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Globulin-Platelet (GP) Model Predicts Severe Fibrosis Better Than FIB-4 in Chronic Hepatitis B (CHB) Patients with Mildly Elevated Alanine Aminotransferase (ALT)

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ABSTRACT

Background: The disease spectrum of chronic HBV infection is variable, ranging from an inactive chronic hepatitis B (CHB) to cirrhosis and hepatocellular carcinoma. Liver fibrosis stage is an im-portant factor in determining prognosis and need for treatment in patients with chronic HBV infec-tion. The globulin-platelet (GP) model is a new noninvasive liver fibrosis model developed in chronic hepatitis B patients. Objectives: This study aimed to evaluate the diagnostic performance of GP mod-el for liver fibrosis and cirrhosis in CHB patients with mildly elevated alanine aminotransferase (ALT) levels and to compare with the Fibrosis index based on 4 factors (FIB-4). Methods: An obser-vational cross sectional study was carried out in the Department of Hepatology, Bangabandhu Sheikh Mujib Medical University, Dhaka from February 2018 to February 2019. Patients who met the inclu-sion criteria and escaped the exclusion criteria were counselled and finally 287 were included in the study. Result: Among 287 CHB patients, age range was 18 to 65 years and the mean age was 28.6 ± 9.2 years. The highest frequency was found at 20-30 age groups with 238 males and 49 females. Of all patients, 119 (41.5%) patients had significant fibrosis and among them 49 (17%) had severe fibrosis. Higher scores were observed for GP model in severe fibrosis or cirrhosis group compared with signif-icant and no or minimal fibrosis group. To predict significant fibrosis, at a cutoff value of 1.37, the AUROC of GP was similar with FIB-4 (0.826 vs 0.827), with 82% sensitivity and 75% specificity. To predict severe fibrosis, at cutoff value of 1.49, the AUROC of GP was higher than FIB-4 (0.914 vs 0.830), with a high (100%) sensitivity but moderate (76.5%) specificity. Conclusion: GP model has better diagnostic accuracy in comparison to FIB-4 for assessment of severe fibrosis in CHB patients with high HBV DNA and mildly elevated ALT levels.

KEYWORDS: ALT, Cirrhosis of liver Globulin, Fibrosis, Cirrhosis of liver.

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INTRODUCTION

Chronic hepatitis B virus (HBV) infection is a global public health problem. Approximately 240 mil-lion people are estimated to be infected with HBV in the world (Inoue and Tanaka 2016). Significant fibrosis is normal requirement for initiation of treatment in Chronic Hepatitis B (CHB) patients with mildly elevated Alanine Aminotransferase (ALT). To know the histological progression, liver biopsy is the gold standard. However, the hurdles associated with the procedure and post procedural risks make it a rather intimidating option for both the physicians and patients alike (Piccinino et al. 1986). Thus, noninvasive tests to evaluate liver fibrosis are particularly needed. The FibroScan device is an excellent tool for the diagnosis of liver fibrosis. However, it is expensive and accessible only in se-lected hospitals in a developing country (Yu and Lee 2017). A large number of CHB patients who have high HBV DNA and mildly elevated ALT are in a vulnerable situation. Despite having signifi-cant fibrosis, they are quite asymptomatic. A reliable non-invasive marker can turn out to be just the thing that these patients need for proper treatment. Patients with more than a two-fold increase in ala-nine transaminase (ALT) levels with high HBV DNA are recommended for treatment. But those who are having high HBVDNA and ALT levels less than 2 fold increases should undergo testing to evalu-ate histological disease severity, especially those >40 years old and who were infected at a young age (i.e., long duration of infection (Terrault et al. 2018). In recent years, numerous noninvasive liver fi-brosis models have been developed, among which the aspartate transaminase (AST)-to-platelet ratio index (APRI) and fibrosis index based on four factors (FIB-4) have been recommended for the detec-tion of liver fibrosis and cirrhosis by the WHO HBV guidelines (WHO 2015). The globulin–platelet

(GP) model is a new noninvasive liver fibrosis model. To date, only few studies have evaluated the GP model in the diagnosis of liver fibrosis and cirrhosis in CHB patients (Liu et al. 2012; Coskun et al. 2015; Li et al. 2018). It includes globulin and platelet for making the model. The formula is as fol-lows:

GP = Globulin (g/dl) x 100 / Platelet count (x109/L)

Individually this serum biochemical markers can be helpful in suspecting the liver fibrosis. As fibro-sis progresses, globulin level increases and platelet level gradually decreases. For that reason, the GP model, using both Globulin and Platelet count, was made to diagnose fibrosis in CHB patients which is easily available and cheap. Combining other laboratory markers (ALT and HBV DNA levels) with the GP model might increase the diagnostic performance for liver fibrosis and cirrhosis (Li et al. 2018).

The aim of this study was to correlate liver stiffness measurements with Globulin-Platelet model and FIB-4 and to assess the potential predictive value of these markers for assessing fibrosis.

Rationale:
Significant fibrosis is normal requirement for initiation of treatment in CHB patients with mildly ele-vated ALT (Alanine Aminotransferase). To know the histological progression, liver biopsy is the gold standard. However, the hurdles associated with the procedure and post procedural risks make it a ra-ther intimidating option for both the physicians and patients alike. Thus, noninvasive tests to evaluate liver fibrosis are particularly needed. The FibroScan device is an excellent tool for the diagnosis of liver fibrosis. However, it is expensive and accessible only in selected hospitals in a developing country.

A large number of CHB patients who have high HBV DNA and mildly elevated ALT are in a vulnera-ble situation. Despite having significant fibrosis, they are quite asymptomatic. A reliable non-invasive marker can turn out to be just the thing that these patients need for proper treatment. Serum Globulin, a plasma protein, is produced in the liver. Its level increases in case of cirrhosis. On the other hand, low Platelet counts is associated with advanced liver fibrosis. A possible explanation may be that the decreased Platelet counts are due to splenomegaly secondary to portal hypertension and the decreased thrombopoietin production associated with liver cell failure in cirrhotic patients. Hence by using Globulin and Platelet a new noninvasive marker of fibrosis is made. Till date, few studies are available on Globulin Platelet model predicting fibrosis and cirrhosis in CHB patients. It is very sim-ple and cost effective. If its sensitivity in predicting liver fibrosis as well as cirrhosis can be deter-mined, it may then be reliably used as an alternative to liver biopsy and fibro scan. On the context of our country, a cheap and readily available marker that can predict the level of fibrosis is not only a requirement but also necessity. Hence by using GP model for the said purpose can prove to be a boon for CHB patients of developing country

Objectives of the study
General objective:
To evaluate Globulin-Platelet model as non-invasive marker of liver fibrosis in CHB patients with mildly elevated alanine aminotransferase.
Specific objectives:
a. To measure serum Globulin and Platelet count.
b. To calculate GP model using serum globulin and platelet count.
c. To calculate FIB-4 scoring using patient's age, AST, platelet count & ALT.
d. To determine liver fibrosis by Transient Elastography (Fibroscan).
e. To compare GP model ad FIB-4 Score with stages of liver fibrosis as determined by fi-broscan.

METHODOLOGY

Type of study: This was an observational, cross sectional study.
Study population: Patient with CHB with high HBV DNA and mildly elevated ALT.
Place of study: Out Patient Department, Hepatology, Bangabandhu Sheikh Mujib Medical University, Dhaka and Lab Aid Specialized Hospital, Dhanmondi, Dhaka (for Fibroscan of liver)
Period of study: February 2018 to February 2019.

Study procedure:
Patients having HBsAg blood test positive visited in Hepatology OPD, BSMMU were primarily target-ed. Patient was of either sex and age was between 18 to 65 years. At baseline, for each patient, demo-graphic and clinical data including age, sex and complications of cirrhosis. Initial investigations such as ALT, HBV profile (HBeAg, Anti HBe and HBV DNA), Anti-HCV, USG of HBS were done. Finally, 287 patients were enrolled in this study. Then other investigations like Complete Blood Count, Serum Bilirubin, AST, Serum Globulin, Prothrombin time, serum creatinine, endoscopy of upper gastro-intestinal tract were done. After obtaining all the investigation reports Globulin Platelet (GP) model and Fib-4 were calculated. All the patients underwent transient elastography (Fibroscan) of liver from a single center for measuring liver stiffness. Scores of GP and Fib-4 were compared with the value of liver stiffness.

Selection criteria:
Inclusion criteria:

1. Chronic HBV infection
a. HBsAg – positive for more than 06 months.
b. ALT level more than 40 U/L but less than 60 U/L.
c. HBV DNA more than 20,000 IU/ml if HBeAg positive.
d. HBV DNA more than 2000 IU/ml if HBeAg negative.
2. Age- 18 to 65 years.

Exclusion criteria:
1. Co- infection with HCV
2. Patient with history of taking anti-viral drugs or on treatment.
3. Alcohol consumption >20gm/day.
4. Non-alcoholic fatty liver disease.
5. Patient with decompensated cirrhosis of liver.
6. Patient with co-morbid condition (DM, HTN, CKD etc.)

Data analysis:
Statistical analysis of the results was done by using computer based software, SPSS version 20 (SPSS Inc. Chicago, IL, USA). All values were presented as mean ± standard deviations (SDs) for continuous data and as percentages for categorical data. Qualitative data were analyzed by Chi-square test & quantitative data were analyzed by independent t-test. Biochemical scoring was calculated using available formula. Anova test was done to compare between biochemical indices and stages of fibro-sis. AUROC, sensitivity, specificity & cut off values for biochemical indices were measured. A prob-ability 'p' value less than 0.05 was considered as significant.

Stage of Fibrosis on Transient Elastography

Disease	Stage of fibrosis	Liver stiffness (kPa)
Chronic Hepatits B	(F_0-F_1)	1 – 7.4
	F_2	7.4 – 9.5
	F_3	9.5 – 12.5
	F_4	12.5 - 75

Ref: (Ledinghen and Vergniol 2008)

RESULTS

This cross-sectional observational study was carried out with the aim to evaluate Globulin-Platelet (GP) model for prediction of fibrosis and cirrhosis in chronic hepatitis B patients with mildly elevat-ed alanine aminotransferase in the department of Hepatology, BSMMU, Dhaka between February 2018 to February 2019. During the study period total 287 patients were enrolled for the study.

Baseline characteristics of the study patients:
Table I shows baseline characteristics of the patients. The mean age was observed 28.6 ± 9.2 years. 238 of them were male and 49 were female. The mean haemoglobin was found 14.4 ± 1.4 gm/dl, the mean Total Leucocyte Count was 7.6 ± 1.7 x 109/L and the mean Platelet count was 244.8 ± 59.7 x 109/L. The mean serum HBV-DNA (log10) was 5.97 ± 1.6 IU/ml. The mean ALT was 48.3 ± 7.0 U/L, AST was 37.4 ± 9.8 U/L, serum Globulin was 3.4 ± 0.5 gm/dl. The mean creatinine was 0.9 ± 0.2 mg/dl.

Table I: Baseline characteristics of the study population (n=287)

Baseline characteristic	Mean ± SD	Range (min, max)
Age (in years)	28.6 ± 9.1	18, 65
Hb% (gm/dl)	14.4 ± 1.4	10.7, 18.3
TLC (--×10^{9}/L)	7.6 ± 1.7	4.6, 12.5
Platelet count (--×10^{9}/L)	244.8 ± 59.6	125, 400
AST (U/L)	37.4 ± 9.8	24, 70
ALT (U/L)	48.3 ± 7.1	40, 60
Alkaline phosphatase (U/L)	102.7 ± 27.9	39, 198
Serum Globulin	3.4 ± 0.5	2.5, 4,9

Serum Creatinine	0.9 ± 0.2	0.6, 1.2

Sex distribution of the study patients

Figure 1 shows Bar chart of distribution of the patients. It was observed that majority of the patients were male (238, 82.9%) and only 49 (17.1%) patients were female.

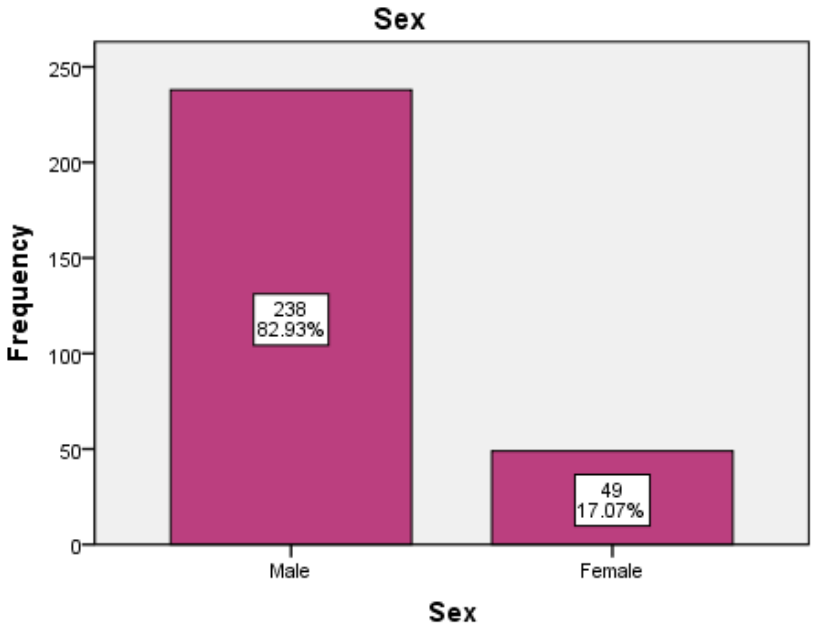

Figure 1: Distribution of sex among the participants

Non-invasive scoring of the study population (n=287)

The mean FIB-4 was 0.71 ± 0.5 and Globulin-Platelet (GP) model 1.48 ± 0.5. The mean liver stiffness measurement was 9.0 ± 6.6 kPa (Table II).

Table II: Non-invasive scoring of the study population (n=287).

Methods	Mean ± SD	Range (min, max)
FIB-4	0.71 ± 0.5	0.25, 2.89
Globulin-Platelet (GP) model	1.48± 0.5	0.79, 3.36
Liver stiffness measurement (kPa)	9.0 ± 6.6	3.8, 42.2

All values are expressed as mean±SD.

Distribution of the study patients by stages of fibrosis

The total study population was 287. All of them underwent transient elastography from a single cen-ter to measure liver stiffness for evaluation of stages of fibrosis. Among the study patients, 168 (58.5%) patients were having F0-F1 fibrosis. 21 patients (7.3%) were having F2 fibrosis. 49 (17.1%) patients and 49 (17.1%) patients were in F3 and F4 stages of fibrosis respectively. In this study F0-F1 (n=168) indicated as non-significant, F2-F3 (n=70) as significant fibrosis and F4 (n=49) as severe fibrosis group.

Table III: Fibrosis stage in transient elastography of the study population (n=287).

Fibrosis stage	Number of patients	Percentage
F_0-F_1 (1-7.4 kPa)	168	58.5
F_2 (7.4-9.5 kPa)	21	7.3
F_3 (9.5-12.5 kPa)	49	17.1
F_4 (12.5-75 kPa)	49	17.1

Comparison between study variables with stages of fibrosis:

Table VI shows that the mean FIB-4 in F0-F1, F2, F3 and F4 were 0.51± 0.2, 0.70 ± 0.2, 0.94 ± 0.4 and 1.20 ± 0.8 respectively. As the stages of fibrosis increase, the mean FIB-4 increases. It was also statis-tically significant P=0.000.

The mean GP model were 1.24± 0.2, 1.44 ± 0.1, 1.63 ± 0.5 and 2.16 ± 0.7 in F0-F1, F2, F3 and F4 respec-tively. As the stages of fibrosis increase, the mean GP model increases. It was also statistically signif-icant P=0.000.

Table VI: Comparison of laboratory findings between significant and severe fibrosis group (n=119).

	Significant fibrosis (n=70)	**Severe fibrosis (n=49)**	**P value**
Platelet count (×10^9/L)	212.0 ± 35.7	186.43 ± 33.6	**.000[s]**
Serum Globulin (gm/dl)	3.2 ± 0.3	3.8 ± 0.6	**.000[s]**
FIB-4 Score	0.9 ± 0.4	1.2 ± 0.8	**.000[s]**
Globulin-Platelet Score	1.6 ± 0.4	2.2 ± 0.7	**.000[s]**
Liver stiffness	9.6 ± 0.9	20.2 ± 9.2	**.000[s]**

All value analysis of Mean ± SD. p value reached from student's T test

Comparison between study variables with non-significant and significant fibrosis:

Table V, the mean FIB-4 in were 0.51± 0.2 in F0-F1 fibrosis and 1.00 ± 0.6 in F2-F4 fibrosis. As the stages of fibrosis increase, the mean FIB-4 increases. It was also statistically significant P=0.000.

The mean GP model were 1.24± 0.2 and 1.82 ± 0.6 in F0-F1 and F2-F4 respectively. It was also statisti-cally significant P=0.000.

Table V: Comparison between study variables with non-significant and significant stage of fibrosis (n=287).

Variables	**Severity fibrosis**		**P value**
	Non-significant (F_0-F_1) (n=168)	**Significant (F_2-F_4) (n=119**	
	Mean ± SD	Mean ± SD	
FIB-4	0.51 ± 0.2	1.00 ± 0.6	**0.000[s]**
GP model	1.24 ± 0.2	1.82 ± 0.6	**0.000[s]**

Comparison of laboratory findings between significant and severe fibrosis group

Table VI showed that 70 (24.4%) patients had significant fibrosis (F2-F3) and only 49 (17.1%) pa-tients had severe fibrosis (F4). Several laboratory findings showed significant differences between two groups. The mean Platelet count were 212.0 ± 35.7 (×109/L) and 186.43 ± 33.6 (×109/L) between two groups. The mean serum globulin was 3.2 ± 0.3 gm/dl in significant fibrosis group and 3.8 ± 0.6 gm/dl in severe fibrosis group. Both the variable was statistically significant. FIB-4 which were 0.9 ± 0.4 and 1.2 ± 0.8 in significant and severe fibrosis group and it was statistically significant. But mean Globulin-Platelet (GP) model showed 1.6 ± 0.4 and 2.2 ± 0.7 in different group which were also statis-tically significant. Liver stiffness value in two different groups were 9.6 ± 0.9 kPa and 20.2 ± 9.3 kPa. It was also statistically significant.

Table VI: Comparison of laboratory findings between significant and severe fibrosis group (n=119).

	Significant fibrosis (n=70)	**Severe fibrosis (n=49)**	**P value**
Platelet count (×10^9/L)	212.0 ± 35.7	186.43 ± 33.6	**.000[s]**
Serum Globulin (gm/dl)	3.2 ± 0.3	3.8 ± 0.6	**.000[s]**
FIB-4 Score	0.9 ± 0.4	1.2 ± 0.8	**.000[s]**
Globulin-Platelet Score	1.6 ± 0.4	2.2 ± 0.7	**.000[s]**
Liver stiffness	9.6 ± 0.9	20.2 ± 9.2	**.000[s]**

All value analysis of Mean ± SD. p value reached from student's T test

Receiver-operator characteristic (ROC) curve of APRI, FIB-4 and GP model for prediction of significant fibrosis:

The area under the receiver-operator characteristic (ROC) curves for prediction of significant fibrosis is depicted in table VII and figure 2. Based on the receiver-operator characteristic (ROC) curve FIB-4 and GP model had area under curve 0.826 and 0.827 respectively. Receiver-operator characteristic (ROC) was constructed by using FIB-4 and GP model which gave a cut off value 0.535 and 1.365 re-spectively with 82.4% sensitivity and 62.5% specificity for FIB-4 and 81.0% sensitivity and 75.0% specificity for GP model for prediction of significant fibrosis.

	Cut of value	Sensitivity (%)	Specificity (%)	Area under the ROC curve	95% Confidence interval (CI)	
					Lower bound	Upper bound

FIB-4	**0.535**	82.4	62.5	0.826	0.779	0.873
GP model	**1.365**	**81.0**	**75.0**	**0.827**	0.778	0.877

Table VII: Receiver-operator characteristic (ROC) curve of FIB-4 and GP model for prediction of significant fibrosis

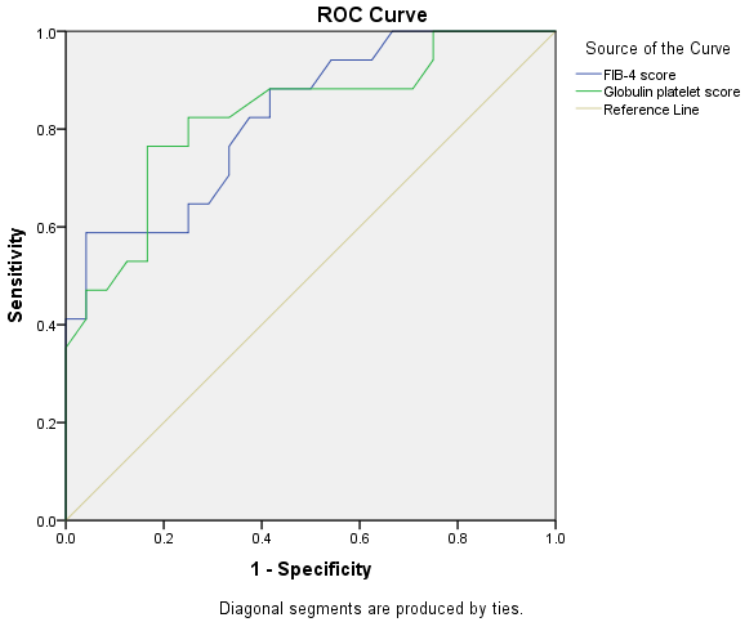

Figure 2: Receiver-operator characteristic (ROC) curve of FIB-4 and GP model for prediction of sig-nificant fibrosis

Table VIII: Receiver-operator characteristic (ROC) curve of FIB-4 and GP model for prediction of severe fibrosis or cirrhosis:

	Cut value	ofSensitivity (%)	Specificity (%)	Area under the ROC curve	95% Confidence interval (CI)	
					Lower bound	Upper bound
FIB-4	0.835	71.4	82.4	0.830	0.776	0.883
GP model	1.490	100.0	76.5	0.914	0.879	0.949

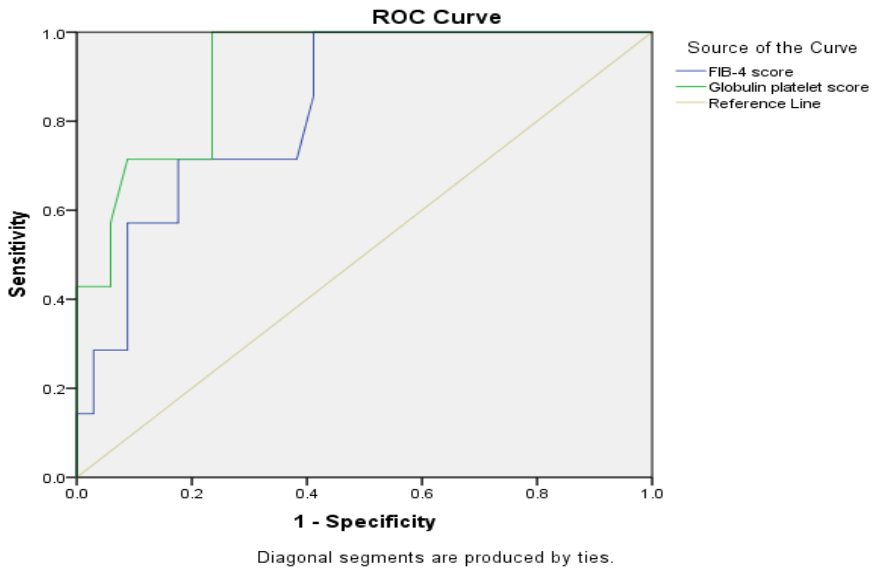

Figure 3: Receiver-operator characteristic (ROC) curve of FIB-4 and GP model for prediction of se-vere fibrosis or cirrhosis

Receiver-operator characteristic (ROC) curve of FIB-4 and GP model for prediction of severe fibrosis:
The area under the receiver-operator characteristic (ROC) curves for prediction of severe fibrosis is depicted in table VIII and figure 3. Based on the receiver-operator characteristic (ROC) curve FIB-4 and GP model had area under curve 0.830 and 0.914 respectively. Receiver-operator characteristic (ROC) was constructed by using FIB-4 and GP model, which gave cut off value 0.835 and 1.490 re-spectively with 71.4% sensitivity and 82.4% specificity for FIB-4 and 100.0% sensitivity and 76.5% specificity for GP model for prediction of severe fibrosis.

DISCUSSION:

Assessment of degree of hepatic fibrosis is essential in deciding antiviral therapy for chronic HBV infection. Accurate diagnosis of liver fibrosis is clinically advantageous. Liver biopsy, the gold standard, is invasive method for evaluation of fibrosis of liver, but hampered by various limitations. Despite these limitations an ideal alternative to liver biopsy has not been found. Transient Elas-tography (Fibroscan) is an excellent noninvasive tool for diagnosis of liver fibrosis but costly. This cross-sectional observational study was carried out with the aim to find out alternatives to liver biop-sy as well as fibroscan in patient with chronic HBV infection.

The aim of the study was to predict significant fibrosis (F2-F3) and severe or cirrhosis (F4) by GP model according to transient elastography report. At first the study population were divided into two groups. The non-significant fibrosis group were having fibrosis stage F0-F1 (168 persons, 58.5%) & significant fibrosis group with fibrosis stage F2-F4 (119 persons, 41.5%).

In this study, most of the patients were young with mean age 28.6 ± 9.1 years (Table I). Along with younger age a male predominance was observed in this study-male 238 (82.9%) and female 49 (17.1%) (Figure 1).

In this study, among 287 CHB patients the mean FIB-4 (1.00 ± 0.6 vs 0.51 ± 0.2) & GP model (1.82 ± 0.6 vs 1.24 ±0.2) at significant fibrosis were higher than non-significant group (Table-V). The P value for measuring significant fibrosis by all the indices were 0.000 which means that these higher indices in significant group were statistically significant. Coskun et al. (2015) also showed that predicting significant fibrosis FIB-4 [1.7(1-3) vs 0.95(0.6-1.5)] and GP model [1.9 (1.5-2.7) vs 1.38 (1.1-1.7)] were statistically significant. P value for FIB-4 was 0.001 and for GP model was 0.001.

Between the significant (F2-F3) and severe fibrosis group (F4), significant statistical difference were found 212.0 ± 35.7 (*109/L) and 186.43 ± 33.6 (*109/L) in platelet counts and in serum Globulin 3.2 ± 0.3 gm/dl was found in significant fibrosis group and 3.8 ± 0.6 gm/dl in severe fibrosis group. FIB-4 which were 0.9 ± 0.4 and 1.2 ± 0.8 in significant and severe fibrosis group and it was statistically sig-nificant. Globulin-Platelet (GP) model showed 1.6 ± 0.4 and 2.2 ± 0.7 in different group which were also statistically significant. Schmilovitz-Weiss et al. (2006) showed that the significant predictors of severe hepatic fibrosis on multivariate analysis were serum globulin level [odds ratio (OR) 5.97, 95% confidence intervals (CI) 1.82–19.53, P=0.0004], platelet count (OR 0.98, CI 0.97–0.99, P=0.001). Coskun et al. (2015) showed that liver fibrosis was positively correlated with globulin level ($r = 0.34$, $p<0.001$) and inversely correlated with the platelet counts ($r = -0.34$, $p<0.001$). In this study, platelet count as well as serum globulin both were statistically significant.

Our study observed higher scores of non- invasive indices namely the FIB-04 score & GP model in the significant fibrosis group compared with no or minimal fibrosis group. With a cut-off value of 0.535 FIB-4 sensitivity was 82.4% and 62.5% & GP model showed 81.0% sensitivity but 75.0% speci-ficity when cut off value was 1.365 (Table-VII and Figure 2). AUROC for predicting significant fibro-sis were found to be 0.826 & 0.827 for FIB-4 & GP model respectively which were similar. Li et al. (2018) showed AUROC of FIB-4 was 0.66 & GP model was 0.64. In this study, to predict significant fibrosis AUROC of FIB-4 and GP model also showed the same result.

This study also showed higher scores of non-invasive indices namely FIB-4 score & GP model in the severe fibrosis (F4) compared with minimal or significant fibrosis group. With a cut-off value of 0.835, FIB-4's sensitivity and specificity were 71.4% and 82.4%. GP model showed 100.0% sensitivi-ty and 76.5% specificity when cut off value was 1.490 (Table-VIII). AUROC of these non-invasive markers for predicting severe fibrosis were found to be 0.830 & 0.914 for FIB-4 & GP model respec-tively. In a study by Li et al. (2018) also showed that to predict severe fibrosis the AUROC of GP was higher than FIB-4 (0.91 vs 0.80).

This study indicates that GP model correlate with liver fibrosis with moderate sensitivity (81.0%) and specificity (75.0%) to predict significnt fibrosis (F2-F4) that was also showed by FIB-4.

For assessing severe fibrosis GP model showed very high sensitivity (100%) and moderate specificity (76.5%) in CHB patients with better diagnostic value than FIB-4 (71.4% sensitivity and 82.4% specificity) in CHB patients with high HBV DNA and mildly elevated ALT levels.

CONCLUSION

The study indicates that for assessment of severe fibrosis (F4) in CHB patients with mildly elevated ALT, GP model has better diagnostic accuracy in comparison to FIB-4.

LIMITATIONS

In this study to assess the diagnostic performance, Globulin-Platelet model was not compared with liver biopsy which is the gold standard method for assessment of fibrosis and cirrhosis of liver.

RECOMMENDATION

Further study can be undertaken to validate the result of this study with healthy control and patients with different stages of fibrosis by using liver biopsy.

Compliance with Ethical Standards:

A research protocol was approved by the ethical review committee of BSMMU before starting this study. Informed written consent (Bengali version) was taken from each patient. The purpose and pro-cedures 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. There was hardly any possibility of mental or social harm in the participation of the study. All sorts of confidentiality were ensured. No money was given to the participants of the study.

Informed Consent:

For this study, a well-informed, voluntarily signed written consent was taken in an understandable local language from the study subjects after convincing them that their privacy & confidentiality was safeguarded. If there was any injury or complication because of the study, proper treatment was available. However, no monetary compensation was provided for the loss of work time.

Use of drugs: No experimental drugs or placebo was used for this study.

Use of hospital records: Hospital records, especially the investigation reports were needed to fill up the data collection sheet. The data collection sheet was filled up after taking a brief interview of 20-30 minutes from the participants.

Procedure of maintaining confidentiality: A signed informed consent was taken after convincing all the study subjects that their confidentiality was safeguarded & privacy maintained. To maintain Con-fidentiality, each of the study subjects was given a special ID number, which was followed during every steps of the study procedure. All the research data was coded and stored in a locked cabinet. Only research personnel were allowed to access the data. Privacy was maintained during physical examination & interview and also at the time of procedure.

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ABBREVIATION

ALT: Alanine aminotransferase
AST: Aspartate aminotransferase
AUROC: Area under Receiver-operator characteristic curve
CHB: Chronic hepatitis B

FIB-4: Fibrosis index based on 4 factors
GP model: Globulin platelet model
HCC: Hepatocellular carcinoma
HCV: Hepatitis C Virus
LS: Liver Stiffness
NAFLD: Nonalcoholic fatty liver disease
TE: Transient Elastography