

# Evaluation of Chitinase 3-like 1 (CHI3L1) as a noninvasive biomarker of hepatic fibrosis in patients with Hepatitis B virus–related compensated chronic liver disease

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## ABSTRACT

**Background:** Liver biopsy is the gold-standard method for diagnosing and staging liver fibrosis, but the procedure is invasive, not available in the primary health care facilities, and not free from complications. Noninvasive serum biomarkers of hepatic fibrosis are the current research focus. **Objectives:** To assess the correlation between serum Chitinase 3-like 1 (CHI3L1) levels and histological severity in patients with Hepatitis B Virus (HBV)-related compensated chronic liver disease (CLD). **Material and Methods:** This cross-sectional study evaluated 50 treatment-naïve patients with chronic hepatitis B with compensated CLD. Liver biopsy was done, and hepatic fibrosis was categorized using the METAVIR scoring system; we divided the study subjects into three groups; group 1 included subjects with F0 and F1, group 2 having F2 group 3 having F3 and F4. Serum CHI3L1 was measured in all by immunoassay. **Result:** Among 50 patients, only one had METAVIR score F0, seven had F1, 33 had F2, nine had F3, and none had METAVIR score F4. The median value of CHI3L1 was 460.8 (IQR 340.1-570.3) in all study subjects; 359.5 (IQR 272.8-526.9) in group 1, 450.0 (IQR 307.75-5332.0) in group 2, and 1355.5 (IQR 530.75-1580.5) in the group 3. The difference in median CHI3L1 across the groups was statistically significant. Serum aspartate aminotransferase (AST) and the AST to Platelet Ratio Index (APRI) score had significant positive correlations with CHI3L1 levels. CHI3L1 also had significant positive correlations with METAVIR scores. **Conclusion:** This study found a positive correlation between serum CHI3L1 level and hepatic histological severity in patients with HBV-related compensated CLD. Further larger-scale research is needed to establish the fact.

**Keywords:** APRI, Chitinase 3-like 1, Chronic hepatitis B virus infection, Compensated chronic liver disease, METAVIR score

## Introduction

To date, chronic hepatitis B virus (HBV) infection is a severe public health problem. HBV affects around 400 million people

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worldwide, causing 1 million deaths per year globally. About 75%–80% of these HBV-infected patients reside in Asia and the Western Pacific region.<sup>[1,2]</sup> The disease spectrum of chronic HBV infection is variable, ranging from an asymptomatic and inactive carrier state to progressive chronic hepatitis B (CHB). CHB infection may eventually evolve into cirrhosis and hepatocellular carcinoma.<sup>[3-5]</sup> Bangladesh is within the intermediate zone (5.4%)

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of HBV infection prevalence. The HBeAg-negative variant is the leading cause of chronic hepatitis in incidentally detected HBsAg positive patients in this country.<sup>[6,7]</sup>

The diagnosis of CHB is based on laboratory tests that include biochemical liver function tests (LFTs), HBV DNA, hepatic ultrasound, and liver biopsy. Patients with higher degrees of hepatic inflammation and fibrosis have significant risks of developing complications like cirrhosis of the liver and hepatocellular carcinoma. A histological assessment of hepatic tissue obtained by liver biopsy is the gold-standard investigation for detecting liver damage, which provides important information on the severity of necroinflammatory activity and fibrosis and is useful for predicting treatment response.<sup>[8]</sup> Its invasive nature and unavailability in nonspecialized centers limit liver biopsy's diagnostic utility. Moreover, there is also a chance of sampling error and poor and interobserver variability.<sup>[9,10]</sup> Therefore, the search for alternative suitable noninvasive markers of hepatic inflammation and fibrosis is desperately going on.<sup>[11]</sup> Chitinase 3-like protein 1 (CHI3L1) is a member of the chitinase family without chitinase activity. The roles of CHI3L1 in both inflammation and tissue remodeling are observed.<sup>[12]</sup> Many researchers have evaluated the utility of CHI3L1 as a noninvasive biomarker for alcoholic cirrhosis and hepatitis C virus (HCV)-induced liver fibrosis with promising results.<sup>[13-15]</sup>

As there is a high burden of HBV disease in our country and liver biopsy, the gold standard investigation for hepatic fibrosis is not widely available in our primary care settings. However, a noninvasive marker for HBV-related hepatic fibrosis may have important diagnostic and therapeutic roles. With this background, we evaluated the correlations of serum CHI3L1 levels with the stages of hepatic fibrosis in patients with HBV-related compensated CLD in this study.

## Material and Methods

We conducted this cross-sectional study among adults (aged  $\geq 18$  years) suffering from chronic HBV infection (HBsAg positive for six months or more) and were attending the Department of Hepatology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh from July 2015 to June 2017. Subjects with the human immunodeficiency viruses (HIV) or HCV co-infection, history of significant consumption of alcohol ( $>30$  gm/day for male and  $>20$  gm/day for female), nonalcoholic fatty liver disease (NAFLD), decompensated CLD, significant comorbidity like chronic obstructive airway disease, diabetes mellitus, thyroid disorders, chronic kidney disease, heart failure, and on previous or current antiviral medication were excluded from the sample. The protocol of the study received approval from the institutional review board of the university.

The sample size was calculated using Buderer's formula for a power level greater than 80%, an  $\alpha$  error of 0.05, and an expected sensitivity of 91.76% based on a previous study.<sup>[16]</sup> The estimated

sample size was 58.24 and we included 50 patients in this study. After explaining the study's objectives and the liver biopsy procedure's hazards, written consent was obtained from all the participants. After enrolment, the patients were admitted to the inpatient department of hepatology, BSMMU. Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), prothrombin time (PT), international normalized ratio (INR), complete blood count (CBC), fasting plasma glucose (FPG), 2-hour postprandial plasma glucose (2-h PPG), and fasting lipid profile were measured. The AST to platelet ratio index (APRI) score was calculated from the formula  $[\{AST \text{ level (IU/L)}/AST \text{ (upper limit of normal) (IU/L)}\}/platelet \text{ count (}10^9/L)] \times 100$ .

## Liver biopsy and histological staging

Percutaneous transthoracic liver biopsy was done after prebiopsy evaluation and proper preparation of patients with the available resuscitation facilities kept in hand. The study subjects were kept under observation for 48 hours in the hospital after the biopsy procedure. All biopsy material were fixed with 10% formalin solution and were stained with hematoxylin–eosin initially and then with the special stain Masson's trichrome. A single pathologist examined all the slides and categorized fibrosis using the METAVIR scoring system where F0 = no fibrosis, F1 = portal fibrosis without septa, F2 = portal fibrosis with rare septa, F3 = numerous septa without cirrhosis, and F4 = cirrhosis; F0 and F1 are considered as having no significant fibrosis and F2, F3, and F4 are considered as having significant fibrosis.<sup>[17]</sup> Blood samples were drawn and sent to measure the CHI3L1 levels performed by immunoassays (Hangzhou Proprium Biotech Co. Ltd, Hangzhou, Zhejiang, China) in the virology laboratory of the university.

## Statistical analysis

We used the Statistical Product and Service Solutions (SPSS) for Windows, version 23.0 software (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.) for data analysis. Categorical variables were presented as frequencies (percentages), measurable variables with normal distribution were presented as mean  $\pm$  standard deviation (SD), and those not following normal distribution were presented as median. Chi-square test, one-way ANOVA, or Kruskal–Wallis tests were performed as applicable for comparing the variables between different groups. The correlations of CHI3L1 with other variables were tested by using Pearson or Spearman's correlation tests. A *P* value  $\leq 0.05$  was considered statistically significant.

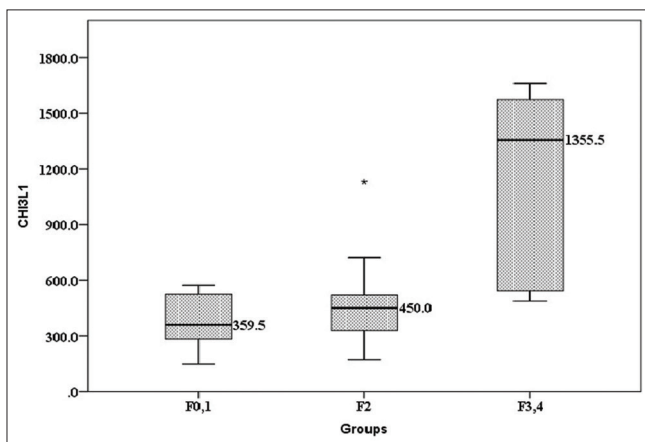
## Results

Among 50 patients, only one had a METAVIR score of F0, seven had F1, 33 had F2, nine had F3, and none had the METAVIR score of F4. For analysis, the subjects were grouped into three groups; group 1 included subjects having F0 and F1, group 2 having F2, and group 3 having F3 and F4.

**Table 1: Baseline characteristics of the study population**

Variables	Mean±SD or median (IQR) or n (%)				P
	Total (n=50)	Group 1 (n=8)	Group 2 (n=33)	Group 3 (n=9)	
Age (years)	27.1±6.3	27.8±6.6	27.0±6.2	26.8±6.9	0.945
Male Gender	39 (78)	5 (62.5)	28 (84.8)	6 (66.7)	0.260
BMI (Kg/M <sup>2</sup> )	23.2±2.4	24.6±3.2	22.9±2.4	22.8±1.5	0.193
Systolic BP (mmHg)	118±5	116±5	118±5	118±5	0.691
Diastolic BP (mmHg)	77±5	77±5	77±5	74±5	0.367
Hemoglobin (%)	14.3±1.3	13.6±1.2	14.3±1.4	14.7±1.4	0.247
Total WBC count (×10 <sup>3</sup> /mm <sup>3</sup> )	7.0 (6.0-8.5)	6.7 (6.0-7.5)	7.5 (6.5-9.0)	7.0 (6.0-7.3)	0.197
Neutrophil (%)	59.7±7.6	56.4±6.6	59.8±7.9	62.3±6.3	0.271
Lymphocyte (%)	31.9±6.7	33.6±5.6	32.1±6.7	29.9±6.7	0.439
Monocyte (%)	4.6±2.5	4.1±2.6	4.5±2.5	5.2±2.4	0.644
Eosinophil (%)	4.0±2.8	5.9±3.9	3.9±2.5	2.6±1.6*	0.042
ESR (mm in 1 <sup>st</sup> hour)	17 (10-30)	17 (6-29)	15 (10-30)	17 (10-30)	0.932
Platelet count (×10 <sup>9</sup> /L)	231.0±57.3	235.0±50.1	241.7±52.4	188.3±66.1	0.042
FPG (mmol/L)	5.2±0.4	5.3±0.6	5.2±0.4	5.3±0.4	0.815
2h-PPG (mmol/L)	6.2±0.9	6.9±0.8	6.0±0.9†	6.2±0.6	0.046
S. Creatinine (mg/dL)	0.81±0.15	0.73±0.11	0.83±0.16	0.82±0.17	0.251
TC (mg/dL)	145.0±45.4	142.8±36.5	147.7±51.3	137.2±28.6	0.826
LDL-C (mg/dL)	89.7±32.7	88.4±31.3	91.9±36.3	82.9±18.4	0.764
HDL-C (mg/dL)	40.7±6.3	39.1±7.6	41.2±6.6	40.1±3.5	0.662
TG (mg/dL)	135.7±65.5	104.0±33.8	148.6±74.2	116.4±34.2	0.141
S. AST (U/L)	33.1±12.6	37.6±9.8	30.0±10.1	40.6±19.6	0.047
S. ALT (U/L)	41.2±16.2	47.9±19.5	39.9±16.2	40.0±12.9	0.449
GGT (U/L)	33.7±11.4	31.9±13.9	35.5±10.5	28.6±11.9	0.244
Prothrombin Time (sec.)	12.16±0.51	11.96±0.35	12.24±0.43	12.08±0.83	0.352
INR	1.02±0.05	1.00±0.03	1.03±0.04	1.01±0.07	0.456
HBeAg Positive	17 (34)	4 (50)	10 (30.3)	3 (33.3)	0.573
Anti-HBeAg Positive	26 (52)	4 (50)	17 (51.5)	5 (55.6)	0.970
HBV-DNA PCR (log value of IU/mL)	12.7 (7.3-20.1)	23.46 (4.79-32.61)	10.92 (7.25-17.62)	12.90 (6.96-22.24)	0.643
Chitinase 3-like 1	460.8 (340.1-570.3)	359.5 (272.8-526.9)	450.0 (307.75-5332.0)	1355.5 (530.75-1580.5)	0.004
APRI score	0.35 (0.25-0.47)	0.41 (0.304-0.486)	0.32 (0.252-0.417)	0.51 (0.296-0.664)	0.092

P by One-way ANOVA, Chi-square test, or Kruskal-Wallis test as applicable. In post hoc analysis, the eosinophil differential count was lower in group 3 than group 1\* and 2h-PPG was lower in group 2 than group 1†. BMI=Body mass index; BP=Blood pressure; WBC=White blood cells; ESR=Erythrocyte sedimentation rate; FPG=Fasting plasma glucose; 2h-PPG=2-hour post-prandial plasma glucose; TC=Total cholesterol; LDL-C=Low-density lipoprotein cholesterol; HDL-C=High-density lipoprotein cholesterol; TG=Triglyceride; S. AST=Serum alanine aminotransferase; S. ALT=Serum aspartate aminotransferase; S. GGT=Serum gamma-glutamyl transferase; INR=International normalized ratio; APRI score=AST to Platelet Ratio Index score



**Figure 1: Comparison of CHI3L1 levels among the three groups**

The clinical, biochemical, virological, and histopathological characteristics of the study participants of the three groups are compared in Table 1. There were significant differences in eosinophil differential counts, platelet counts, 2-hour postprandial plasma glucose values, and serum AST levels among

the three groups. Regarding the other variables, the three groups were indifferent.

The comparison of the CHI3L1 levels among the three groups is presented as a boxplot in Figure 1. The median value of CHI3L1 was 460.8 (IQR 340.1–570.3) in all the study subjects. The value was 359.5 (IQR 272.8–526.9) in Group 1, 450.0 (IQR 307.75–5332.0) in Group 2, and 1355.5 (IQR 530.75–1580.5) in Group 3. The difference in median CHI3L1 across the groups was statistically significant.

Table 2 shows the correlations of CHI3L1 with other variables. Platelet count had a significant negative correlation. The serum AST and APRI score had significant positive correlations with the CHI3L1 levels. CHI3L1 also had significant positive correlations with METAVIR scores.

## Discussion

In the present study, conducted among 50 patients with HBV-related compensated CLD, we observed that subjects with

**Table 2: Correlations of CHI3L1 with the other parameters studied**

Variables	r	P
Age	0.145	0.315
BMI	-0.159	0.269
Systolic BP	0.056	0.697
Diastolic BP	-0.095	0.510
Hb	0.023	0.873
Total WBC count	-0.037	0.799
Platelet count	-0.421	0.002
ESR	0.100	0.488
FPG	0.093	0.521
2h-PPG	0.134	0.353
Total Cholesterol	0.142	0.326
Triglyceride	-0.036	0.802
LDL-Cholesterol	0.017	0.908
HDL-Cholesterol	0.007	0.959
HBV DNA	-0.044	0.763
S. AST	0.372	0.008
S. ALT	-0.024	0.870
S. GTT	-0.268	0.060
Prothrombin time	-0.249	0.081
INR	-0.235	0.100
S. Creatinine	-0.047	0.743
APRI score	0.382	0.006
METAVIR score	0.485	<0.001

higher stages of hepatic fibrosis had higher serum CHI3L1 levels. A strong positive correlation was observed between CHI3L1 and APRI score, both of which are used as noninvasive markers of hepatic fibrosis.

Chitinase 3-like protein 1 (CHI3L1, also known as YKL-40) is a chitinase family member that lacks chitinase activity. CHI3L1 encodes a glycoprotein that is a member of the 18-glycosyl hydrolase family. This glycoprotein's exact physiological role is not well established. CHI3L1 may have roles in inflammation and tissue remodeling.<sup>[12]</sup> Areas with fibrosis, particularly those with active fibrogenesis, demonstrated positive staining for CHI3L1 antigens in immunohistochemical analysis.<sup>[16]</sup> Researchers have found the usefulness of CHI3L1 as a noninvasive biomarker for alcoholic cirrhosis, NAFLD, and HCV-induced liver fibrosis.<sup>[14,15,17-19]</sup>

The utility of CHI3L1 in diagnosing and staging HBV-related hepatic fibrosis is also promising.<sup>[16,20,21]</sup> Previous literature showed that the CHI3L1 levels of CHB patients were higher than those of healthy controls.<sup>[22]</sup> Jiang *et al.* have observed the superiority of serum CHI3L1 to other noninvasive methods (LSM, FIB-4, and APRI) in diagnosing significant fibrosis.<sup>[23]</sup> In a recent study conducted by Jin *et al.* in China, CHB patients with significant hepatic fibrosis had significantly higher serum CHI3L1 levels than those without substantial hepatic fibrosis; the performance of CHI3L1 in predicting significant fibrosis CHB patients in terms of specificity and sensitivity was high.<sup>[20]</sup> Huang *et al.* also observed higher CHI3L1 levels within the subjects with higher histological grades of hepatic

fibrosis.<sup>[16]</sup> In addition to its usefulness as a noninvasive marker for assessing hepatic fibrosis in CHB patients before treatment, Wang *et al.*, in their study, found CHI3L1 as a potential helpful marker for monitoring the changes in fibrosis during therapy.<sup>[24]</sup> The present study had a quite similar observation. The serum CHI3L1 level was found to increase in a stepwise fashion with the advancement in fibrosis. We observed a significant positive correlation between serum CHI3L1 level with the METAVIR fibrosis score in the current study. Similarly, Huang *et al.* found CHI3L1 to be significantly correlated with hepatic fibrosis.<sup>[16]</sup>

Among the 50 patients evaluated, 17 (34%) were positive for HBeAg and 33 (66%) were HBeAg negative. Previously, Mahtab *et al.* also observed a higher prevalence of HBeAg negativity among CHB infected subjects in Bangladesh.<sup>[7]</sup>

In this study, although the APRI score was highest in the advanced fibrosis (F3 and F4) group, the statistical difference across the three groups was not significant. However, the APRI score had a strong positive correlation with CHI3L1 levels in the study subjects. The observations are similar to those of Jin *et al.*<sup>[20]</sup> Besides, like Jin *et al.*, we also found a strong positive correlation between CHI3L1 and AST levels.<sup>[20]</sup>

### Limitation of the study

The study has several limitations. It was a cross-sectional observational study and the sample size was small. No randomization was done in the selection of samples, which may result in potential selection bias.

### Conclusion

In this study, conducted among patients with CHB with compensated CLD, we found higher serum CHI3L1 levels in higher stages of hepatic fibrosis. A strong positive correlation was observed between CHI3L1 and APRI score, both of which are used as noninvasive markers of hepatic fibrosis. CHI3L1 may be used as a biomarker for distinguishing patients with significant fibrosis from those without significant fibrosis in patients with CHB. A further large-scale study may clarify its utility in this field.

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### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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