

Hepatitis B Viral Load has No Relation with Degree of Liver Fibrosis in Patients with Chronic Hepatitis B Infection

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ABSTRACT

Background: Fibrosis is the most important predictor of prognosis in patients with Chronic hepatitis B (CHB) related liver disease. Detecting early fibrosis is vital to reduce complications of CHB like cirrhosis and HCC. High viral load is an important predictor of fibrosis. There are many studies reporting the association of hepatitis B (HBV) viral load with degree of liver fibrosis, but results are inconsistent. Hence, this study was undertaken to assess the relationship of HBV DNA titre with liver fibrosis.

Methods: We recruited all newly detected treatment naive CHB patients between May 2021 to January 2023 at Department of Hepatology SCB medical college Cuttack. HBVDNA quantification and fibrosis assessment using 2D shear wave elastography (SWE) were done. The primary endpoint was the relation between HBV viral load and liver fibrosis stage and the estimation of HBV DNA cut off levels for advanced fibrosis \geq F3.

Results: Ninety-eight patients were enrolled (mean age: 46.05 ± 13.21 years, male to female ratio-2.76:1). HBV DNA levels were higher in patients with advanced fibrosis $LSM \geq 8$ kpa (F3) although the difference was statistically not significant ($P=0.6$). HBV DNA levels were also higher in CHB patients with significant fibrosis than those with less degree of fibrosis, in both HBeAg positive and HBeAg negative individuals, although this difference did not achieve statistical significance ($p=0.655$ and $p=0.685$). Age, serum albumin, serum ALT levels, total platelet count, CTP score and MELD-Na score were significant predictors of fibrosis on univariate analysis. But on multivariate analysis, platelet count (OR=0.999, CI=0.981-0.997, $p=0.006$) and MELD-Na score (OR=1.064, CI=1.01-1.198, $p=0.024$) were independent predictors of liver stiffness. A cut off HBV DNA of 17500 (IU/ML) with sensitivity of 51 % and specificity of 41% had a poor diagnostic accuracy to predict F3 fibrosis.

Conclusion: There was no significant correlation between HBV DNA levels and stage of liver fibrosis.

KEYWORDS: Chronic hepatitis B, Shear wave elastography, Fibroscan, HBV DNA.

Introduction

Chronic Hepatitis B virus (CHB) infection is a global public health problem. There are 296 million HBV carriers with 1.5 million new infections occurring every year across the world and with an annual mortality of 820,000 individuals.¹ Approximately, 15-40% patients with CHB will develop life-threatening consequences such as cirrhosis of liver and hepatocellular Carcinoma (HCC).² High levels of hepatitis b(HBV) DNA is a marker of accelerated disease activity and is an independent risk factor for development of HCC. Persistent viral replication in patients with CHB may lead to development of liver fibrosis. Interestingly, fibrosis is the most important predictor of prognosis in CHB related liver disease and has a significant role in deciding treatment initiation.³

There are various invasive and non invasive modalities used to assess the degree of fibrosis. Till now, liver biopsy is still considered as the gold standard modality for detection of liver fibrosis. However, the liver biopsy (LB) has its own limitations including high intra and interobserver variability, sampling variability, and LB is an invasive method, with associated possible morbidity and mortality.⁴ Many non-invasive alternatives such as transient elastography have been developed to evaluate liver fibrosis and to monitor the progression of fibrosis.⁵

Transient elastography is based on the principle of Hooke's law. Measurement of liver stiffness is performed and measured in kilopascals.⁶ However, 2D shear wave elastography (SWE) is relatively recent tool in the era of USG based liver fibrosis assessment which uses the usual 2D US probe to obtain accurate results, even in the presence of ascites and obesity. However, there are no definitive criteria for confirming the reliability of measurements observed in 2D-SWE techniques.⁸ Though there are many reports describing the use of TE in patients with chronic hepatitis B, there are fewer publications on the use of 2D-SWE. Hence, this study was carried out to assess the relationship of HBV DNA titre with the degree of liver fibrosis assessed by SWE in patients with CHB.

Materials and Methods

Methods: All consecutive HBV patients more than 14 years of age with detectable HBV DNA levels

presenting to Department of Hepatology, SCB Medical College, Cuttack between August 2021 to January 2023 were included. Those with hepatocellular carcinoma, autoimmune hepatitis, alcoholic liver disease, NASH, pregnancy, gross ascites and small rib spaces were excluded. Informed consent was taken from all the patients. The study was approved by Institutional ethics committee of SCB Medical College, Cuttack, Odisha (IEC no 898 dt-3.8.2021).

Demographic and Clinical Data: Demographic details, clinical findings, and investigations were obtained and incorporated in a structured format. Patients or their relatives were explained in detail both verbally and in written form about the aims and objectives of the study. All patients underwent 2D SWE to estimate the median liver stiffness.

HBV DNA Quantitative Assay: It was done by Trueprep® AUTO v2 Universal Cartridge based Sample Prep Device (Molbio's INDIA). Truelab micro PCR System is a nucleic acid amplification platform that works on Real Time Polymerase Chain Reaction (PCR) technology that enables near patient diagnosis through disposable, disease specific micro PCR chips and a portable, automated Truelab Real Time micro PCR analyzer. Analysis of the data was used to determine the concentration of the respective DNA with 95% probability of detection. LoD (limit of detection) was determined to be 55.92 IU/ml for HBV in plasma.

Shear Wave Elastography: Median liver stiffness was measured using LOGIQ shear wave elastography (GE LOGIQ™ S8 XDclear; C1-6-D convex transducer 16MHz, GE Healthcare, Milwaukee, WI, USA) as per our hospital protocol. Patient were advised fasting for at least 4h before measurement to limit the effect of portal vein flow.⁹ The test was performed by the hepatologist with experience of performing over 1000 procedures.

A region of interest (ROI) was placed over an area of the liver, at least 1 cm below the liver capsule, taking care not to include large vasculature or biliary structures. Patients were in positioned in supine or slightly left decubitus position with right arm overhead, imaging approach targeting right liver lobe (segments 7 or 8) of

the liver.¹⁰ Serial measurements, at least ten, were taken through multiple scans. Liver stiffness measurement (LSM) value was shown automatically on the machine. The median was measured, and the IQR/median ratio cutoff of 30% was taken for valid measurements. Liver fibrosis staging was done based on LSM values.¹¹ Those with LSM values between 6.48 to 6.60 kpa were F1, 6.6 to 8.07 were F2, 8.07 to 9.31 were F3 and LSM value more than 9.31 were designated F4.¹¹

Aspartate platelet ratio index (APRI) and FIB4 index were calculated for all patients as per standard formulae.

Statistical Analysis: The quantitative data with continuous variables were expressed as mean ± standard deviation (S.D.) or median (interquartile range: IQR) as appropriate whereas categorical variables were expressed in terms of percentages. The significant difference of continuous variables were assessed by independent t test. Logistic regression analysis was done to find out significant independent predictors of fibrosis. Those variables which were found to be predictors of liver fibrosis on univariate analysis were taken into consideration for multivariate logistic regression analysis. All the statistical analysis were done by using SPSS version 20.0 (IBM, Chicago, USA).

Results

Baseline Clinical Characteristics: A total of 98 patients were evaluated in this cross sectional observational study. The baseline characteristics are depicted in **Table 1**. The mean age of patients was 46.05±13.21 years. The male to female ratio was 2.76:1. The mean platelet counts, mean ALT, and mean serum albumin were 234±103×10⁹/L, 50±87 IU/ml, 3.61±0.75 mg/dl respectively. Majority of patients were non-cirrhotics (n=67-68%) while 31(31%) were cirrhotics. Eighty seven (88.8%) patients had HBV DNA levels <10⁶ IU/ml and 11 (11.2%) patients had DNA levels >10⁶ IU/ml. The mean HBV DNA levels was 9761115±397415 IU/ml. Thirty seven (37.8%) patients had advanced fibrosis (≥F3). The mean LSM was 9.89±8.05 kpa, mean APRI score was 1.01±1.32 and the mean FIB-4 was 2.65±3.54.

Table 1: Baseline characteristics of study population.

Parameters	Value (n=98)
Age in years	46.05±13.21
Gender	Males-72% Females-26%
Hemoglobin (g/dl)	11.6±2.02 (6.5-17.5)
Platelets (in 10 ⁹ /L)	234±103 (450-24)
Bilirubin (mg/dl)	1.75±0.88 (7.1-0.8)
AST (IU/ml)	59.03±45.38 (24-548)
ALT (IU/ml)	50.87-31.008 (14-179)
Albumin (g/dl)	3.61±0.75 (1.8-4.5)
INR	1.25±0.42 (0.7-2.9)
Creatinine (mg/dl)	0.9±0.7 (0.2-7)
Sodium (meq/l)	134±4.78 (123-145)
Fibroscore (LSM) (in kpa)	9.89±8.05 (3.7-62)
APRI Score	1.01
FIB 4	2.65 ± 3.54
CTP	A=67 B=15 C=16
MELD Na	12.24±6.74 (6-33)
Variceal grading	Grade I=10 (10%) Grade II=9 (9.4%) Grade III=7 (7.1%)
HBV DNA (IU/mL)	9761115±397415(20-2800000)

MELD - Model for End Stage Liver Disease; ALT - Alanine Transaminase; AST - Aspartate Transaminase; CTP - Child-Turcotte-Pugh; INR - International Normalized Ratio.

Comparison of Variables in HBeAg Positive CHB Patients Between Those with LSM ≥8 (≥F3) and LSM<8: **Table 2** reveals comparison of variables between HBeAg positive patients LSM ≥8(F3) versus those with LSM<8. Mean age was significantly higher among those with LSM ≥8 kpa as compared to those with LSM<8 kpa (50.46±8.57 vs 38.78±13.34; p<0.001). Similarly mean ALT (68.16 ± 38.81 vs 39.62 ± 19.90, p<0.001), mean MELD Na score (16.54 ± 7.39 vs 9.73±4.55, p<0.001) and mean CTP score (9.88±3.5 vs 5.95±0.74, p<0.001) were significantly higher among those with LSM≥8 kpa compared to LSM<8 kpa where as mean serum albumin (3.18±0.83 vs 3.95±0.42, p<0.001) and mean platelet counts (170±109 vs 279±68.73, p<0.001) were significantly lower among those with LSM≥8 kpa

compared to those with LSM<8 kpa. Though HBV DNA was higher among those with LSM≥8 kpa compared to LSM<8 kpa, the difference was not statistically significant.

Comparison of Variables in HBeAg Negative CHB Patients Between Those with LSM ≥8 (≥F3) and LSM<8: As depicted in **Table 3**, mean serum albumin (2.83±0.74 vs 3.94±0.53, p <0.001) and mean platelet count (130.85±78.4 vs 284±79.03, p<0.001) were significantly lower among those with LSM≥8 kpa as compared to those with LSM<8 kpa, whereas mean CTP score (9±3.2 vs 5.88±0.94, p<0.001) and mean MELDNa score (16.77±8.55 vs 9.38±4.10, p<0.001) were significantly higher among those with LSM≥8 kpa compared to LSM<8 kpa. Though HBV DNA was higher among those with LSM≥8 kpa compared to LSM<8 kpa, the difference was statistically non-significant.

Predictor of Liver Fibrosis in Patients of Chronic Hepatitis B: As depicted in **Table 4**, age was a

significant predictor of liver fibrosis (OR=1.039 with CI 1.004-1.075, p=0.028). Platelet count (OR=0.983, CI=0.976-0.990, p=0.001), and serum albumin (OR=0.125, CI=0.054-0.289, p=0.001) had significant inverse relationship with liver fibrosis. ALT levels (OR=5.278, CI=1.517-18.36, p=0.009), CTP score (OR=2.341, CI=1.560-3.511, p=0.000) and MELD Na score (OR=1.207, CI=1.109-1.313, p=0.000) were also significantly associated with liver fibrosis. HBV DNA (OR=1.000 with CI=1.000-1.000 p=0.602) and HBeAg (OR= 1.198, p=0.677) were not found to be significant predictors. However, on multi-variate analysis, platelet count (OR=0.999,CI=0.981-0.997, p=0.006) and MELD Na score (OR=1.064, CI=1.01-1.198, p=0.024) were the only parameters found to be significant independent predictors of liver fibrosis. As depicted in **Table 5** both APRI (correlation coefficient 0.58, p <0.001) and FIB-4 (correlation coefficient 0.57, p <0.001) had excellent correlation with liver fibrosis.

Table 2: Comparison of laboratory variables in HB eAg positive CHB patients between those with LSM ≥8 (F3) and LSM<8.

Variable	LSM ≥8 (n=24)	LSM<8 (n=37)	P-Value
Age in years	50.46±8.57	38.78±13.34	0.001
Platelet (10 ⁹ /L)	170±109	279±68.73	0.001
ALT (IU/ml)	68.16±38.81	39.62±19.90	0.001
Albumin (g/dl)	3.18±0.83	3.95±0.42	0.001
HBVDNA (IU/ml)	19238633.3±5783295	1336311±441392	0.655
MELD Na	16.54±7.39	9.73±4.55	0.001
CTP	9.88±3.5	5.95±0.74	0.001

MELD - Model for End Stage Liver Disease; ALT - Alanine Transaminase; AST - Aspartate Transaminase; CTP - Child-Turcotte-Pugh.

Table 3: Comparison of laboratory variables in HB eAg negative CHB patients between those with LSM ≥8 (F3) and LSM<8.

Variable	LSM ≥8 (n=13)	LSM<8 (n=24)	P-Value
Age in years	48.85± 11.68	51.33 ± 13.22	0.57
Platelet (10 ⁹ /L)	130.85±78.4	284±79.03	0.001
ALT (IU/ml)	58.23±30.24	46.95±29.8	0.282
Albumin (g/dl)	2.83±0.74	3.94±0.53	0.001
HBVDNA (IU/ml)	1319.23±1448	1241±1637.81	0.685
CTP score	9 ±3.2	5.88±0.94	0.001
MELD NA	16.77±8.55	9.38±4.10	0.001

MELD - Model for End Stage Liver Disease; ALT - Alanine Transaminase; AST - Aspartate Transaminase; CTP - Child-Turcotte-Pugh.

Table 4: Multivariate analysis of demographic profile and laboratory parameters to predict median Liver stiffness.

Variable	Univariate analysis			Multivariate analysis		
	OR	95% CI	P value	AOR	95% CI	P value
Age	1.03	1.004-1.075	0.028	1.01	0.97-1.06	0.44
Platelet count	0.98	0.97-0.99	0.000	0.99	0.98-0.99	0.006
ALT	5.27	1.51-18.36	0.009	3.85	0.61-24.2	0.15
Albumin	0.12	0.054-0.289	0.000	-	-	-
CTP	2.34	1.56-3.51	0.000	-	-	-
MELD Na	1.2	1.109-1.313	0.000	1.06	1.01-1.19	0.024
HBV DNA	1.00	1.00-1.00	0.57	-	-	-

MELD - Model for End Stage Liver Disease; ALT - Alanine Transaminase; AST - Aspartate Transaminase; CTP - Child-Turcotte-Pugh; OR - Odds Ratio; AOR - Adjusted Odds Ratio.

Table 5: Comparison of APRI, and FIB-4 with FibroScan for the assessment of liver fibrosis in patients with chronic hepatitis B.

First variable	Second variable	Correlation coefficient	P value *
Fibro Scan Values	APRI	0.58	<0.001
	FIB 4	0.57	<0.001

*Analyzed by Spearman’s correlation.

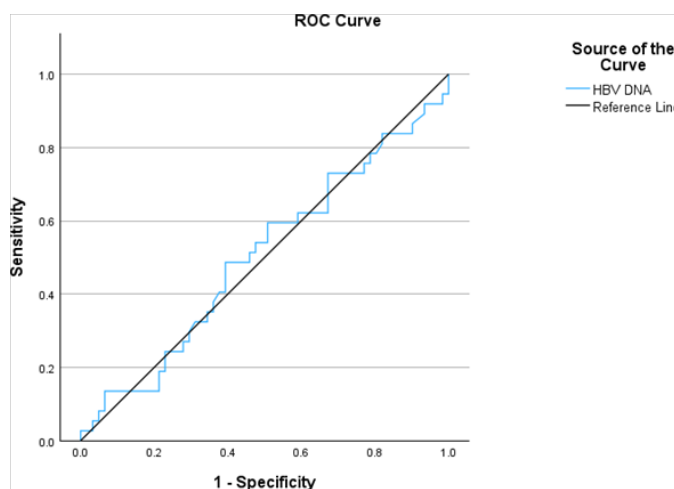
Diagnostic Value of HBVDNA For Predicting Advanced Fibrosis ($\geq F3$): ROC curve analysis were done in all patients of CHB to determine the diagnostic accuracy of HBV DNA levels for predicting liver fibrosis, as shown **Figure 1**. The AUROC for HBV DNA to detect advanced fibrosis in patients with CHB was found to be 0.53 (95% CI 0.383-0.623; $p=0.95$). Hence, HBV DNA titre was not found to be reliable for predicting advanced fibrosis.

Diagnostic Value of APRI and FIB-4 Scores for Predicting Advanced Fibrosis ($\geq F3$): ROC curve analysis were done in all patients of CHB to determine the diagnostic accuracy of APRI and FIB-4 scores for predicting liver fibrosis, as shown **Figure 2**. The AUROC for APRI and FIB-4 scores to detect advanced fibrosis (LSM ≥ 8) were 0.879 (95% CI 0.77-0.98; $p=0.001$) and 0.880 (95% CI 0.78-0.97; $p=0.001$) respectively. Hence APRI and FIB-4 scores were good predictors of advanced fibrosis.

Discussion

Liver fibrosis is key predictor of progression of liver disease in patients with chronic hepatitis B.¹² Liver biopsy

is still the gold standard method to assess degree of liver fibrosis but owing to its invasiveness, various non-invasive modalities like fibroscan and elastography have been developed and practised in the recent years.¹³ The utility of transient elastography in assessing the degree of



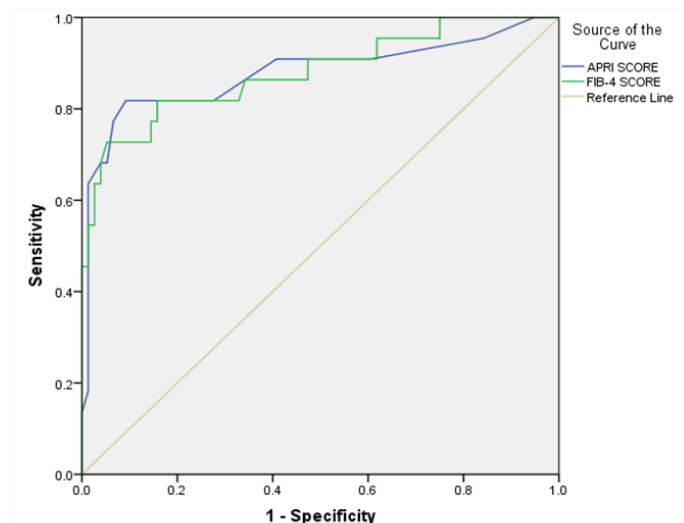
Variable	AUROC	95% CI	P value
HBV DNA	0.503	0.383-0.623	0.959

Figure 1: ROC curve for HBV DNA as a predictor for advanced fibrosis(F3 LSM ≥ 8 kpa).

fibrosis have been evaluated in earlier studies and liver stiffness values directly correlated with the degree of fibrosis.¹⁴ However, there were few studies assessing the correlation of Hepatitis B viral load with liver fibrosis. Hence, the current study was undertaken to ascertain the relationship between HBV DNA and liver fibrosis using 2D SWE .

In our study, mean HBV DNA levels were higher in the group with chronic hepatitis B patients with LSM ≥ 8 kpa (F3) as compared to those with LSM < 8 kpa but this was not statistically significant. HBV DNA was not found to be independent predictor of liver fibrosis in multivariate regression analysis. Although high replication of hepatitis B virus is an independent risk factor for development of cirrhosis and HCC (15), HBV DNA titre did not correlate with degree of fibrosis in our study. Various previous studies have made similar observations as ours. A study from Egypt by Saleh et.al observed that HBV DNA levels showed the highest levels in patients with advanced fibrosis as compared to earlier stages of fibrosis. However, it showed weak diagnostic performance in the differentiation between different stages of liver fibrosis and there was nonsignificant correlation between fibrosis score and viral load in their study.¹⁶ Another cross sectional study from Turkey also found poor diagnostic accuracy of HBV DNA > 20000 IU/ml in detecting advanced fibrosis.¹⁷ However, an Iranian study with a very small cohort of 30 patients by Bizar et al found a significant correlation between HBV DNA and stage of liver fibrosis by histopathology.¹⁸ Another Iranian study of 236 treatment naive CHB patients showed that HBV DNA was correlated with liver fibrosis only in HBeAg negative CHB patients, but this correlation was not seen with HBeAg positive subjects.

In our study, mean age was significantly higher in patients with LSM ≥ 8 kpa as compared those with LSM < 8 , suggesting that age has a significant correlation with grade of fibrosis. This findings was also evident in many other studies.^{19,20,21} We also found that serum albumin was independent predictor of liver fibrosis and was significantly lower in patients with LSM ≥ 8 kpa as compared with LSM < 8 kpa. Previous studies had also shown similar relationship of serum albumin with liver fibrosis.^{20,21,22} Hypoalbuminemia results from decreased synthesis of albumin from hepatocytes in patients of



Variables	AUROC	95% CI	P value
APRI SCORE	.879	0.77-0.98	0.001
FIB-4 SCORE	.880	0.78-0.97	0.001

Figure 2: AUROC for APRI and FIB-4 for significant fibrosis (\geq F3) in patients with chronic hepatitis B.

chronic liver disease, hence serum albumin levels correlated with degree of liver fibrosis.^{22,23}

In the present study, platelet count was significantly lower patients with LSM ≥ 8 kpa (F3 fibrosis) as compared with LSM < 8 kpa in both HBeAg positive and negative group. In addition, platelet count was a significant negative predictor of liver fibrosis. This association of low platelet count with liver fibrosis is also established in numerous previous studies.^{24,25,26} Reduced hepatocyte mass due to liver fibrosis resulting in decreased production of thrombopoietin might be the explanation for low platelet count in liver fibrosis. It was also found that APRI and FIB-4 were good predictors of advanced fibrosis. A recent study comprising of 253 patients also revealed that liver stiffness by 2DSWE was positively correlated with FIB-4 but not with APRI score.²⁷

There are many strengths of current study. It comprises of real time data of CHB patients in relation to HBV DNA and liver fibrosis. Moreover, 2D SWE is relatively newer, more accurate modality of assessment of liver fibrosis and literature is limited. And also, such types of studies are scarce in this part of the world. However, this study has few limitations. Sample size was low. Results of study were not correlated with liver biopsy which is still the gold standard for assessment of liver fibrosis.

Conclusion

HBV DNA levels does not correlate with the degree of fibrosis in patients with chronic hepatitis B, in both HBeAg positive and HbeAg negative individuals. In addition HBV DNA is also not an independent predictor of fibrosis. Low platelet count and hypoalbuminemia were significant negative predictor of liver fibrosis. Large well designed future studies evaluating the predictive value of HBV DNA on liver fibrosis should be undertaken.

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