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Original Research Article **Gastroenterology**

Correlation between Transient Elastography and Liver Biopsy in Chronic Hepatitis B Patients with Elevated HBV DNA and Normal Alanine Aminotransferase Level

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Abstract

Background: Chronic hepatitis B (CHB) is a significant global health burden, Patients with CHB are at increased risk of developing cirrhosis, liver failure and hepatocellular carcinoma (HCC). Even in asymptomatic state, there may be much progression of necroinflammation and fibrosis in liver in many patients specially in patients with elevated HBV DNA with normal alanine aminotransferase. Liver biopsy is the gold standard for fibrosis evaluation but has limitations, necessitating non-invasive alternatives like transient elastography in CHB patients with elevated DNA and normal ALT. ***Objective:*** This study aims to assess the correlation between TE and liver biopsy findings in CHB patients with elevated HBV DNA and normal ALT, evaluating TE's diagnostic accuracy in detecting significant fibrosis. ***Methodology:*** A cross-sectional study was conducted at the Department of Hepatology, Bangabandhu Sheikh Mujib Medical University, Dhaka, from June 2019 to February 2020. Forty CHB patients (HBsAg positive >6 months, ALT <40 IU/L, HBV DNA >2,000 IU/mL) underwent TE and percutaneous liver biopsy. Fibrosis stages were evaluated using the METAVIR scoring system. TE findings were correlated with histological fibrosis using Pearson's correlation test, with statistical analysis performed via SPSS version 23. ***Results:*** The mean age of patients was 30.20 ± 8.3 years, with a male predominance (75%). TE classified 77.5% of patients as having F0-F1 fibrosis and 22.5% as F2 fibrosis. Histological analysis identified 57.5% with F0-F1 fibrosis and 42.5% with significant fibrosis (F2-F4). TE and biopsy findings showed a positive correlation ($p<0.001$). The receiver-operating characteristic (ROC) curve for TE demonstrated an area under the curve (AUC) of 0.774, with a cut-off value of 5.9 kPa yielding a sensitivity of 70% and specificity of 91% for detecting significant fibrosis. ***Conclusion:*** TE shows a strong correlation with liver biopsy findings in CHB patients with elevated HBV DNA and normal ALT, demonstrating its potential as a reliable, non-invasive alternative for fibrosis assessment. Utilizing TE in clinical settings could enhance early detection and management of liver fibrosis, reducing the need for invasive biopsies.

Keywords: Chronic hepatitis B, transient elastography, liver fibrosis, HBV DNA, alanine aminotransferase, liver biopsy, non-invasive assessment.

INTRODUCTION

Chronic hepatitis B (CHB) remains a major global health challenge, affecting millions worldwide and significantly contributing to liver-related morbidity and mortality. While serum alanine aminotransferase (ALT) is commonly used as a marker of liver inflammation, many CHB patients with elevated hepatitis B virus (HBV) DNA levels may present with persistently normal ALT. This poses a diagnostic challenge, as significant liver fibrosis or cirrhosis can still be present despite the absence of biochemical abnormalities. Identifying liver disease severity in this subset of patients is crucial for optimizing treatment strategies and preventing long-term complications. [1-3]

Liver biopsy has long been considered the gold standard for assessing hepatic fibrosis and inflammation. However, its invasiveness, associated risks, and potential for sampling errors limit its widespread use, particularly in patients with seemingly mild or asymptomatic disease. As a result, non-invasive alternatives have gained attention for their ability to provide reliable fibrosis assessment without the risks of an invasive procedure.[4]

Transient elastography (TE), commonly known as FibroScan, is a non-invasive imaging technique that measures liver stiffness, serving as a surrogate marker for fibrosis. TE has demonstrated strong correlation with histological fibrosis stages in various liver diseases, including CHB. However, its diagnostic accuracy in patients with elevated HBV DNA but normal ALT remains a subject of ongoing investigation. This specific patient population may harbor significant fibrosis despite normal biochemical profiles, necessitating a precise assessment method. [5-6]

Several studies have explored the correlation between TE and liver biopsy findings in CHB patients, with varying results depending on disease stage, inflammatory activity, and HBV genotype. [7]Understanding how TE compares with histological findings in patients with normal ALT but active viral replication is essential to determining its role in clinical decision-making. If TE can reliably predict fibrosis in these individuals, it could serve as an alternative to biopsy, facilitating early intervention and improved disease management.

Objective

This study aims to evaluate the correlation between transient elastography and liver biopsy findings in CHB patients with elevated HBV DNA and normal ALT. By assessing the diagnostic performance of TE in this population, we seek to determine its reliability in detecting clinically significant fibrosis and its potential role in guiding treatment decisions.

METHODOLOGY

Type of study: Cross-sectional study.

Place of Study: Department of Hepatology, Bangabandhu Sheikh Mujib Medical University, Dhaka.

Period of Study: June 2019 to February 2020.

Study Population: Patient with CHB with elevated HBV DNA and normal ALT.

Sampling Method: Purposive sampling.

Sample Size (N1) Calculation: Based on sensitivity

$n1 = z2\ p\ (1-p) / \Delta 2$

n1= required sample size

P= anticipated sensitivity

Z= 1.96

Δ= Margin of Error

Calculation:

P= 89 %(Oliveri *et al*. 2008)

Z = 1.96

Δ = 0.1

n1 = 37.59

Thus, 40 patients will be taken considering exclusion & inclusion criteria.

Inclusion Criteria:

- Chronic HBV infection
- HBsAg positive for more than 06 months.
- ALT less than 40 IU/L.
- HBV DNA more than 2,000 IU/ml
- Age- 18 to 65 years.

Exclusion Criteria:

- Co- infection with HCV.
- Patient with history of taking anti HBV therapy (Nucleotide or nucleo-side analogue and pegylated interferon).
- History of alcohol consumption >20 gm/day for female and >30 gm/day for male.
- Non-alcoholic fatty liver disease.
- Autoimmune liver disease.
- Wilson's disease.
- Patient with decompensated cirrhosis of liver.
- Patients of hepatocellular carcinoma.
- Patient with co-morbid condition (COPD, CCF).
- Pregnancy

Study Procedure:

Before going to study procedure, a protocol was approved by university IRB. HBsAg positive patients attended in Hepatology OPD, BSMMU were primarily targeted. Patients were of either sex, age between 18 to 65 years. They were evaluated by proper his-tory and clinical examinations. After explaining details about the study procedure and risks as well as hazards of biopsy procedure, the patients who gave the informed written consent were primarily enrolled. After obtaining written

informed consent, they were evaluated with investigations; complete blood count (CBC), liver function test (ALT, prothrombin time), HBV profile (HBeAg, AntiHBe and HBV DNA)), endoscopy of upper gastrointestinal tract, prothrombin time to meet up inclusion criteria. Exclusion criteria's were fulfilled as follows, co-infection with HCV by anti-HCV, Wilson disease by ceruloplasmin, autoimmuno hepatitis by ANA, non alcoholic fatty liver disease by ultrasonography ((USG) of hepatobilliary system, hcc by alpha fetoprotein and USG. CBC and prothrombine time were done in department of Hematology, BSMMU, Liver func-tion tests including ALT, in Biochemistry department of BSMMU which were done by photometric method, HBV profile in Virology department of BSMMU, abdominal USG in Radiology department of BSMMU and endoscopy of upper gastrointestinal tract in Hepatology department of BSMMU were done. Blood samples were collected with strict aseptic precautions. Patients who met up the selection criteria were finally included in the study. All the patients underwent transient elastography (Fibroscan, Echosens, paris) of liver from a single center for measuring liver stiffness. Pre biopsy evaluation was also completed. Then the patients were admitted in the hospital. Percutaneous liver biopsy was done after proper preparation of patients with available resuscitation facilities including analgesic, I/V fluid, blood transfusion. All biopsy specimens were fixed with 10% formalin solution and were stained with haematoxylin and Eosin and Masson's trichrome stain. Experienced single pathologist, evaluated biopsy specimens using the METAVIR scoring system. He was unaware about the clinical and biochemical parameters of patients. Each patient was observed for 24 hours after liver biopsy and then was discharged from hospital. According to the histopathological reports, patients were divided into two groups: significant fibrosis group and non- significant fibrosis group. The values of liver stiffness were compared with Metavir score of hepatic fibrosis.

Data Processing and Data Analysis:

- The demographic information, relevant history, examination findings &investigation reports of all the study subjects were recorded in previously pre-pared data collection sheet.
- After compilation, the data were presented in the form of tables, figures and graphs as necessary.
- Statistical analysis of the results was done by using computer based software, SPSS version 23 (SPSS Inc. Chicago, IL, USA).
- All values were presented as mean ± standard deviations (SDs) for continuous da-ta and as percentages for categorical data. Qualitative data were analyzed by Chi-square test & quantitative data were analyzed by student, t - test.
- Fibrosis stage derived from transient elastography will be correlated with fibrosis stages on histology by using Pearson correlation test.
- $P < 0.05$ was considered statistically significant.

Ethical Consideration:

The ethical review committee of BSMMU had approved a research protocol before starting this study. Informed written consent (English/Bengali version) was taken from each patient. The purpose and procedures were briefly explained to all participants. The participants had freedom to refuse to answer any question. Final data base and report did not contain the name of participants. There was no major chance of physical risk as it is an observational study. There was hardly any possibility of mental or social harm in the participation of the study. All the participants were treated if they desired. All sorts of confidentiality were ensured. No money was given to the participants of the study.

RESULTS

Table-1 shows baseline characteristics of the patients. The age range was 18-55 years. With mean age was observed 30.20 ± 8.3 years. 30 of them were male and 10 were female. The mean hemoglobin was found 14.04gm/dl, the mean total leucocyte Count was 7.3 ± 1.8x 10^9/L and the mean Platelet count was 263 ± 64.0 x 10^9/L. The mean serum HBV-DNA (log10) was 4.5± 1.5 IU/ml. The mean ALT was 27 ± 7.5 U/L, Prothrombine time was 12.25 ± .68 sec and the mean creatinine was 0.93 ± 0.17 mg/dl.

Table 1: Baseline characteristics of the study population (n=40)

Baseline characteristic	Mean ± SD	Range (min, max)
Age (in years)	30.20 ± 8.3	18, 55
Hb% (gm/dl)	14.04 ± 1.7	10, 16.4
TLC (--×10^9/L)	7.38 ± 1.8	5, 13
Platelet count (--×10^9/L)	263± 64	190, 400
HBV DNA PCR (in logarithmic scale)	4.57 ± 1.5	3.3, 8.34
ALT (U/L)	27.75± 7.5	10, 39
Prothrombine time (sec)	12.25± .68	10, 13.9
Serum Creatinine	0.93 ± 0.17	0.56, 1.3

All values are expressed as mean ± SD and range

Bar chart shows sex distribution of the patients. It was observed that majority of the patients were male 30, (75%) and only 10 (25%) patients were female.

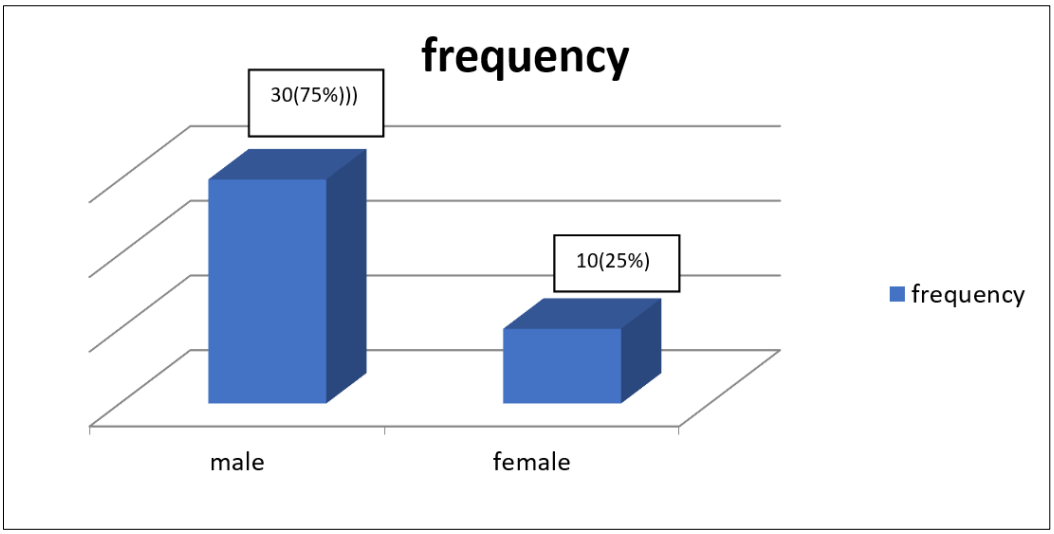

Figure 1: Bar chart shows sex distribution of the study population

The total study population was 40. All of them underwent transient elastography from a single center to measure liver stiffness for evaluation of stages of fibrosis. Mean liver stiffness was 5.6±1.5Kpa. Among the study patients, 31(77.5%) patients were having F_0-F_1 fibrosis. nine (22.5%) were having F_2 fibrosis. Considering F_0-F_1 as non-significant and F_2-F_4 as significant fibrosis, 31(77.5%) patients were in non-significant group and 9 (22.5%) were in significant group.

Table 2: Stages of fibrosis on transient elastography

Fibrosis stage	Number of patients n=40	Percentage %
F_0-F_1 (1-7.4 kPa)	31	77.5
F_2 (7.4-9.5 kPa)	9	22.5
F_3 (9.5-12.5 kPa)	0	0
F_4 (12.5-75 kPa)	0	0
Total	**40**	**100**

The total study population was 40. All of them underwent liver biopsy to evaluate the stage of fibrosis. Among the study patients, 23 (57.5%) patients were having F_0-F_1 fibrosis. Fourteen patients (35%) were having F_2 fibrosis. Two (5%) patients and 1 (2.5%) patients were in F_3 and F_4 stages of fibrosis respectively. Considering F_0-F_1 as non-significant and F_2-F_4 as significant fibrosis, 23 (57.5%) patients were in non-significant group and 17 (42.5%) were in significant group.

Table 3: Fibrosis stage in liver biopsy by metavir scoring of the study population (n=40)

Fibrosis stage	Number of patients N=40	Percentage %
F_0-F_1	23	57.5
F_2	14	35
F_3	2	5
F_4	1	2.5
Total	**40**	**100**

The comparison between significant fibrosis detected by transient elastography and liver biopsy using the METAVIR scoring system (n=40) showed that transient elastography identified fibrosis in 22.5% (F2) of patients, while liver biopsy detected significant fibrosis in 42.5% (F2-F4). Notably, transient elastography failed to detect advanced fibrosis (F3) and cirrhosis (F4), which were identified in 5% and 2.5% of cases, respectively, by liver biopsy. These findings suggest that transient elastography may underestimate fibrosis severity compared to histological assessment.

Table 4: Comparison between significant fibrosis on transient elastography and significant fibrosis by histology with metavir score n=40:

Stages of fibrosis	Transient elastography n=40(%)	Liver biopsy n=40(%)
F_2	9 (22.5)	14 (35)
F_3	0	2 (5)
F_4	0	1 (2.5)
Total	**9 (22.5)**	**17 (42.5)**

Correlation between stages of fibrosis by transient elastography with histological stages fibrosis by metavir scoring: Stages of hepatic fibrosis obtained by transient elastography were correlated with stages of fibrosis observed by histology with metavir scoring system using pearson correlation test. Stages of hepatic fibrosis by transient elastography was positively correlated with histological stages of hepatic fibrosis (p value <o.ooo)

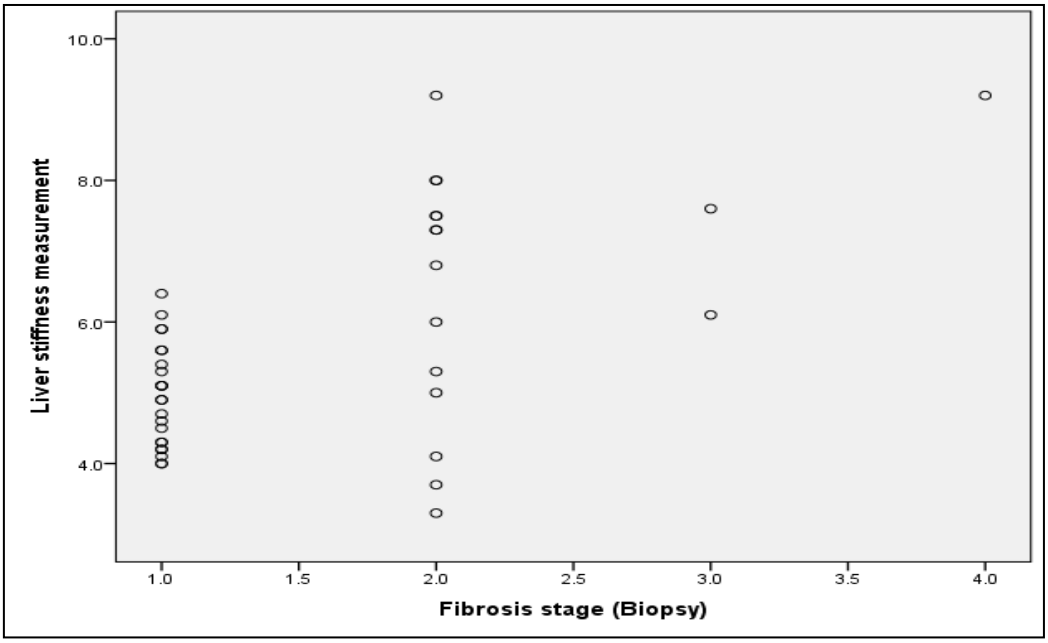

Figure 2: Correlation between stages of fibrosis on transient elastography and histological stages of fibrosis by metavir scoring system

The comparison of laboratory findings between non-significant and significant fibrosis groups (n=40) based on the METAVIR scoring system revealed no statistically significant differences in age, hemoglobin levels, total leukocyte count, platelet count, HBV DNA PCR levels, ALT levels, prothrombin time, and creatinine levels (P > 0.05 for all). However, liver stiffness was significantly higher in the significant fibrosis group (6.58 ± 1.7) compared to the non-significant fibrosis group (4.96 ± 0.71), with a P-value of 0.000, indicating a strong association between fibrosis severity and liver stiffness.

Table 5: Comparison of laboratory findings between non-significant and significant fibrosis group (n=40) on liver biopsy by metavir scoring system

	All patients n=40	Non-significant fibrosis n=22	Significant fibrosis n=17	P value
Age (years)	30.20± 8.2	31.13 ± 6.8	28.94 ± 10	0.418
Hb(gm/dl)	14.04 ± 1.7	14.19± 1.6	13.82 ± 1.7	0.508
TLC (--×109/L)	7.38 ± 1.88	7.60 ± 1.9	7.09 ± 1.8	0.409

Platelet count (--×109/L)	263 ± 64	267.39 ± 52	258± 41	0.667
HBV DNA PCR (log10)	4.57 ± 1.5	4.58 ± 1.6	4.55 ± 1.3	0.958
ALT (U/L)	27.75± 7.5	27.91 ± 7.5	27.53 ± 7.7	0.876
Prothrombine time (sec	12.25± .68	12.4 ± 0.57	12.04 ± 0.78	0.099
Creatinine	0.93 ± 0.17	0.92 ± 0.18	0.93 ± 0.15	0.927
Liver stiffness	5.6± 1.5	4.96 ± 0.71	6.58 ± 1.7	0.000

Based on the receiver-operator characteristic (ROC) curve Transient elastography had area under curve 0.774. At cut off value of 5.9, Sensitivity and specificity of transient elastograpgy are 70% and 91% respectively.

Table 6: receiver-operator characteristic (ROC) curve of Transient elastography for prediction of significant fibrosis

	Cut of value	Sensitivity (%)	Specificity (%)	Area under the ROC curve	95% Confidence interval (CI)	
					Lower bound	Upper bound
Transient Elastography	5.4	70	91	0.774	0.596	0.951

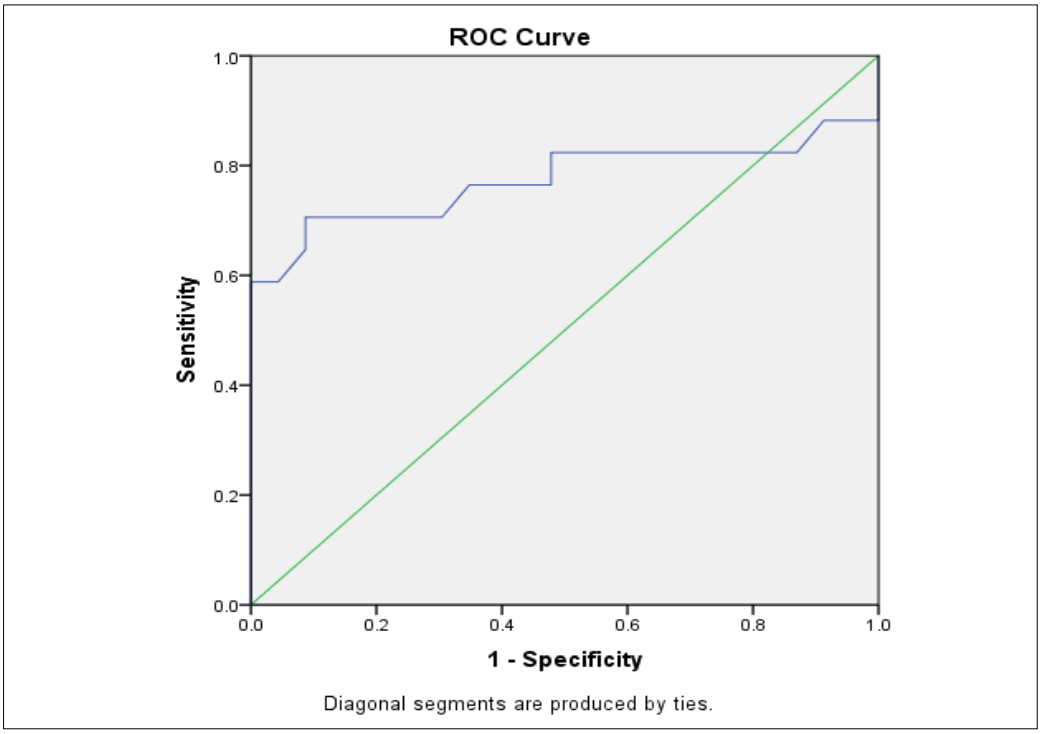

Figure 3: Receiver-operator characteristic (ROC) curve of transient elastography for prediction of significant fibrosis

DISCUSSION

Total 40 CHB patients who were HBsAg positive for 6 months were included in the study. Age range of the patients was 18-55 years, mean age was (30.20 ± 8.32) years which was similar to a study in BSMMU (Asaduzzaman 2010).[7]Thirty (75%) patient were male and 10 (25%) patients were female. This male prepondence was observed in the study was similar with the study conducted among Bangladesh general population (Ah-mad *et al*.2008). [8]

Alaninineaminotransferese range was 10-39 U/L with mean ALT was (27.75 ± 7.45) U/L This study showed no difference in ALT level between significant and non significant fibrosis group on histology (p value 0.876). Xing *et al*. (2018) studied 455 Chinese CHB PNALT patient and found that mean was ALT 27.29 ± 8.19 U/L which is similar to our study. Xing also found ALT level was higher (30.63 ±7.08) U/L among patient with Ishak fibrosis score ≥ 3 than ALT level (26.86 ±8.23) U/L of patients with Ishak fibro-sis score ≤ 3 (p value 0.003). [9] This findings show dissimilarity with my study. Podder *et al*. (2009) studied 30 CHB normal ALT patient with mean HBV DNA >105 copies/ml and found mean ALT was 35.25 ± 2.8 U/L in male and 33.33 ± 5.33 U/L in female. This finding is slightly higher than our study.

In our study mean HBV DNA log10 was 4.57 ± 1.5 IU/ml. This study did not found any difference in HBV DNA level between significant and nonsignificant fibrosis on histology (p value 0.958). Xing *et al*. (2018)

studied 455 PNALT CHB patient and found mean HBV DNA log (8.14 ± 0.99) U/ml which is higher than our study. Xing (2018) also found that HBV DNA was slightly lower in significant fibrosis group (7.6 ± 1.39) U/ml than nonsignificant fibrosis group (8.21 ± 0.91) U/ml, (p value 0.002). This result is dissimilar with our study.[8]

Thirteen (32.50%) patients were HBeAg positive and 27 (67.50%) patients were HBeAgnegative. Alam *et al.,* (2011) studied 181 PNALT CHB patients with mean HBV DNA log (6.4 ± 2.3) U/ml and found HBeAg positive and HBeAg negative cases were 55 and 126 respectively. Predominance of HBeAg is similar to my study. Alam (2011) also found significant fibrosis was also more common in HBeAg negative cases 31 (10.8%) than HBeAg positive cases5 (9.1%). [9] This result is similar to our study.

This study showed mean liver stiffness measured by transient elastography was (5.6 ±1.5) kpa. F1 fibrosis was found in 31(77.5%) patients and F2 fibrosis was found in 9(22.5%) patients. No patients were found in stage F3 or F4 fibrosis. Significant Fibrosis was observed in 9(22.5%) patients. Wong *et al*. (2018) studied 136 asian CHB patient with PNALT and increased HBV DNA levels with mean age 55.1 years at California. He found 28.1% of patients had F2 fibrosis and 4.4 % of patients had F3 and higher fibrosis on transient elastography. Total 32.5% of CHB patient with PNALT and increased HBV DNA had significant fibrosis on transient elastography which is higher than our study. Wong *et al*. (2009) studied 453 CHB patients with mean age 37 years having mean HBV DNA log 7.8 copies/ml with mean ALT 55 U/L and found mean liver stiffness was 6.8kpa which is higher than our study. Wong also (2009) found F1 fibrosis in 216 (48%) patients, F2 fibrosis in 135 patients (30%) and F3-4 fibrosis in 102 patients (22%) on transient elastography. Significant fibrosis was found in 52% of patients on transient elastography which is higher than our study. [10]

This study showed F1 fibrosis were 23 (57.5%), F2 fibrosis were 14 (35%), F3 fibrosis were 2 (5%), F4 fibrosis were 1(2.5%) on metavir scoring system. Significant F2 or higher fibrosis were found in 17 (42.5%) cases. F2 and higher fibrosis were more prevalent in HBeAg negative (30%) people than HBeAg positive CHB (15%) patients. Kumar *et al*. (2008) studied 186 CHB patients with PNALT and found F0-1, fibrosis in 23 (57.5%), F2 F3 and F4fibrosis in 60.3%, 26%, 11% and 2.7% respectively on histology in HBeAg-positive cases. He also found F0-1 fibrosis in 86.3% of patients, F2, F3 and F4 fibrosis were found in 8.6%, 5.2% and 0% of patient on histology in HBeAg negative PNALT CHB patients. Number of significant fibrosis were higher among HBeAg positive cases (63%) than HBeAg negative cases (13.8%) which is dissimilar to our study [11]. Alam (2011), Asaduzzman (2010), Xing (2018), and Lai (2007) found significant fibrosis on liver biopsy in PNALT patients in 33%, 22.8%,10.1% (Ishak score ≥3), and 37% respectively which are lower than our study.

CONCLUSION

TE demonstrates a strong correlation with liver biopsy findings in CHB patients with normal ALT, highlighting its potential as a reliable, non-invasive tool for fibrosis assessment. Its clinical use could improve early detection and management of liver fibrosis while minimizing the need for invasive biopsies.

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