Original Article

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Non Invasive Methods versus Liver Biopsy for Making Therapeutic Decisions in Chronic Hepatitis B Patients with High HBV DNA Levels and Mildly Elevated Transaminases

Internal Medicine Section

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ABSTRACT

Introduction: Staging of liver fibrosis is essential for making therapeutic decisions in patients with Chronic Hepatitis B (CHB) having raised Hepatitis B Virus Deoxyribonucleic Acid (HBV DNA) levels (>2000 IU/ml) and normal or mildly elevated Alanine Transaminase (ALT). Though the gold standard for assessment of liver fibrosis has been liver biopsy, many non invasive models have been developed to mitigate the risks associated with liver biopsy and overcome its limitations.

Aim: To evaluate the non invasive models predictive of significant fibrosis in this selected subgroup of Chronic Hepatitis B patients.

Materials and Methods: Fifty-six CHB patients were evaluated. This longitudinal observational study was conducted at Sir Sunderlal Hospital, Institute of Medical Sciences, Banaras Hindu University from February 2017 to July 2018 on 56 patients. Liver Stiffness Measurement (LSM), Aspartate Aminotransferase (AST) to Platelet Ratio Index (APRI), FIBROSIS-4 (FIB-4) and Gamma-Glutamyl Transpeptidase (GGT) to platelet ratio (GPR) were estimated. Liver fibrosis staging was done using Metavir score. Significant fibrosis corresponds to Metavir score F2-F4 and advanced fibrosis as more than F3.The performance of non invasive methods was assessed using Receiver Operating Characteristic (ROC) curves. Z -test was used to compare Area Under ROC Curves (AUROCs).

Results: Twenty-one patients (37.5%) had significant fibrosis, out of which seven had F3-F4 fibrosis. Patients with F2-F4 fibrosis had higher age, Hepatitis B e antigen (HBeAg) positivity, HBV DNA, ALT, AST, GGT, LSM, APRI, FIB-4 and GPR values than patients with F0-F1 fibrosis. Metavir fibrosis stages positively correlated with LSM values (r=0.831, p<0.0001), APRI (r=0.338, p=0.011), FIB-4 (r=0.375, p=0.003) and GPR (r=0.36, p=0.012). To predict advanced fibrosis, the AUROC of LSM had higher AUROC than APRI (0.956 vs 0.755, p=0.01), FIB-4 (0.956vs 0.786, p=0.01) and was comparable to GPR (0.956 vs 0.895, p=0.2).

Conclusion: Transient Elastography (TE) is a reliable non invasive test for the diagnosis of liver fibrosis. GPR is a new model which is comparable to APRI and FIB-4 but inferior to TE.

Keywords: Deoxyribonucleic acid, Fibrosis-4, Gamma glutamate to platelet ratio, Hepatitis B Virus, Liver fibrosis, Transient elastography

INTRODUCTION

Hepatic inflammation in patients with Chronic Hepatitis B (CHB) is a dynamic process. One of the most important prognostic markers in patients with CHB is the degree of hepatic fibrosis which is associated with the risk of progression to cirrhosis. Hence, timely diagnosis of significant hepatic fibrosis is of utmost importance in patients with CHB as prompt treatment can prevent cirrhosis and hepatocellular carcinoma [1]. The recent guidelines on the management of CHB have proposed that the presence of moderate to severe necroinflammation or significant fibrosis in patients with elevated HBV DNA levels and ALT (Alanine Aminotransferase) levels which are borderline, normal or slightly elevated persistently, especially in patients more than 40 years of age is an indication for initiating treatment and liver biopsy can be substituted by non invasive methods in order to assess the severity of fibrosis and/or inflammation [2]. Though liver biopsy is the gold standard for fibrosis assessment,its use has been limited due to sampling errors, interobserver variability and poor reproducibility and invasiveness including risk of death [3-5].

Various studies have compared non invasive methods with liver biopsy for estimation of fibrosis. Li Q et al., evaluated the Diagnostic Accuracy (DA) of Liver Stiffness Measurement (LSM) in 188 patients with chronic hepatitis B (CHB) patients and alanine transaminase (ALT) less than twice the upper limit of normal (ULN) [6]. Irrespective of the ALT levels, LSM had a DA of 81% for F2-F4, and 89% for F4 fibrosis. Jia J et al., in a multicentric study validated the accuracy of LSM in the assessment of liver fibrosis in 469 Chinese CHB patients concluding transient elastography was a reliable non invasive modality for estimation of significant liver fibrosis in Chinese CHB patients [7]. In an Indian study conducted by Goyal R et al., in 382 CHB patients there was significant correlation between LSM and fibrosis estimated after liver biopsy was significant (r=0.58, p<0.001) [8].

The FIBROSIS-4 (FIB-4) index was initially evaluated in patients with chronic Hepatitis C Virus (HCV)/HIV co-infection and has been validated subsequently for other liver diseases as well [9].The variables needed for FIB-4 index include Aspartate Aminotransferase (AST), alanine aminotransferase (ALT), and Platelet (PLT) count. Wai CT et al., proposed AST/APRI to predict significant fibrosis in patients with chronic HCV infection [10]. Studies have shown that APRI and FIB-4 are suitable indices for estimation of significant fibrosis and cirrhosis in patients with CHB [11,12].

However, the validity of these non invasive markers needs to be ascertained in patients with different clinical and biochemical profiles. Accurate assessment of liver fibrosis becomes essential in patients with CHB having high HBV DNA levels and mildly related transaminases as this is the subgroup of patients where therapeutic decision is governed by the degree of liver fibrosis.

MATERIALS AND METHODS

This longitudinal observational study was conducted at Sir Sunderlal Hospital, Institute of Medical Sciences, Banaras Hindu University from February 2017 to July 2018. The study was approved by Institutional Ethics Committee (Registration no. ECR/526/Inst/UP/2014) and informed consent was taken from the participants. Laboratory data of patients with CHB visiting Gastroenterology Outpatient Department (OPD) was collected.

Inclusion criteria: Patients with - 1) CHB; 2) HBV DNA load >2000 IU/ml; 3) ALT normal or 1-2 times ULN (40 IU/L) were included.

Exclusion criteria: Patients were excluded in either of the following conditions: 1) HCV or HIV Co-infection; 2) Significant alcohol consumption (≥20 g/day for females and ≥30 g/day for males); 3) Possibility of co-existing autoimmune liver disease as suggested by positive serum autoimmune hepatitis markers; 4) Body Mass Index (BMI) ≥30 Kg/m^2; 5) Cirrhosis; 6) ALT ≥2 times ULN; 7) Hepatocellular carcinoma; 8) Prior or current antiviral treatment.

Finally, 56 patients were included in the study. Liver biopsy was done within one week of OPD visit and laboratory investigations. Non invasive scores were also calculated in the same OPD setting.

Liver Histological Assessment

After taking informed consent, liver biopsy was done under aseptic precautions and under local anaesthesia using a 16G Bard liver biopsy gun. Percutaneous liver biopsy was performed under ultrasound guidance and the biopsied sample was sent to Department of Pathology, IMS, BHU for analysis. A threshold minimum of 15 mm size liver tissue with at least 6 portal tracts was considered sufficient for histopathological study. Haematoxylin and eosin stain was used for histopathological study and reticulin stain to look for fibrosis. The Metavir scoring system [13] was used to determine liver fibrosis grade: F0- no fibrosis; F1- portal fibrosis without septa; F2- portal fibrosis with rare septa; F3- numerous septa without cirrhosis; and F4- cirrhosis. Significant fibrosis was defined as F2-F4, advanced fibrosis as F3-F4, and cirrhosis as F4.

Routine Laboratory Tests

HBsAg positive status was established using the enzyme-linked immunosorbent assay kit (ERBA Diagnostics, Transasia biomedicals Limited). Serum HBV DNA was measured by Real Time Polymerase Chain Reaction (PCR) assay (MiniopticonTM, Biorad, USA) with a lower limit detection of 20 IU/mL. Serum transaminases and other biochemical parameters were measured using fully automated clinical chemistry analyser.

Transient Elastography (TE) (Fibroscan): LSM was performed following an overnight period of fasting using an M probe. A reliable exam was defined as ten measurements with a 60% success rate and the inter quartile range less than 30% of the median.

Serum fibrosis models calculation: The non invasive scores were calculated using following equations [14-17].

(1) APRI= {AST (IU/L)/ULN of AST}/Platelet count (10^9/L) × 100; ULN of AST = 40 IU/L.

(2) FIB-4= {Age (years) × AST (IU/L)}/{Platelet count (10^9/L) × √ALT (IU/L)}

(3) GPR= {GGT(IU/L)/ULN of GGT}/Platelet count (10^9/L) X 100; ULN of GGT=45 IU/L.

(4) AAR= AST (IU/L) /ALT (IU/L)

STATISTICAL ANALYSIS

The IBM Statistical Package for the Social Sciences (SPSS) statistics version 17.0 and Med Calc Statistical Software version 16.1 were used for statistical calculations. Normally distributed quantitative variables were expressed as mean (standard deviation). Median (inter quartile range) was used for skewed variables. To study the statistical difference between two groups, t-test was used for normally distribution variables. Mann-Whitney test for skewed continuous variables and Chi-squared test for categorical variables was used. Correlation between two variables was assessed using Spearman's Rank Order correlation coefficient. The diagnostic performance was assessed using the ROC curves. The AUROCs were compared using Z-test. The optimal cut-off was obtained by maximising Youden index (sensitivity + specificity-1). Diagnostic performance was evaluated by sensitivity, specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPV) and Diagnostic Accuracy (DA). The tests of significance used were two sided, and $p<0.05$ was considered statistically significant.

RESULTS

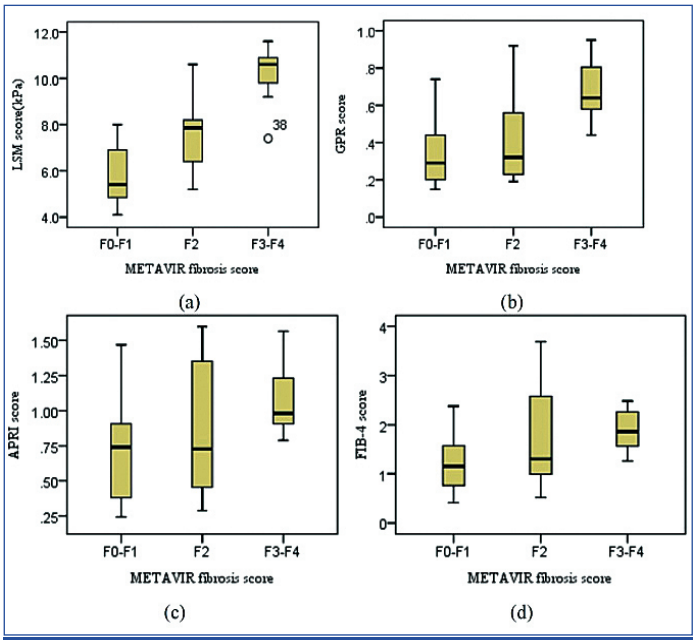
Baseline characteristics of patients: [Table/Fig-1] represents the baseline characteristics of the patients included in study. The majority of patients were male (60.7%), HBeAg negative (57.1%), middle aged (34±9 years) and belonged to lower middle class [18] socio-economic status (42.8).

Characteristics	All patients (n=56)	F0-F1 (n=35)	F2-F4 (n=21)	p-value (Mann-Whitney/Chi-squared test)
Age (year) (Mean±SD)	34±9	31±7	40±9	0.001
Sex (Male) (%)	34 (60.7%)	20 (57.1%)	14 (66.7%)	0.48
Socio-economic status Lower-Upper lower Lower middle-Upper middle-upper	5 (8.9%)/12 (21.4%)/24 (42.8%)/8 (14.2%)/7 (12.5%)			
BMI Kg/m^2 (Mean±SD)	23.5±1.6	23.3±1.3	23.9±1.8	0.18
Hb (g/dL) (Mean±SD)	13.2±1.5	13.4±1.5	13±1.4	0.33
PLT count (10^9/L) (Mean±SD)	202±71	208±70	193±74	0.46
ALT (IU/L) (Mean±SD)	55±13	51±12	62±12	0.003
AST (IU/L) (Mean±SD)	53±13	50±13	58±11	0.03
Albumin (g/dL) (Mean±SD)	4±0.38	4.0±0.38	4.1±0.39	0.57
ALP (IU/L) (Median) (IQR)	136 (105-147)	137 (108-154)	110 (101-139)	0.263
GGT (IU/L) (Mean±SD)	31±8	27±7	36±6	<0.0001
HBeAg positive (n,%)	24 (42.9%)	9 (25.7%)	15 (71.4%)	0.001
HBV DNA (IU/mL) (Median)(IQR)	4.5×10^4 (9.4×10^3-2.3×10^5)	2.5×10^4 (4.4×10^3-1.3×10^5)	1.3×10^5 (2.3×10^4-8.2×10^5)	0.001
LSM value (kPa) (Mean±SD)	6.7±1.9	5.7±1.2	8.4±1.8	<0.0001
APRI (Mean±SD)	0.78±0.39	0.70±0.35	0.93±0.43	0.03
FIB-4 (Mean±SD)	1.4±0.68	1.1±0.5	1.7±0.8	0.002
GPR (Mean±SD)	0.4±0.21	0.32±0.14	0.51±0.26	0.002
AAR (Mean±SD)	0.97±0.21	0.99±0.25	0.94±0.2	0.97
Metavir Inflammation grade (A0/A1/A2/A3)	5 (9%)/44 (78.5%)/7 (12.5%)/0			
Metavir fibrosis grade (F0/F1/F2/F3/F4)	18 (32.1%)/17 (30.4%)/14 (25%)/5 (8.9%)/2 (3.6%)			

[Table/Fig-1]: Baseline characteristics of patients.
BMI: Basal metabolic index; Hb: Haemoglobin; PLT: Platelet; ALT: Alanine transaminase; AST: Aspartate aminotransferase; to APRI: Aspartate platelet ratio index; FIB-4: FIBROSIS-4; GGT: Gamma-glutamyl transpeptidase; to GPR: Gamma platelet ratio; ALP: Alkaline phosphatase; LSM: Liver stiffness measurement; AAR: Automatic anatomy recognition

Patients with F2-F4 fibrosis had higher age (40±9 vs 31±7 years, p=0.001), more number of HBeAg-positive patients (71.4% vs 25.7%, p=0.001), higher HBV DNA levels ($1.3x10^5$ vs $2.5x10^4$ IU/mL, p=0.001) and higher ALT (62±12 vs 51±12 IU/L, p=0.003), AST (58±11 vs 50±13 IU/L, p=.03) and GGT (36±6 vs 27±7 IU/L, p<0.0001) values as compared to those with F0-F1 fibrosis. LSM, APRI, FIB-4 and GPR values were significantly higher than that of patients with F0-F1 fibrosis. No significant differences were seen in sex, BMI, haemoglobin, PLT count, albumin, alkaline phosphatase and Automatic Anatomy Recognition (AAR) ratio.

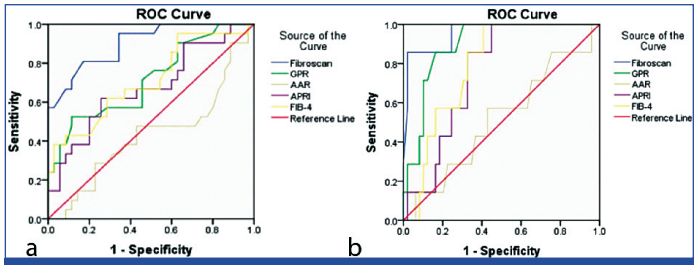
Correlation between non invasive fibrosis tests and Metavir fibrosis stages: The association between Metavir fibrosis stages and non invasive fibrosis tests has been presented in [Table/Fig-2]. The Metavir fibrosis stages positively correlated with LSM (r=0.831, p<0.0001), APRI (r=0.338,p=0.011), FIB-4 (r=0.375, p=0.003) and GPR (r=0.36, p=0.012) values. AAR showed non significant correlation with Metavir fibrosis stages (r=0.09, p=0.94). LSM showed highest order correlation among the non invasive fibrosis test. LSM, APRI, FIB-4 and GPR showed an increasing trend with increased Metavir fibrosis stages [Table/Fig-2].



[Table/Fig-2]: Association between Metavir fibrosis scores and non invasive fibrosis tests. (a) LSM- Liver Stiffness Measurement (b) GPR- Gamma glutamyl transpeptidase to platelet ratio (c) APRI- Aspartate transaminase to platelet ratio index (d) FIB-4- Fibrosis-4.

Diagnostic performances of non invasive fibrosis tests:The ROC curves of non invasive fibrosis tests have been shown in [Table/Fig-3]. To predict F2-F4, the AUROC of LSM was higher than that of APRI (0.901 vs 0.673, p=0.002), FIB-4 (0.901 vs 0.71, p=0.007) and GPR (0.901 vs 0.716, p=0.012). For F3-F4 fibrosis too, the AUROC of LSM was higher than that of APRI (0.956 vs 0.755, p=0.01), FIB-4 (0.956 vs 0.786, p=0.01) and comparable with GPR (0.956 vs 0.895, p=0.2). To predict F2 F4, AUROC of GPR was comparable with that of APRI (0.716 vs 0.673, p=0.46) and FIB-4 (0.716 vs 0.710, p=0.9). For F3-F4, AUROC of GPR was higher than APRI (0.895 vs 0.755, p=0.02) and was comparable to that of FIB-4 (0.895 vs 0.786, p=0.06).

Diagnostic thresholds of non invasive fibrosis tests:The diagnostic thresholds of non invasive fibrosis tests have been presented in [Table/Fig-4].Maximising Youden index, the cut-off values of LSM, APRI, FIB-4 and GPR for predicting F2-F4 fibrosis were 7.1, 0.89, 2.13 and 0.54, respectively.



[Table/Fig-3]: ROC curves for significant fibrosis (a) and advanced fibrosis (b).

Variable	Cut-off value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	DA (%)
Fibroscan (kPa)	>7.1	82	80	73	87	82
APRI	>0.89	61	74	56	75	67
FIB-4	>2.13	38	97	80	71	73
GPR	>0.54	52	88	73	75	75

[Table/Fig-4]: Optimal cut-off values of models in diagnosing significant liver fibrosis. PPV: Positive predictive value; NPV: Negative predictive value; DA: Diagnostic accuracy

DISCUSSION

There is lack of data from India on non invasive models to predict liver fibrosis in CHB patients, especially in patients with normal or mildly raised transaminases and high DNA level. This is the subgroup of patients where there is dilemma regarding treatment and liver biopsy is required which is invasive with minimal but significant risk of morbidity and mortality. In the present study, non invasive models (Fibroscan, APRI, GPR and FIB-4) predictive of liver fibrosis were assessed in high viral load CHB patients with normal or mildly raised ALT level and diagnostic performance of LSM was compared with that of serum fibrosis models (APRI, FIB-4 and GPR). Diagnostic performance of LSM was significantly better than that of APRI and FIB-4 for the diagnosis of significant fibrosis. In advanced fibrosis also, LSM showed higher diagnostic performance than APRI and FIB-4 but was comparable with GPR. The advantages of this study included comparison with serum fibrosis models and using liver biopsy as reference.

We confirmed the good performance of LSM to predict significant fibrosis in high viral load Indian CHB patients with ALT ≤ 2ULN.These results were consistent with previous studies. A retrospective study in 188 CHB patients with ALT ≤2 times ULN found that the AUROC of LSM was higher than that of APRI and FIB-4 to predict F2-F4 and F4 and using cut-off values regardless of ALT levels, the DA of LSM was 81% for F2-F4 and 89% for F4 [6]. Another study included 125 European patients, where they found that the AUROC of LSM is 0.85 for predicting significant fibrosis, and 0.90 for predicting cirrhosis [19].

The optimal cut-off values of LSM in this study (7.1 kPa for significant fibrosis) was similar to that reported by Jia J et al., (7.3 kPa for significant fibrosis and 10.7 kPa for cirrhosis) and Marcellin P et al., (7.2 kPa for significant fibrosis and 11 kPa for cirrhosis) [7,20]. A meta-analysis found that the optimal cut-off values of LSM were 7.9 kPa for significant fibrosis and 11.7 kPa for cirrhosis [21]. As we can see, the LSM cut-off values in this study were lower than previous studies, the possible reason can be that this study was performed in patients with ALT either within normal limit or mildly raised (1-2 times ULN), whereas other studies were done with general CHB patients including those with ALT > 2 ULN. Higher ALT values could have led to higher LSM values in previous studies and hence, a higher cut off value overall.

In our study, both APRI and FIB-4 showed positive and significant correlation with the Metavir fibrosis stages. This finding was consistent with previous studies which suggested that APRI and FIB-4 indices were higher in patients with CHB and significant fibrosis [22,23].

Based on evidence from the systematic review, the WHO recommended in its guidelines that in settings with limited resources, APRI and LSM are the most useful tests [24]. Although APRI had been recommended for the assessment of cirrhosis, our results suggests that APRI and FIB-4 are significantly inferior to LSM. Based on current results, authors recommended that LSM should be considered as the preferred non invasive test for fibrosis assessment, and APRI should be considered when LSM is unavailable. Liver biopsy remains the gold standard when there are discordances between clinical symptoms and the extent of fibrosis assessed by non invasive approaches.

The APRI and FIB-4 cut-off values obtained in this study were lower than that proposed by WHO which were derived from studies on patients with chronic hepatitis C infection [24]. However, present findings were similar to the study conducted by Li Q et al., in 236 HBeAg-negative CHB patients with ALT≤2 ULN [25]. Compared with HCV patients, the different magnitude of inflammation and related ALT levels observed in CHB patients might render different cut-off values. One recent study, showing varying patterns of fibrosis according to different causes of chronic liver disease, also justify the need for different cut-off values of scoring systems for assessment of fibrosis resulting from varying causes [26].

The GGT to GPR is a novel index recently developed for estimation of liver fibrosis in patients with CHB. Lemoine M et al.,showed that GGT and PLT count were independent predictors of significant fibrosis and GPR was found to be a more accurate marker than APRI and FIB-4 to stage liver fibrosis in patients with CHB in West Africa [27]. In our study too, GPR showed positive and significant correlation with the Metavir fibrosis stages. For significant fibrosis AUROC of GPR was comparable with APRI and for advanced fibrosis, AUROC of GPR was higher than APRI and was comparable with FIB-4 which is consistent with previous studies [28].

To the best of our knowledge, this is the first study from India which evaluated non invasive methods (Fibroscan, APRI, GPR and FIB-4) predictive of liver fibrosis in high viral load Indian CHB patients with normal or mildly raised ALT level and did a comparative analysis of LSM and other indices for liver fibrosis (APRI, FIB-4 and GPR) in the selected patient group.

Limitation(s)

However, this study has few limitations. First, sample size of the study was small and second, the number of patients with advanced fibrosis and cirrhosis was limited which could have biased the results. Therefore, larger sample, prospective, multicentre studies will be necessary to validate these findings.

CONCLUSION(S)

High viral load CHB patients can have F3-F4 fibrosis even when ALT is normal or mildly raised. Non invasive models can be used to assess fibrosis status and TE is a reliable non invasive test for the diagnosis of liver fibrosis. GPR is a new model which is comparable to that of APRI and FIB-4 but was inferior to TE in predicting significant fibrosis in this subgroup of CHB patients.

REFERENCES

[1] European Association for the Study of the Liver. EASL 2017 Clinical practice guidelines on the management of hepatitis B virus infection. J Hepatol.2017;67:370-98.

[2] Terrault NA , Lok ASF , McMahon BJ, Chang KM, Hwang JP, Jonas MM, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology. 2018;67:1560-99.

[3] Shiha G, Ibrahim A, Helmy A, Sarin SK, Omata M, Kumar A, et al. Asian-Pacific Association for the Study of the Liver (APASL) consensus guidelines on invasive and non invasive assessment of hepatic fibrosis: a 2016 update. Hepato Int.2017;11:1-30.

[4] Vuppalanchi R, Unalp A, Van Natta ML, Cummings OW, Sandrasegaran KE, Hameed T, et al. Effects of liver biopsy sample length and number of readings on sampling variability in non alcoholic fatty liver disease. Clin Gastroenterol Hepatol. 2009;7:481-86.

[5] Ratziu V, Charlotte F, Heurtier A, Gombert S, Giral P, Bruckert E, et al. Sampling variability of liver biopsy in non alcoholic fatty liver disease. Gastroenterology. 2005;128:1898-906.

[6] Li Q, Chen L, Zhou Y. Diagnostic accuracy of liver stiffness measurement in chronic hepatitis B patients with normal or mildly elevated alanine transaminase levels. Sci Rep 2018;8(1):5224.

[7] Jia J, Hou J, Ding H, Chen G, Xie Q, Wang Y, et al. Transient elastography compared to serum markers to predict liver fibrosis in a cohort of Chinese patients with chronic hepatitis B.J Gastroenterol Hepatol. 2015;30:756-62.

[8] Goyal R, Mallick SR, Mahanta M, Kedia S, Shalimar, Dhingra R, et al. Fibroscan can avoid liver biopsy in Indian patients with chronic hepatitis B.J Gastroenterol Hepatol.2013;28:1738-45.

[9] Sterling RK, Lissen E, Clumeck N, Sola R, Correa MC, Montaner J, et al. Development of a simple non invasive index to predict significant fibrosis in patients with HIV/HCV co-infection. Hepatology. 2006;43:1317-25.

[10] Wai CT, Greenson JK, Fontana RJ, Kalbfleisch JD, Marrero JA, Conjeevaram HS, et al. A simple non invasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis Hepatology. 2003;38:518-26.

[11] Xiao G, Yang J, Yan L. Comparison of diagnostic accuracy of aspartate aminotransferase to platelet ratio index and fibrosis-4 index for detecting liver fibrosis in adult patients with chronic hepatitis B virus infection: a systemic review and meta-analysis. Hepatology. 2015;61(1):292-302.

[12] Başar O, Yimaz B, Ekiz F, Giniş Z, Altinbaş A, Aktaş B, et al. Non invasive tests in prediction of liver fibrosis in chronic hepatitis B and comparison with post-antiviral treatment results. Clin Res Hepatol Gastroenterol. 2013;37(2):152-58.

[13] Bedossa P, Poynard T, The French METAVIR Cooperative Study Group. An algorithm for grading activity in chronic hepatitis C. Hepatology. 1996;24:289-93.

[14] Aurora Loaeza-del-Castillo, Francisco Paz-Pineda, Edgar Oviedo-Cárdenas, Francisco Sánchez-Ávila, Florencia Vargas-Voráckovᡠ,AST to platelet ratio index (APRI) for the non invasive evaluation of liver fibrosis: Annals of Hepatology,Volume 7, Issue 4,2008,Pages 350-357.

[15] Sterling RK, Lissen E, Clumeck N, Sola R,Correa MC, Montaner J, et al. Development of a simple non invasive index to predict significant fibrosis in patients with HIV/HCV co-infection. HEPATOLOGY 2006; 43:1317-1325.

[16] Y.E. Park, B.K. Kim, J.Y. Park, D.Y. Kim, S.H. Ahn, K.H. Han, et al.Gamma-glutamyl transpeptidase-to-platelet ratio is an independent predictor of hepatitis B virus-related liver cancer J Gastroenterol Hepatol, 32 (2017), pp. 1221-1229.

[17] Giannini E, Risso D, Botta F, et al. Validity and clinical utility of the aspartate aminotransferase-alanine aminotransferase ratio in assessing disease severity and prognosis in patients with hepatitis C virus-related chronic liver disease. Arch Intern Med. 2003;163(2):218-24.

[18] Sharma R. Revised Kuppuswamy's Socioeconomic Status Scale: Explained and Updated. Indian Pediatr. 2017;54:867-70.

[19] Verveer C, Zondervan PE, ten Kate FJ, Hansen BE, Janssen HL, de Knegt RJ. Evaluation of transient elastography for fibrosis assessment compared with large biopsies in chronic hepatitis B and C. Liver Int 2012;32:622-628

[20] Marcellin P, Ziol M, Bedossa P, Douvin C, Poupon R, de Ledinghen V, et al. Non-invasive assessment of liver fibrosis by stiffness measurement in patients with chronic hepatitis B. Liver Int 2009;29(2):242-247

[21] Chon YE, Choi EH, Song KJ, Park JY, Kim DY, Han KH, et al. Performance of transient elastography for the staging of liver fibrosis in patients with chronic hepatitis B: a meta analysis.PLoS One 2012;7:e44930

[22] Ucar F, Sezer S, Ginis Z, Ozturk G, Albayrak A, Basar O, et al. APRI, the FIB-4 score, and Forn's index have noninvasive diagnostic value for liver fibrosis in patients with chronic hepatitis B. Eur J Gastroenterol Hepatol 2013;25:1076-1081

[23] Shin WG, Park SH, Jang MK, Hahn TH, Kim JB, Lee MS, et al. Aspartate aminotransferase to platelet ratio index (APRI) can predict liver fibrosis in chronic hepatitis B. Dig Liver Dis 2008;40:267-274

[24] Guidelines for the Prevention, Care and Treatment of Persons with Chronic Hepatitis B Infection. Geneva: World Health Organization; 2015

[25] Li Q, Ren X, Lu C, Li W, Huang Y, Chen L. Evaluation of APRI and FIB-4 for noninvasive assessment of significant fibrosis and cirrhosis in HBeAg-negative CHB patients with ALT≤2 ULN.Medicine (Baltimore) 2017; 96(12): e6336

[26] Quaglia A, AlvesVA, BalabaudC, Bhathal PS, Bioulac-Sage P, Crawford JM, et al. Role of aetiology in the progression,regression, and parenchymal remodelling of liver disease:implications for liver biopsy interpretation. Histopathology 2016;68: 953-967

[27] Lemoine M, Shimakawa Y, Nayagam S, Khalil M, Suso P, Lloyd J, et al. The gamma-glutamyl transpeptidase to platelet ratio (GPR) predicts significant liver fibrosis and cirrhosis in patients with chronic HBV infection in West Africa. Gut 2016;65:1369-76

[28] Huang R, Wang G, Tian C, Liu Y, Jia B, Wang J, et al. Gamma-glutamyl-transpeptidase to platelet ratio is not superior to APRI, FIB-4 and RPR for diagnosing liver fibrosis in CHB patients in China.Sci Rep 2017;7: 8543.

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