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Original Article

Non-invasive diagnosis of liver fibrosis in children with chronic hepatitis B by transient elastography

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Abstract

Background Chronic hepatitis B (CHB) is one of the most alarming global health problems. Children with CHB mostly remain asymptomatic but serious sequelae like cirrhosis and hepatocellular carcinoma may develop at any age. Liver biopsy, despite being the gold standard, is not preferable for the diagnosis of liver fibrosis because it is invasive and painful. Transient elastography, a noninvasive marker for fibrosis, could play an important role in this disease.

Objective To observe the role of transient elastography in the assessment of the progression of liver damage in children with chronic hepatitis B.

Methods This cross-sectional study was conducted at The Department of Paediatric Gastroenterology and Nutrition of Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh. Based on the inclusion and exclusion criteria, there were a total of 55 cases of CHB. Besides proper clinical history, physical examination, and initial investigation, transient elastography was performed in all of the cases. Liver biopsy was taken in 20 patients with raised serum ALT level after taking proper consent. Elastographic findings were compared with clinical, biochemical, virological, and histological findings.

Results The mean age was 11.46 (SD 3.6) years and 68.7% were male. Most (65.4%) of the patients were asymptomatic at presentation and biochemically normal. Liver stiffness measurements had positive but insignificant correlation with liver biopsy (r=0.43, P=0.06). Sensitivity, specificity, positive predictive value, negative predictive value, diagnostic accuracy for transient elastography were 80%, 53.3%, 36.3%, 88%, and 60% respectively. Areas under the ROC curve were 0.76 (95%CI 0.47 to 1.0) for patients with significant fibrosis (F≥ 2). Using a cut off value of 8.05 kPa, patients with significant fibrosis were detected with a sensitivity, specificity of 80% and 53%, respectively.

Findings of transient elastography were significantly associated with clinical findings like anaemia, jaundice, hepatosplenomegaly, stigmata of CLD and biochemical findings like serum ALT, AST as well as virological parameters.

Conclusion Transient elastography has a limited role in confirming a diagnosis of significant fibrosis. But because of good sensitivity, transient elastography can be used as an initial presumptive diagnostic tool for assessing significant hepatic fibrosis. A cut off value of less than 8.05 in transient elastography can be used for exclusion of significant fibrosis. **[Paediatr Indones. 2023;63:274-81; DOI: https://doi.org/10.14238/pi63.4.2023.274-81**].

Keywords: *hepatitis B; liver fibrosis; transient elastography; serum ALT*

Chronic hepatitis B (CHB) is a major causative factor of liver disease affecting approximately 240 million people worldwide.[1] It is a mysterious and dynamic viral disease with a natural history that remains largely unpredictable to the clinician. In spite of a rather benign course during childhood and adolescence, hepatitis B viral (HBV) chronic carriers have a lifetime risk of up to 25% of developing hepatocellular carcinoma (HCC), and a 2-3% risk of incidence of cirrhosisper year.[2]

The progression of CHB may exhibit several clinical phases: the immune tolerant phase, the

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immune active phase, the inactive carrier phase, the HBeAg negative CHB phase and the HBsAg negative phase. Individual patients do not necessarily experience these clinical phases in a continuous manner, and these clinical phases are not always correlated with criteria or indications for antiviral therapy.[3]

Early detection of liver fibrosis and inflammation is necessary to prevent disease progression by providing treatment in time. Serum biochemical markers such as AST and ALT are very commonly used for the assessment of severity of liver inflammation but fibrosis is considered as a better predictor of disease progression than inflammation.[4] Liver biopsy is currently considered the gold standard for assessing hepatic fibrosis. However, it is an invasive and painful procedure, with rare but potential life threatening complications, limiting its acceptance and repetition in usually asymptomatic patients.[5] In addition, the accuracy of liver biopsy in assessing fibrosis may be questioned because of sampling error and inter-observer variability, which may lead to the under staging of cirrhosis.[6] Thus there is a need to develop and validate non-invasive tests that can accurately reflect the full spectrum of hepatic fibrosis, cirrhosis, and its severity in liver diseases.

Transient elastography is an imaging method that can measure hepatic elasticity and stiffness which provides a rapid, pain-free non-invasive evaluation of the severity of fibrosis.[7-9] The technique is based on changes in tissue elasticity induced by hepatic fibrosis. However, many authors have recommended transient elastography as a surrogate marker for assessing fibrosis in children with chronic hepatitis B.[10,11] This study will be undertaken to observe the elastographic findings in children with CHB to conclude wether it is important to further evaluate the extent of liver disease or not.

Methods

This cross-sectional observational study was conducted at The Department of Paediatric Gastroenterology and Nutrition of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh, from January, 2018 through January, 2019. A total of 55 cases of chronic hepatitis B of either gender, aged < 18 years were studied. Chronic hepatitis B was defined as either persistence of HBsAg for more than 6 months or HBsAg positive and anti HBc IgM negative at one time.[12] Patients with acute hepatitis, obesity, ascites, chronic liver disease (CLD) due to other causes, and who were unwilling to give consent, were excluded from the study.

This study was approved by our Institute of Ethical Committee. Informed written consent was obtained from each patient and his/her parents and they were assured about the privacy of the information. During the recruitment period, the objectives of the study were explained to the potential participants. Detailed history and clinical examinations including presence of jaundice, hepatosplenomegaly, ascites, were done by the researcher herself. For all patients a panel of complete blood count, liver function test, HBsAg, anti HBc IgM, HBeAg, Hepatitis B virus DNA were done. Anti HBe test was done for those who were negative for HBeAg. Transient elastography was performed in all the patients. Liver biopsy was done in selected patients. The indications for the liver biopsy were based on the current practical recommendations of the *European Society of Pediatric Gastroenterology, Hepatology and Nutrition* (ESPGHAN) and the European Association for the Study of the Liver (EASL).[13] It was done in 20 patients with raised serum ALT level under the guidance of ultrasonography. At least 15 mm of tissue was obtained and stained with Masson's trichrome and observed under a microscope in The Department of Pathology, BSMMU. Fibrosis was staged according to the METAVIR scoring system. Fibrosis was staged according to the METAVIR scoring system as follows: no or mild fibrosis (no fibrosis or portal fibrosis without septa, F0F1), moderate fibrosis (portal fibrosis and few septa, F2), severe fibrosis (numerous septa without cirrhosis, F3), and cirrhosis (F4).[14] Fibrosis grade ≥ F2 was also known as significant fibrosis. In this present study emphasis was given on this fibrosis grade as it was considered a trigger to initiate treatment as per current treatment guidelines.[13]

Transient elastography (TE) using *FibroScan* (*EchoSens*, Paris, France) was a noninvasive method of assessing liver fibrosis. It was used for both detection and staging of fibrosis such as F0, F1, F2, F3, and F4 fibrosis. It was performed with an ultrasound transducer probe that produced vibrations of mild

amplitude and low frequency. This induced an elastic shear wave that passed through the liver tissue. The velocity of the shear wave was directly related to liver tissue stiffness; the harder the tissue was, the faster the shear wave propagated.[9] Ultrasound transducer probe was placed 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. Measurements with an incorrect vibration shape or an inappropriate follow up of the vibration propagation were automatically rejected by the software. Up to 10 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 acquisitions. The results were expressed in kilopascal. Median value of the successful measurements was kept as representation of liver stiffness. The whole examination took less than five minutes. Studies examining liver stiffness measurement values in apparently healthy subjects reported normal values ranging from 4.8 to 6.9 kPa.[15,16] These values were not influenced by age, but higher values were reported in the presence of steatosis or components of metabolic syndrome.

After collection, data was checked manually, processed and analyzed by computer based program *SPSS version 20* for *Windows XP.* Results were expressed as mean (standard deviation/SD) or number or percentage. For the comparison of elastographic findings with METAVIR stages box plots were drawn and Spearman's rank correlation coefficient was established. A P value of <0.05 was considered as statistically significant. Sensitivity, specificity, accuracy, positive and negative predictive values of transient elastography werecalculated. Receiver operation characteristic (ROC) curve and the area under the curve (AUC) were used to determine the optimal cut-off value for transient elastography. For categorical variables (age, sex, history, clinical presentations, HBeAg, etc.) the Chi-squre test for independence was used. Univariate analysis for determining the correlation between elastography and serum ALT, serum AST, was performed using the Pearson correlation test. A scatter diagram was used for graphical presentation of correlation.

Results

The mean age was 11.46 (SD 3.6) years and 68.7% were male. Most (65.4%) of the patients were asymptomatic at presentation. Among the symptomatic patients, 17 (30.9%) had anorexia/nausea/vomiting, 16 (29.1%) had abdominal pain, 19 (34.5%) had anaemia, 7 (12.72%) had jaundice, 9 (16.36%) had hepatomegaly, 4 (7.3%) had splenomegaly , 2 (3.6%) had stigmata of CLD. The majority of them were biochemically normal (**Table 1**).

Table 1. Biochemical and haematological profiles of the studied patients (N=55)

Characteristics	Number of patients, n (%)	Mean (SD)
ALT (5-40 U/L)		
Normal	35 (63.6)	27.74 (10.22)
Raised	20 (36.4)	212.85 (209.59)
AST (5-40 U/L)		
Normal	37 (67.3)	28.45 (13.46)
Raised	18 (32.7)	162.4 (77.81)
INR		
Normal	52 (94.0)	1.27 (0.11)
Raised	3 (5.5)	1.63 (0.05)
Albumin (3.5-5g/dL)		
Normal	52 (94.0)	39.13 (3.27)
Low	3 (5.5)	25.0 (3.0)
Platelet count, (150-400)×10³/cm		
Normal	49 (89.1)	256×10³ (69×10³)
Low	6 (10.9)	109×10³ (16×10³)
Hb level, g/dL		
<6	1 (1.8)	5.90 (0.0)
6-9	3 (5.5)	8.70 (0.8)
>9	51 (92.7)	12.58 (6.0)

Regarding the virological profiles 33 (60%) patients were HBeAg positive, 13 (23.6%) were anti HBe positive, andHBV DNA was detected in 42 (76.4%) patients. A total of 20 patients had previously undergone liver biopsy at the time of the liver stiffness measurement. Fibrosis stage distribution was as follows: 3 patients had no (F0) fibrosis, 12 patients had mild fibrosis (F1), 3 patients had moderate fibrosis (F2), no patients had severe fibrosis (F3), and 2 patients had cirrhosis (F4).

Figure 1 shows box plots of liver stiffness for each fibrosis stage. Median liver stiffness measurement values for F0, F1 fibrosis were 7.6 kPa (range 2.9-12.3) and 7.7 kPa (range 3.5-25.0) respectively. For patients with moderate fibrosis (F2), median liver stiffness was 8.4 kPa (range 4.6-35.3). For patients with cirrhosis, median liver stiffness was 30.3 kPa (range 26.3-34.3). Liver stiffness was significantly higher in F4 fibrosis than other stages but there was no significant difference between F0, F1, F2 fibrosis stages. Liver stiffness measurements had positive but insignificant correlation with liver biopsy (r=0.43, P=0.06). Sensitivity, specificity, positive predictive value, negative predictive value, diagnostic accuracy for transient elastography were 80%, 53.3%, 36.3%, 88% and 60% respectively. Areas under the ROC curve were 0.76 (95%CI 0.47 to 1.0) for patients with significant fibrosis (F≥2). Using a cut off value of 8.05 kPa, patients with significant fibrosis were detected with a sensitivity and specificity of 80% and 53%, respectively (**Figure 2**). Findings of transient elastography were significantly associated with clinical findings like anaemia, jaundice, hepatosplenomegaly, stigmata of CLD, virological parameters (**Table 2**) and biochemical findings like serum ALT (**Figure 3**).

Discussion

Chronic hepatitis B is a disease with variable presentations which has made the disease unique and difficult to treat. Early prediction of fibrosis can ease some of these difficulties . Transient elastography as a newer diagnostic tool for diagnosis of fibrosis is verified in the present study.

Clinical characteristics of the study population showed that most of the patients were asymptomatic. This observation is similar to the finding of other studies.[17,18] However hepatitis B virus is a non cytopathic virus and does not cause direct injury to the hepatocyte. Here hepatocytic injury is caused by an activated immune system which takes course over a long period of time.[19] For this reason most of the children may remain asymptomatic and in the immune tolerant phase throughout their childhood.

Among the symptomatic patients anorexia/

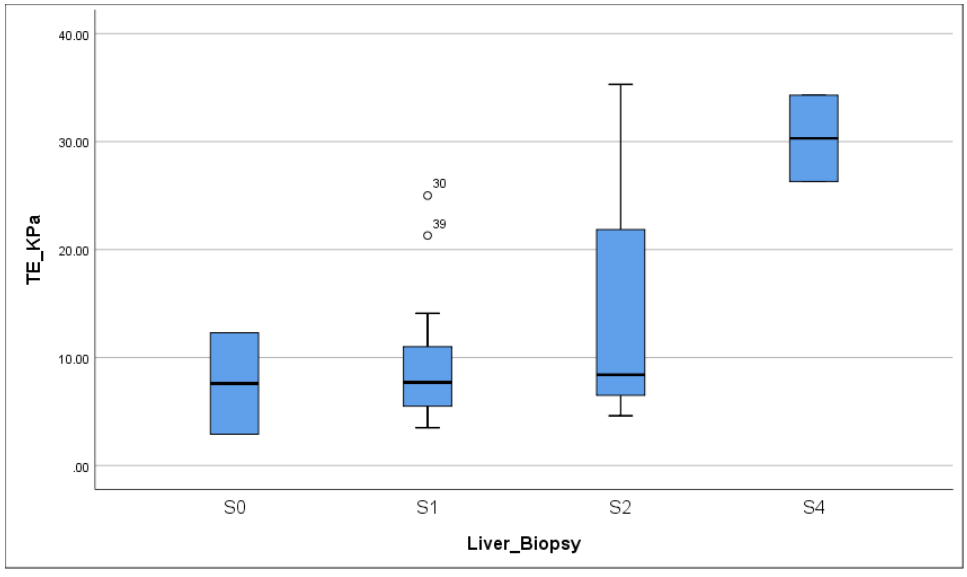

Figure 1. Liver stiffness evaluated using transient elastography according to the METAVIR stages of liver fibrosis (F) in patients with chronic hepatitis B virus infection (n=20). The horizontal line within each box represents the median; the ends of the box represent the interquartile range. Here S corresponds to F grade.

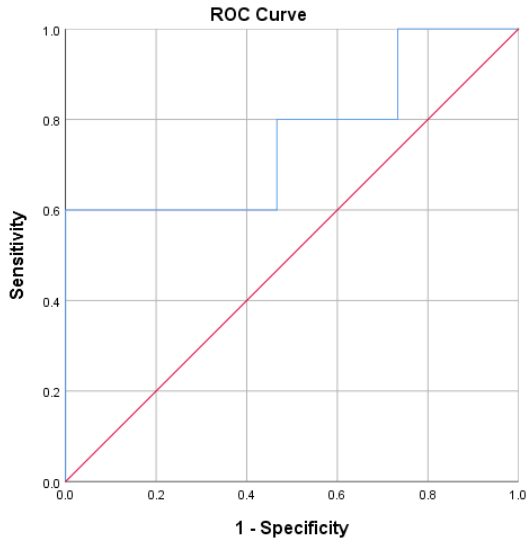

Figure 2. The ROC curve of transient elastography

Table 2. Comparison between clinical and virological parameter with fibrosis score obtained from transient elastography in studied population (N=55)

Variables	Transient elastography				P value
	F1(%)	F2(%)	F3(%)	F4(%)	
Anemia					<0.001
Mild	68.4	5.3	15.8	10.5	
Moderate	0.0	0.0	0.0	100.0	
Jaundice	33.3	0.0	0.0	66.7	<0.001
Hepatomegaly	22.2	11.1	0.0	66.7	<0.001
Splenomegaly	25.0	0.0	0.0	75.0	0.002
HBeAg					
Positive	66.7	100	66.7	00.0	0.004
Anti HBe					
Positive	61.5	00	7.7	30.8	0.696

vomiting (30.9%), abdominal pain (29.1%), anaemia (27.27%), were the commonly presented complaints. Other presentations were jaundice, hepatomegaly and splenomegaly. These findings are similar to the findings of Rukunuzzaman *et al.*[17] The present study revealed that most of the patient had normal biochemical profiles; raised serum ALT and serum AST were found in 36.4% and 32.7% of the cases; prothrombin time was prolonged in 5.5% of the patients; albumin and platelet count were low in 6% and 10.9% of the cases, respectively. These findings are similar to another study.[17] One patient was severely anaemic while three patients were moderately anaemic. Similar findings were presented in another study.[20] In this study most of the patients had no (F0) or mild fibrosis (F1). Only 3 patients had significant fibrosis (F2), 2 patients had cirrhosis (F4). This may be due to the fact that most of the children were in the immune tolerant phase in which biopsy findings showed no or mild fibrosis.

The box plots of liver stiffness for each fibrosis stage shows that median liver stiffness value was significantly higher in F4 fibrosis than other stages but there was no significant difference between F0, F1, F2 fibrosis stages. Rather, there was overlapping between these stages. Here, hyper-reflection of fibrosis stages occurred shown by transient elastography. Liver stiffness measurement correlates positively but insignificantly with the stage of liver fibrosis (P=0.06). A meta-analysis showed that transient elastography had a suboptimal accuracy in the detection of

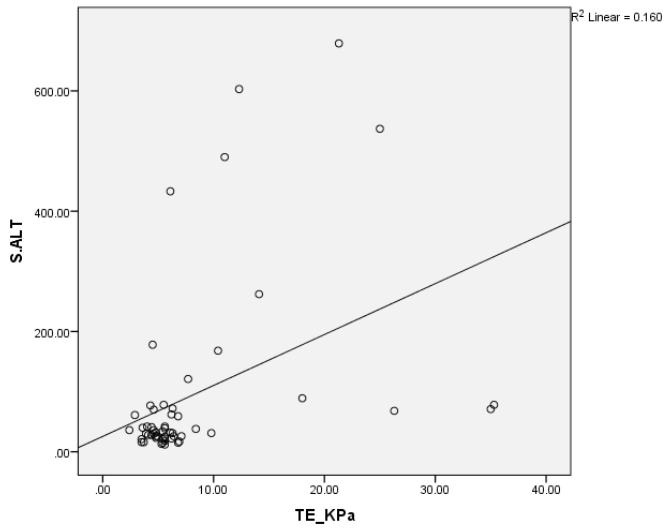

Figure 3. Correlation between transient elastography and serum ALT level (r= +0.41; P=0.002)

significant fibrosis.[21]

In the present study sensitivity, specificity, positive predictive value, negative predictive value and accuracy of transient elastography are 80%, 53.3%, 36.3%, 88% and 60%, respectively. The area under the ROC curve for the prediction of significant fibrosis development was 0.76, which is similar to previous finding (AUROC 0.74).[22] On the other hand other study showed contradictory result (AUROC 0.80) for patients with significant fibrosis (F2). A diagnostic tool is considered a good tool if the AUROC is greater than 80%, excellent if the AUROC is greater than 90%, and perfect if the AUROC is 100%.[23] According to these results, transient elastography may not be considered as a good tool for confirmatory diagnosis of hepatitis B-related significant fibrosis. However, in this study the optimal cut-off value was 8.0 kPa in the patients with stage F2 liver fibrosis with a sensitivity of 80% and a specificity of 53%. A previous study found the same cut off value for F2 fibrosis but with a sensitivity of 86.4% and a specificity of 85.3%.[24] Yet another study showed that for significant fibrosis a cut-off value of 7.7 kPa was 68% sensitive and 69% specificity.[22] In this present study the high false positive rate is responsible for low specificity.

Studies have shown that liver stiffness may be influenced by factors other than fibrosis. Indeed, spuriously elevated liver stiffness measurements have been reported in patients with acute flares of viral hepatitis,[25] necroinflammation in chronic viral hepatitis,[25-27] extrahepatic cholestasis,[28] and hepatic congestion.[29] Although previous studies have shown that severe necroinflammatory activity (as defined by ALT>1000) can affect liver stiffness, recent studies suggest that a much lesser degree of inflammation may also increase liver stiffness, and therefore reduce the accuracy of transient elastography.[25,30,31] In the present study liver stiffness measurements correlate positively and significantly with serum ALT, and negatively correlate with platelet count. These findings are similar to another study.[10] Raised serum ALT level may have an influence on the results of the present study as there was significant positive correlation with serum ALT. Some limitations of this study were limited time and resources, small sample size, and single center study.

In conclusion, transient elastography should not be used to confirm the diagnosis of significant fibrosis. But because of good sensitivity it can be used as an initial presumptive diagnostic tool for assessing significant hepatic fibrosis. A cut off value of less than 8.05 kpa in transient elastography can be used for exclusion of significant fibrosis. Based on the results of this study, we recommend that transient elastography may be use as an adjunct test in assessing the extent of liver disease. Further prospective studies with larger sample size are necessary to evaluate the role of transient elastography for the detection of significant fibrosis.

Conflict of interest

None declared.

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