictive value for ruling out cirrhosis, as a valid non-invasive test for assessing liver fibrosis in HCV-infected patients.

What this study adds?

The prevalence of liver cirrhosis identified by VCTE ≥12.5 kPa was 51.4% in CHC patients in Rajavithi Hospital, Thailand.

The present study confirmed that the simple surrogate biomarkers of liver fibrosis, high AST level and low platelet count, were indicators of advanced liver disease in Thai CHC patients.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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